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Hybrid closed-loop glucose control with faster insulin aspart compared with standard insulin aspart in adults with type 1 diabetes: A double-blind, multicentre, multinational, randomized, crossover study

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Abstract

Aim: To evaluate the use of hybrid closed-loop glucose control with faster-acting insulin aspart (Fiasp) in adults with type 1 diabetes (T1D).

Research Design and Methods: In a double-blind, multinational, randomized, crossover study, 25 adults with T1D using insulin pump therapy (mean ± SD, age 38 ± 9 years, HbA1c 7.4% ± 0.8% [57 ± 8 mmol/mol]) underwent two 8-week periods of unrestricted living comparing hybrid closed-loop with Fiasp and hybrid closed-loop with standard insulin aspart in random order. During both interventions the CamAPS FX closed-loop system incorporating the Cambridge model predictive control algorithm was used.

Results: In an intention-to-treat analysis, the proportion of time sensor glucose was in the target range (3.9–10.0 mmol/L; primary endpoint) was not different between interventions (75% ± 8% vs. 75% ± 8% for hybrid closed-loop with Fiasp vs. hybrid closed-loop with standard insulin aspart; mean-adjusted difference −0.6% [95% CI −1.8% to 0.7%]; $p < .001$ for non-inferiority [non-inferiority margin 5%]). The proportion of time with sensor glucose less than 3.9 mmol/L (median [IQR] 2.4% [1.2%–3.2%] vs. 2.9% [1.7%–4.0%]; $p = .01$) and less than 3.0 mmol/L (median [IQR] 0.4% [0.2%–0.7%] vs. 0.7% [0.2%–0.9%]; $p = .03$) was reduced with Fiasp versus standard insulin aspart. There was no difference in mean glucose (8.1 ± 0.8 vs. 8.0 ± 0.8 mmol/L;

p = .13) or glucose variability (SD of sensor glucose 2.9 ± 0.5 vs. 2.9 ± 0.5 mmol/L; p = .90). Total daily insulin requirements did not differ (49 ± 15 vs. 49 ± 15 units/day; p = .45). No severe hypoglycaