



Fast-Acting Insulin Aspart Versus Insulin Aspart Using a Second-Generation Hybrid Closed-Loop System in Adults With Type 1 Diabetes: A Randomized, Open-Label, Crossover Trial

Diabetes Care 2021;44:2371–2378 | <https://doi.org/10.2337/dc21-0814>

Melissa H. Lee,^{1,2} Barbora Paldus,^{1,2}
Sara Vogrin,¹ Dale Morrison,¹
Dessi P. Zaharieva,³ Jean Lu,¹
Hannah M. Jones,^{1,2} Emma Netzer,¹
Lesley Robinson,¹ Benjamin Grosman,⁴
Anirban Roy,⁴ Natalie Kurtz,⁴
Glenn M. Ward,^{2,5} Richard J. Maclsaac,^{1,2}
Alicia J. Jenkins,^{1,2,6} and
David N. O'Neal^{1,2}

OBJECTIVE

To evaluate glucose control using fast-acting insulin aspart (faster aspart) compared with insulin aspart (IAsp) delivered by the MiniMed Advanced Hybrid Closed-Loop (AHCL) system in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

In this randomized, open-label, crossover study, participants were assigned to receive faster aspart or IAsp in random order. Stages 1 and 2 comprised of 6 weeks in closed loop, preceded by 2 weeks in open loop. This was followed by stage 3, whereby participants changed directly back to the insulin formulation used in stage 1 for 1 week in closed loop. Participants chose their own meals except for two standardized meal tests, a missed meal bolus and late meal bolus. The primary outcome was the percentage of time sensor glucose values were from 70 to 180 mg/dL (time in range [TIR]).

RESULTS

Twenty-five adults (52% male) were recruited; the median (interquartile range) age was 48 (37, 57) years, and the median HbA_{1c} was 7.0% (6.6, 7.2) (53 [49, 55] mmol/mol). Faster aspart demonstrated greater overall TIR compared with IAsp (82.3% [78.5, 83.7] vs. 79.6% [77.0, 83.4], respectively; mean difference 1.9% [0.5, 3.3]; $P = 0.007$). Four-hour postprandial glucose TIR was higher using faster aspart compared with IAsp for all meals combined (73.6% [69.4, 80.2] vs. 72.1% [64.5, 78.5], respectively; median difference 3.5% [1.0, 7.3]; $P = 0.003$). There was no ketoacidosis or severe hypoglycemia.

CONCLUSIONS

Faster aspart safely improved glucose control compared with IAsp in a group of adults with well-controlled type 1 diabetes using AHCL. The modest improvement was mainly related to mealtime glycemia. While the primary outcome demonstrated statistical significance, the clinical impact may be small, given an overall difference in TIR of 1.9%.

¹Department of Medicine, University of Melbourne, Melbourne, Australia

²Department of Endocrinology & Diabetes, St Vincent's Hospital Melbourne, Melbourne, Australia

³Division of Endocrinology, Department of Pediatrics, School of Medicine, Stanford University, Stanford, CA

⁴Medtronic, Northridge, CA

⁵Department of Pathology, University of Melbourne, Melbourne, Australia

⁶National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, Australia

Corresponding author: David O'Neal, dno@unimelb.edu.au

Received 13 April 2021 and accepted 30 June 2021

Clinical trial reg. no. ACTRN12619000469112, www.anzctr.org.au

This article contains supplementary material online at <https://doi.org/10.2337/figshare.14900547>.

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Despite significant advances in insulin formulations and delivery systems, many people with type 1 diabetes do not achieve optimal glycemic control (1). A major contributor is suboptimal postprandial glucose (PPG) control (2). An important limitation with the subcutaneous administration of current rapid-acting insulin analogs (e.g., insulin lispro, insulin aspart [IAsp], insulin glulisine) is their delayed onset and offset of action relative to endogenous insulin (3,4); boluses should therefore ideally be administered 15–20 min premeal (2,5). Insulin formulations that more closely mimic physiological insulin secretion with faster absorption and onset of action may improve PPG control without increasing risk of delayed hypoglycemia.

Fast-acting insulin aspart (faster aspart) is a novel formulation of IAsp with earlier onset and offset than IAsp (6,7). Faster aspart contains two additional excipients, niacinamide and L-arginine. Niacinamide accelerates monomer formation, thereby promoting transendothelial transport of IAsp and accelerated insulin absorption (8), and L-arginine ensures formulation stability. Faster aspart is approved for use via injections and continuous subcutaneous insulin infusion (CSII) by the U.S. Food and Drug Administration, European Medicines Agency, and Therapeutic Goods Administration.

CSII may be better suited to take advantage of the pharmacokinetics of faster aspart than multiple daily injections (MDI) (9,10) because of the continuous supply of niacinamide through CSII, augmenting rates of insulin monomer dissociation and resulting in earlier absorption (10). Additionally, the smaller subcutaneous insulin depot with CSII may accelerate insulin kinetics compared with MDI (10). CSII studies have shown superior PPG control using faster aspart compared with IAsp following both standardized meals and unrestricted regular meals (11,12).

Automated closed-loop (CL) insulin delivery systems are rapidly becoming an important component of type 1 diabetes management. CL systems demonstrate superior glycemia and improved quality of life (13–15); however, PPG control remains a challenge (16). The pharmacological profile of rapid-acting insulin analogs administered subcutaneously limits the ability of CL systems to respond to rapid increases in glucose levels. Furthermore, late postprandial

hypoglycemia remains a risk because of their persistent action. Ultrarapid-acting insulin analogs may improve the effectiveness of CL systems (16); however, results from CL studies comparing glycemia using faster aspart versus IAsp have been inconsistent (17–20).

The MiniMed Advanced Hybrid Closed-Loop (AHCL) (Medtronic, Northridge, CA) system is a second-generation system incorporating enhancements informed by clinical experience with the Medtronic MiniMed 670G hybrid CL system. New features, including the Auto Bolus function enabling automated correction boluses, improved automated basal control, and options for lower Auto Basal targets (100 or 120 mg/dL) (21), may take advantage of the pharmacokinetic properties of faster aspart. The AHCL system is similar to the Medtronic MiniMed 780G, although it does not include Bluetooth functionality, which was given Conformité Européenne Mark approval in June 2020 for use in people with type 1 diabetes aged 7–80 years. Studies evaluating AHCL have shown safety and efficacy with improved glucose control compared with previous systems, including the 670G system and sensor-augmented pump therapy with predictive low-glucose management (PLGM) (22–24).

Our aim was to compare glucose control, in particular PPG levels, with faster aspart versus IAsp delivered by the MiniMed AHCL system in free-living conditions. We hypothesized that the AHCL enhancements would leverage the pharmacokinetics of faster aspart so as to provide superior overall and PPG control compared with IAsp.

RESEARCH DESIGN AND METHODS

Study Design

This was a 17-week randomized, open-label, crossover study comparing faster aspart with IAsp delivered by the MiniMed AHCL system in free-living adults with type 1 diabetes. It was conducted at St Vincent's Hospital Melbourne in accordance with the Declaration of Helsinki. The study was approved by the local human research ethics committee (Melbourne, Australia) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000469112).

Participants received faster aspart and IAsp in random order. Stages 1 and 2 comprised a 2-week period in open loop followed by 6 weeks in CL. In stage

3, participants changed to the alternate insulin formulation for 1 week in CL (Supplementary Fig. 1).

Participants

Main inclusion criteria included aged ≥ 18 years, clinical diagnosis of type 1 diabetes for ≥ 1 year, CSII use for > 3 months, current or prior use of continuous glucose monitoring (CGM), $HbA_{1c} < 10.0\%$ (< 86 mmol/mol), and ability to count carbohydrates. Main exclusion criteria were current or planned pregnancy, estimated glomerular filtration rate < 40 mL/min/1.73m², history of diabetic ketoacidosis or severe hypoglycemia in the prior 3 months, and major medical or psychiatric illness.

Study Devices and Insulin Delivery

The MiniMed AHCL system consisted of a MiniMed 600 series insulin pump with the AHCL algorithm, a Medtronic Guardian 3 sensor, a Guardian Link 3 glucose sensor transmitter, and a CONTOUR NEXTLINK 2.4 blood glucose meter (Ascensia Diabetes Care, Parsippany, NJ). Medtronic and DreaMed collaborated in the development of the AHCL algorithm which includes technology developed by DreaMed Diabetes (Petah Tikvah, Israel). The MiniMed AHCL system incorporates enhanced features compared with the MiniMed 670G system, including 1) option of two fixed Auto Basal targets of 100 or 120 mg/dL, 2) automated correction boluses based on sensor glucose (SG) levels delivered up to every 5 min to achieve a target of 120 mg/dL, and 3) improved safety features to enable increased time spent in CL (21). For study purposes, basal targets were set at 100 mg/dL, active insulin time (AIT) was set at 4 h, and the automated correction bolus feature was turned on during the entire study for all participants. Faster aspart and IAsp formulations (Novo Nordisk, Bagsvaerd, Denmark) were used in the pump.

Study Protocol

All participants provided written informed consent. Randomization used computer-generated allocation, which was unmasked to both participants and investigators. Baseline venous samples were taken for HbA_{1c} and general biochemistry. Following provision of study equipment, individualized education was provided by diabetes

nurse educators at the initial visit, and the study pump was programmed with participants' established insulin delivery settings. Participants were instructed to administer meal-related insulin boluses immediately prior to meal commencement, calculated using the bolus calculator. Participants undertook their usual daily activities, with no restrictions imposed on meals except for two allocated standardized meal tests during each study stage.

Following the initial visit, participants entered stage 1, which used open loop delivery with the PLGM feature activated for 2 weeks to enable the AHCL algorithm to adapt to their individual insulin requirements. AHCL was activated thereafter for 6 weeks. In stage 2, participants changed to the alternate insulin and reverted to open loop with PLGM for 2 weeks, followed by AHCL activation for 6 weeks. In stage 3, participants continued in AHCL without a washout period in open loop and reverted to the insulin formulation used in stage 1 for 1 week.

Venous blood was collected for serum fructosamine measurements at baseline and at the end of stages 1 and 2.

Participants uploaded their study pump every 2 days for the first 4 weeks of stages 1 and 2 and weekly thereafter. Study investigators reviewed pump downloads, adjusted pump settings according to clinical judgment, and provided a 24-h support service.

Standardized Meal Tests

All participants performed four meal tests: two standardized 40 g carbohydrate-containing meal tests in each stage. Other macronutrient contents of the meal tests consisted of 28 g protein and 12 g fat and totaled 1,560 kJ energy.

The standardized meal tests included a 1) missed bolus consumed without an insulin bolus and 2) late bolus consumed with the insulin bolus, determined using the bolus calculator, and administered 20-min after meal commencement.

Participants were instructed to change their sensor and infusion set the day prior to the meal tests and to refrain from intentional exercise on the day of the meal test. The meal test was conducted between 1800 and 2000 h, with the same standardized meal consumed for each of the four tests. Participants did not consume food or liquids

(other than water) for 4 h postmeal, apart from hypoglycemia treatment (<70 mg/dL).

Outcomes

The primary outcome was total percentage of CGM time in range (TIR; 70–180 mg/dL). Secondary outcomes included percentage of time spent above and below the target range, mean glucose, glucose SD and coefficient of variation, hypoglycemia episodes, serum fructosamine levels, total daily insulin doses, safety outcomes, and overall system performance. CGM outcomes were evaluated separately for overall (24 h per day), daytime (0600–2359 h), and overnight (0000–0559 h) periods. Hypoglycemia episodes, defined as lasting ≥ 15 min (i.e., four or more consecutive CGM readings), were analyzed for level 1 (<70 mg/dL) and level 2 hypoglycemia (<54 mg/dL) (25). Comparisons were made between faster aspart and IAsp study stages (stages 1 and 2).

Postprandial analysis (defined as the 4-h period postmeal) was undertaken following each meal test, in addition to using the bolus calculator carbohydrate entries to signal a meal. Entries included in the analyses fulfilled the following criteria: 1) >20 g carbohydrate entered into the bolus calculator, 2) no preceding carbohydrate entries for >60 min, 3) no subsequent carbohydrate entries for >240 min, and 4) $\geq 70\%$ valid corresponding CGM data. Meals that fell within 0600–1000 h were labeled as breakfast, 1100–1500 h as lunch, and 1800–2200 h as dinner.

Statistical Analysis

Sample size calculations used data from an antecedent study (26). Assuming a conservative SD of 7% to detect $\geq 5\%$ improvement in TIR (27) with 80% power and 5% significance level, 21 participants were required. To allow for a 15% dropout rate, 25 participants were recruited.

Baseline characteristics are presented as median (interquartile range [IQR]) or frequency (percentage). All outcome comparisons between faster aspart and IAsp used mixed-effects linear regression with unstructured covariance and restricted maximum likelihood estimation, where participants were entered as random coefficients. If the model fit

was insufficient (visual exploration of residuals), Wilcoxon signed rank test was performed. Results are expressed as mean difference with 95% CI (where linear model was performed) or median difference with 95% CI (for nonparametric tests). $\Delta SG_{av,0-4\ h}$ was calculated as $AUC_{glucose,0-4\ h}/4\text{-h } SG_{premeal}$, where $AUC_{glucose,0-4\ h}$ was the area under the glucose concentration-time profile between 0 and 4 h (using trapezoidal method), and $SG_{premeal}$ was the SG concentration immediately premeal. A post hoc analysis compared data regarding insulin delivery (Auto Basal and Auto Bolus) in the 4-h poststandardized missed meal bolus tests with the estimated optimal Auto Basal insulin delivery over the same period. The latter was calculated to achieve a desired equilibrium glucose of 100 mg/dL (glucose target of the algorithm) by using the person's insulin sensitivity (a function of the total daily dose) and the observed fasting conditions (fasting SG and corresponding estimated plasma insulin). Conditional logistic regression was used to examine differences in the number of participants reporting one or more infusion-site reaction (expressed as odds ratio [OR] with 95% CI). Analyses were performed using Stata 16.1 (Stata statistical software, release 16, 2019; StataCorp, LLC, College Station, TX).

RESULTS

All 25 participants approached and recruited between June 2019 and March 2020 completed the study (Supplementary Fig. 2). Baseline characteristics are summarized in Supplementary Table 1. All participants had long-duration diabetes managed with CSII and had CGM experience; 52% were male; median (IQR) age was 48 (37, 57) years, and median HbA_{1c} was 7.0% (6.6, 7.2) (53 [49, 55] mmol/mol); and 68% were using IAsp at baseline. Twenty-one (84%) participants were using CSII with CGM in the absence of CL functionality prior to study entry. During run-in using open loop with PLGM, median (IQR) glucose TIR was 76.4% (70.9, 80.8).

Overall Glucose Control

Faster aspart demonstrated greater glucose TIR compared with IAsp (82.3% [78.5, 83.7] vs. 79.6% [77.0, 83.4], respectively; mean difference 1.9% [0.5,

Table 1—Overall CGM outcomes for the study duration

	Faster aspart (n = 25)	IAsp (n = 25)	Difference (95% CI)	P*
Percentage of TIR, mg/dL				
70–180†	82.3 (78.5, 83.7)	79.6 (77.0, 83.4)	1.9 (0.5, 3.3)	0.007
70–140†	58.9 (53.9, 62.4)	54.7 (53.3, 61.0)	2.4 (0.5, 4.3)	0.013
>180†	15.1 (12.5, 19.7)	17.6 (13.1, 20.4)	−1.4 (−2.8, 0.0)	0.044
>250‡	1.9 (1.2, 2.6)	2.0 (1.3, 3.6)	−0.4 (−1.0, 0.0)	0.16
<70†	2.4 (1.4, 3.2)	2.8 (1.4, 4.3)	−0.5 (−0.9, −0.1)	0.028
<54‡	0.2 (0.1, 0.6)	0.4 (0.1, 0.6)	−0.1 (−0.3, 0.0)	0.09
Mean glucose, mg/dL‡	135.0 (132.3, 142.6)	137.7 (131.2, 143.3)	−2.5 (−3.8, 0.0)	0.039
Glucose SD, mg/dL‡	43.7 (42.1, 47.9)	46.1 (42.1, 49.0)	−2.5 (−4.3, −0.5)	0.02
Glucose CV, %‡	32.4 (30.8, 34.0)	33.8 (31.3, 34.8)	−1.2 (−2.3, −0.1)	0.08
Hypoglycemia episodes§				
<70 mg/dL				
Participants with ≥1 episode, n (%)	25 (100)	25 (100)		
Episode duration, min	30 (25, 50)	35 (25, 50)		
Incidence per 7 days	3.7 (2.2, 5.7)	4.4 (1.8, 6.8)	−0.5 (−1.9, 0.2)	0.08
<54 mg/dL				
Participants with ≥1 episode, n (%)	19 (76)	19 (76)		
Episode duration, min	30 (20, 40)	25 (20, 35)		
Incidence per 7 days	0.3 (0.0, 0.7)	0.4 (0.0, 0.7)	0.0 (−0.4, 0.0)	0.20

* $P < 0.05$ considered significant. †Results presented as median (IQR) and mean difference (95% CI); analyzed using mixed-effects linear model. ‡Results presented as median (IQR) and median difference (95% CI); analyzed using Wilcoxon signed rank test. §Hypoglycemia episode was defined as lasting ≥ 15 min (i.e., ≥ 4 consecutive CGM readings).

3.3]; $P = 0.007$) (Table 1 and Fig. 1). All but one participant achieved TIR $>70\%$ in all study stages. Secondary CGM outcomes favored faster aspart with less time spent in hyperglycemia (>180 mg/dL) and hypoglycemia (<70 mg/dL), lower mean glucose, and lower glucose SD compared with IAsp (Table 1 and Fig. 1). Incidence

and duration of hypoglycemia episodes were similar between faster aspart and IAsp for both level 1 (<70 mg/dL) and level 2 (<54 mg/dL) hypoglycemia (Table 1). There were no significant differences in fructosamine levels at the end of each study stage (mean difference -6.4 $\mu\text{mol/L}$ [$-28.7, 15.9$]; $P = 0.58$).

Analysis of daytime CGM (0600–2359 h) showed greater TIR with faster aspart than IAsp (80.7% [76.8, 83.9] vs. 78.5% [73.0, 84.6], respectively; median difference 3.2% [1.3, 4.2]; $P = 0.002$), less hyperglycemia (>180 mg/dL; 17.9% [13.1, 21.6] vs. 19.4% [13.4, 23.9], respectively; median difference -2.3% [$-4.5, -0.5$]; $P = 0.017$), less hypoglycemia (<70 mg/dL; 2.3% [1.3, 3.8] vs. 2.6% [1.4, 4.8], respectively; median difference -0.4% [$-0.9, 0.2$]; $P = 0.037$), and lower mean glucose (137 mg/dL [131, 145] vs. 140 mg/dL [134, 148], respectively; median difference -3.2 mg/dL [$-6.3, 0.0$]; $P = 0.024$) (Supplementary Fig. 3). No significant differences in glucose parameters between faster aspart and IAsp were observed overnight (Supplementary Fig. 3).

PPG Control

Overall, 1,838 (52.7%) of 3,486 carbohydrate entries using faster aspart and 1,774 (71.6%) of 2,478 entries using IAsp qualified for postprandial analysis using bolus calculator data. Meal carbohydrate content was similar between groups (median [IQR] 35 g [29, 45] for faster aspart vs. 38 g [30, 50] for IAsp). Four-hour PPG TIR was greater with faster aspart (median difference 3.5% [1.0, 7.3];

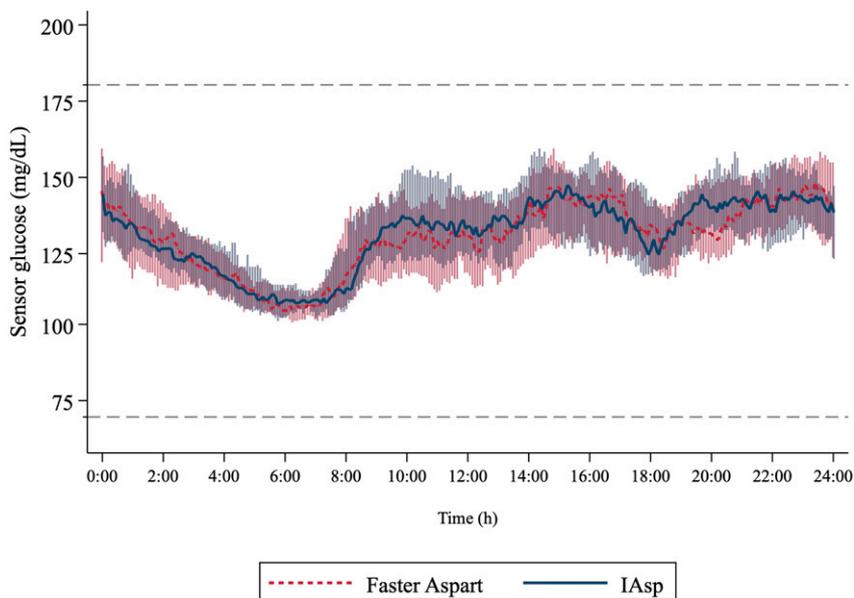


Figure 1—24-h SG levels during CL for the study duration. Faster aspart (red) and IAsp (blue) data lines represent median values, and shaded regions represent IQRs. Dashed gray lines denote glucose target range (70–180 mg/dL).

Table 2—CGM outcomes for all meals combined 4-h postprandial period

	Faster aspart	IAsp	Difference (95% CI)	<i>P</i> *
Percentage of TIR, mg/dL				
70–180†	73.6 (69.4, 80.2)	72.1 (64.5, 78.5)	3.5 (1.0, 7.3)	0.003
70–140†	49.0 (43.3, 53.2)	43.7 (36.4, 54.6)	2.4 (−0.4, 6.9)	0.028
>180†	20.6 (13.3, 25.2)	21.2 (15.6, 32.7)	−2.7 (−8.4, 0.8)	0.024
>250†	2.2 (1.3, 4.4)	3.3 (1.4, 7.0)	−0.5 (−2.3, 0.4)	0.14
<70†	2.8 (1.3, 4.2)	2.4 (1.5, 4.4)	−0.3 (−1.0, 0.0)	0.042
<54†	0.3 (0.1, 0.6)	0.3 (0.1, 0.9)	0.0 (−0.1, 0.2)	0.80
Mean glucose, mg/dL†	144.4 (136.4, 148.0)	149.2 (135.2, 161.8)	−4.9 (−9.2, 1.3)	0.08
Glucose SD, mg/dL†	47.5 (42.1, 50.9)	50.6 (43.7, 55.1)	−2.5 (−5.4, 1.1)	0.045
Glucose CV, %†	31.7 (29.9, 33.8)	33.2 (30.1, 35.3)	−0.9 (−1.9, 0.0)	0.13
Δ SG _{av,0–2 h} , mg/dL‡§	6.8 (−14.0, 27.9)	12.8 (−7.9, 34.9)	−6.3 (−8.5, −4.0)	<0.001
Δ SG _{av,0–4 h} , mg/dL‡§	8.6 (−17.6, 32.6)	12.1 (−13.1, 37.4)	−4.0 (−6.7, −1.3)	0.003

**P* < 0.05 considered significant. †Results presented as median (IQR) and median difference (95% CI); analyzed using Wilcoxon signed rank test. ‡Results presented as median (IQR) and mean difference (95% CI); analyzed using Wilcoxon signed rank test. § Δ SG_{av,0–2 h} and Δ SG_{av,0–4 h} were calculated as $AUC_{\text{glucose},0–2 \text{ h}}/2\text{-h } SG_{\text{premeal}}$ and $AUC_{\text{glucose},0–4 \text{ h}}/4\text{-h } SG_{\text{premeal}}$, where $AUC_{\text{glucose},0–2 \text{ h}}$ and $AUC_{\text{glucose},0–4 \text{ h}}$ were the areas under the glucose concentration-time profile between 0 and 2 h and 0 and 4 h, respectively.

P = 0.003) and Δ SG_{av,0–4 h} was lower with faster aspart compared with IAsp (mean difference −4.0 mg/dL [−6.7, −1.3]; *P* = 0.003) (Table 2 and Fig. 2). At all meal periods, faster aspart demonstrated greater TIR than IAsp (breakfast: median difference 2.4% [−0.6, 8.2]; *P* = 0.016; lunch: 5.4% [−1.2, 11.2]; *P* = 0.022; dinner: 4.9% [0.8, 9.0]; *P* = 0.014) (Supplementary Fig. 4).

In the 60 min prior to the missed and late meal bolus tests, one participant using IAsp consumed a 21 g carbohydrate-containing meal and one participant

using IAsp consumed a 40 g carbohydrate-containing meal, respectively. No participants using faster aspart consumed a carbohydrate-containing meal in the 60 min prior to the standardized meal tests. Differences between insulin formulations with missed (*n* = 25) and late meal boluses (*n* = 25) for standardized 40-g meals did not reach statistical significance (Supplementary Fig. 5, Supplementary Fig. 6, and Supplementary Table 2). A trend favoring faster aspart was observed following a missed meal bolus (TIR 87.8% [61.2, 100.0] vs. 71.4% [38.8, 87.8],

respectively; median difference 18.4% [−6.1, 32.7]; *P* = 0.06) with minimal hypoglycemia. For the faster aspart group, in the 4 h following the missed meal bolus test, the mean (SD) total amount of insulin delivered was 6.0 (2.4) units (61% Auto Basal; 39% Auto Bolus) compared with an estimated optimal Auto Basal insulin delivery of 5.5 (2.4) units. Similarly, for the IAsp group, the total amount of insulin delivered was 6.3 (2.9) units (57% Auto Basal; 43% Auto Bolus) compared with an estimated optimal Auto Basal insulin delivery of 4.8 (2.0) units.

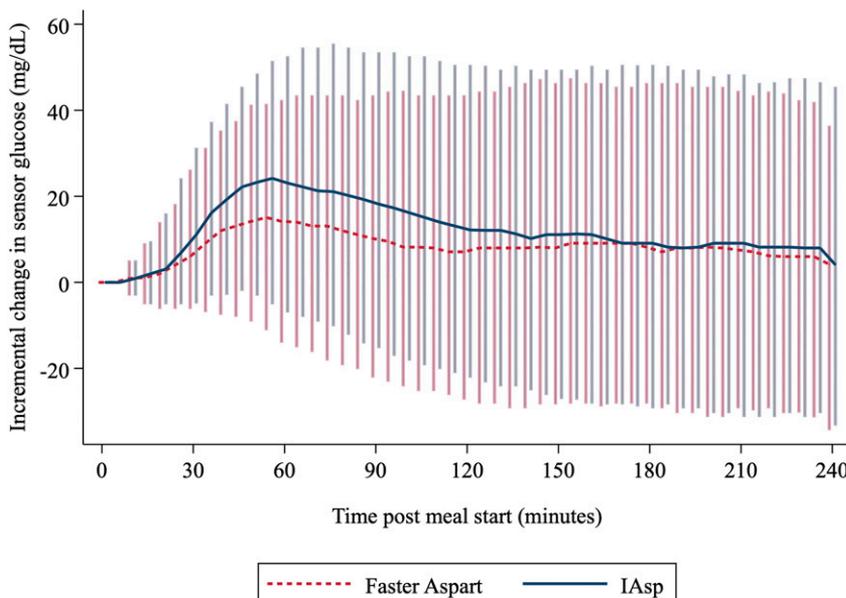


Figure 2—Incremental change in SG from baseline for combined (all meals) 4-h postprandial period. Faster aspart (red) and IAsp (blue) lines represent median values, and vertical bars represent IQRs.

Total Daily Insulin Dosing and System Performance

Total daily insulin, including basal and bolus proportions, was similar between faster aspart and IAsp (44.2 [34.5, 58.0] vs. 45.1 [34.4, 63.3] units, respectively; *P* = 0.4). The median percentage of time in CL was 99.9% in the faster aspart group and 99.8% in IAsp group. The sensor mean absolute relative difference of 7.8% was equivalent in both insulin groups over the entire study, using self-monitoring blood glucose values as a reference.

Safety Outcomes

No severe hypoglycemia, diabetic ketoacidosis or other serious adverse events were reported.

The number of pump alarms relating to no insulin delivery, presumed to be due to line occlusion, was similar

between faster aspart and IAsp (20 alarms in six [24%] participants vs. 38 alarms in nine [36%] participants, respectively; $P = 0.22$). However, participants using faster aspart self-reported four times higher odds of ≥ 1 infusion-site reaction compared with IAsp participants (12 reactions in nine [36%] participants vs. four reactions in three [12%] participants, respectively; OR [95% CI] 4.0 [0.9, 18.8]; $P = 0.08$). All but three episodes were perceived by participants to be due to suspected line occlusion following unexplained hyperglycemia, necessitating premature infusion set change. The remaining three episodes were due to local reaction at the infusion site (pain, erythema, and mild exudate). All episodes resolved with infusion set change.

Transition from study stage 2 to 3 using the alternate insulin formulation without a washout while using AHCL was safe, with no difference in glycemia. Glucose TIR was similar when changing from faster aspart to IAsp and vice versa (median difference -2.0% [$-5.3, 0.4$] vs. 1.8% [$-1.5, 5.6$], respectively). No infusion-site reactions were reported in stage 3.

CONCLUSIONS

In this first clinical trial comparing faster aspart and IAsp delivered by the MiniMed AHCL system, we demonstrate modest improvements in overall glycemia with faster aspart, particularly for daytime and PPG control. While statistically significant, the clinical impact is likely small, because the overall TIR difference was 1.9% , and there was no change in fructosamine levels between groups. However, given our participants' good baseline glucose control (HbA_{1c} 7.0% [53 mmol/mol]) and TIR during run-in already exceeding consensus clinical target recommendations (27), a clinically relevant improvement in TIR of $\geq 5\%$ would be challenging to achieve. The clinical significance of an improvement of $\sim 2\%$ TIR is unknown; however, we speculate that an incremental improvement in TIR of this order, without an increase in hypoglycemia, along with decreased glycemic variability and improved PPG may have long-term benefits.

Two studies of short duration evaluated faster aspart versus IAsp using the MiniMed 670G hybrid CL system. Hsu et al. (17) reported no overall difference

in TIR; however, in keeping with our findings, Ozer et al. (18) reported a higher overall TIR of 1.81% using faster aspart. Our results extend these studies (17,18) by utilizing a second-generation MiniMed hybrid CL system. Our findings using AHCL translate to ~ 27 additional min per day spent within a healthy glucose range using faster aspart compared with IAsp. We also found a reduction in level 1 hypoglycemia (< 70 mg/dL), equating to ~ 7 min per day, favoring faster aspart versus IAsp. Our findings reflect those of Boughton et al. (20) using a CamAPS FX hybrid CL system, whereby a reduction in hypoglycemia of ~ 5 min per day was observed without compromising overall glycemia with faster aspart compared with IAsp.

This is the first free-living study to evaluate PPG control. Previous CL studies comparing faster aspart and IAsp evaluated PPG following standardized meals in a controlled environment (17–19). While Hsu et al. (17) reported no difference in PPG control, Ozer et al. (18) reported a greater reduction in the 1-h PPG increment using faster aspart compared with IAsp (treatment difference [\pm SD] 70.3 [± 17.4] vs. 98.4 [± 17.4] mg/dL, respectively; $P = 0.008$) following a standardized meal, which complements our findings. We evaluated glycemia up to 4 h post-meal ingestion, which is important given postmeal carbohydrate absorption profiles and duration of action of both insulin formulations. The median carbohydrate content of meals in our study was modest (< 40 g), potentially underestimating the benefit of faster aspart compared with IAsp in terms of PPG control.

While differences in glycemia between faster aspart and IAsp following a missed and late bolus meal did not reach statistical significance, the magnitude of the differences observed are of clinical relevance, particularly following a missed meal bolus. It is possible that the moderate amount of protein in the standardized meal may have dampened the early (0–60 min) PPG rise; however, there was no excess delayed postprandial hyperglycemia. We hypothesize that the high TIR postmeal was consequent upon several factors, including the modest carbohydrate and protein meal content; participants' overall excellent glycemia, which meant that premeal glucose levels were usually optimal; and the rapid responsiveness of the AHCL algorithm to

changing glucose levels. In the 4 h following a missed meal bolus, we observed that a greater total amount of insulin was delivered compared with the estimated optimal Auto Basal delivery for the same period. While Auto Basal continued to be responsible for the majority of insulin delivered, the increment in insulin delivery was entirely accounted for by Auto Bolus insulin delivery.

It is possible that the faster aspart used in the AHCL system may be advantageous in common situations in the real-world setting, where people forget to bolus for their meal or delay their bolus until they know how much they have eaten. Our findings contrast with those of Dovc et al. (19), who used a fully automated CL system (DreaMed GlucoSitter) incorporating a fuzzy-logic control algorithm, where no differences were observed in TIR between faster aspart and IAsp following unannounced standardized meals in a supervised inpatient study. It may be that the AHCL system, with its Auto Bolus function and glucose target of 100 mg/dL, is better positioned to take advantage of the pharmacokinetic characteristics of faster aspart. However, differences in outcomes between the two studies may also relate to differences in meal carbohydrate, fat, and protein content, differences in study duration and baseline characteristics of participants, and the impact of the proximity of the exercise intervention to the meals in the protocol by Dovc et al. (19).

While our results support the superiority of faster aspart compared with IAsp delivered by the AHCL system, further modification of the pharmacological properties of ultrarapid-acting insulins is likely to further improve glycemia. CL algorithms may require further modification of the improving pharmacological profiles of novel insulins, with the ultimate goal that manual boluses and meal and exercise announcements will no longer be required, yet PPG control is maintained.

Regardless of the insulin formulation used, the AHCL system achieved the consensus clinical target recommendations for TIR of $> 70\%$ for all but one participant, without excessive hypoglycemia. The overall TIR of $\geq 79\%$ for both faster aspart and IAsp groups was higher than those in previously reported CL studies comparing the insulin formulations (17–20) and recent studies evaluating

AHCL (22–24), most likely reflecting differences in participant characteristics. The overall AHCL system performance was broadly similar between faster aspart and IAsp groups, with a long time spent in CL. There were no differences in total insulin requirements. Changing from faster aspart to IAsp or vice versa without interruption of CL function was safe, and glucose control was maintained. This is relevant when circumstances demand insulin substitution at short notice.

Studies have demonstrated similar compatibility of faster aspart and IAsp with CSII, with no increased observations of microscopically confirmed infusion set occlusions (9). Similarly, while we did not find an excess in pump alarms relating to line occlusions with faster aspart, participant-reported infusion-site reactions were numerically higher with faster aspart than IAsp. Although not statistically significant, our results are congruent with an earlier report by Klonoff et al. (12). Unexplained hyperglycemia has been traditionally used as a clinical surrogate for possible line occlusions (28) and was the most common reason cited by our study participants for their infusion-site reactions. However, there was no evidence that participant safety was compromised in this study. Larger, more robust trials are required, and standard clinical practice advising pump users to regularly change infusion sets should be reinforced.

Study strengths include the randomized crossover design, free-living conditions, and longer study duration. This is the only study to evaluate PPG control in real-world conditions with faster aspart, which enables the system to be tested robustly following different meal compositions and sizes. To complete a comprehensive postprandial analysis, the system was also tested following a missed and late meal bolus, because these are common bolusing errors consequent upon the day-to-day challenges faced by individuals living with type 1 diabetes. Evaluating real-world use supports generalizability to the general population with type 1 diabetes. We recognize as a limitation that this study was conducted in a well-controlled, motivated cohort of pump users, which does not necessarily represent the broader type 1 diabetes population.

However, we hypothesize that in a cohort with less satisfactory glycemia, the differences observed between faster aspart and IAsp may be more apparent and of greater clinical relevance. We also recognize that postprandial glycemia using IAsp may have been compromised by participants bolusing at meal onset rather than 15–20 min premeal. However, this is a common bolusing strategy in the real world. Furthermore, while this was a free-living study, close remote monitoring of participant data was undertaken in the initial stages of each study arm to ensure safety, which does not reflect real-world clinical practice. Our findings utilizing the AHCL system may not extend to other CL systems using different control algorithms and mechanics. The AIT was fixed at 4 h for this study for safety purposes; however, AHCL permits an AIT as low as 2 h, generating a more aggressive algorithm. Such tuning might enhance differences between the two insulin formulations, particularly in the postprandial period. Lastly, altered pharmacokinetic and pharmacodynamic parameters in situations such as those involving pediatric and elderly populations and those with diminished hepatic and renal function may affect the action of faster aspart and have yet to be studied.

In conclusion, a modest benefit in glycemia was observed with faster aspart compared with IAsp delivered by the AHCL system in a well-controlled group of adults with type 1 diabetes. The main clinical advantage associated with faster aspart relates to PPG control, and these differences may be magnified following a missed meal bolus. More detailed exploration of the effect of meal size and composition is warranted. Our findings support the safety and efficacy of faster aspart delivered by the AHCL system. Additional advances in novel ultrarapid-acting insulin formulations with pharmacokinetic properties that more closely mimic endogenous prandial insulin secretion, in conjunction with a CL algorithm modified and tailored to this, will be required to make a greater difference to people living with type 1 diabetes.

Acknowledgments. The authors thank all the participants for their dedication and commitment to this study and acknowledge

Catriona Sims (Department of Medicine, University of Melbourne, Melbourne, Australia), Katie Brown (Department of Medicine, University of Melbourne, Melbourne, Australia), and Marion Jamieson (Medtronic, Melbourne, Australia) for providing administrative and logistical support.

Funding. M.H.L. is supported by a National Health and Medical Research Council postgraduate scholarship, cofunded by Diabetes Australia. B.P. is supported by a University of Melbourne scholarship and research support from JDRF. D.P.Z. is supported by the Leona M. and Harry B. Helmsley Charitable Trust and the International Society for Pediatric and Adolescent Diabetes Fellowship.

Duality of Interest. Medtronic and Novo Nordisk provided research and material support for this investigator-initiated study. Material support was provided from Medtronic and Novo Nordisk. M.H.L. and B.P. have received speaker honoraria from Medtronic. D.P.Z. has received speaker honoraria from Medtronic, Insulet, and Ascensia Diabetes Care. B.G., A.R., and N.K. are employees of Medtronic. R.J.M. has received research support and honoraria from Medtronic, Novo Nordisk, Eli Lilly, and Sanofi. A.J.J. has served on advisory boards for Medtronic, Sanofi, and Abbott. D.N.O. has served on advisory boards and received research support and honoraria from Medtronic, Novo Nordisk, Sanofi, and Abbott. No other potential conflicts of interest relevant to this article were reported.

The funders of the study had no role in the study design, the collection, analysis, or interpretation of data, or the writing of the report and did not impose any restrictions regarding the publication of the report.

Author Contributions. M.H.L., B.P., S.V., D.M., D.P.Z., J.L., G.M.W., R.J.M., A.J.J., and D.N.O. contributed to the study design. M.H.L., B.P., D.M., D.P.Z., J.L., H.M.J., E.N., L.R., and D.N.O. assisted with implementation of the study. M.H.L., B.P., S.V., and D.N.O. contributed to data analysis and interpreted the data. B.G., A.R., and N.K. provided technical support for the study and reviewed the final manuscript for technical accuracy. All authors critically reviewed and approved the final version of the manuscript. D.N.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented orally at the 80th Scientific Sessions of the American Diabetes Association, 12–16 June 2020, and in poster form at the 13th International Conference on Advanced Technologies & Treatments For Diabetes, Madrid, Spain, 19–22 February 2020, the 56th Annual Meeting of the European Association for the Study of Diabetes, 21–15 September 2020, and the Australasian Diabetes Congress, 11–13 November 2020.

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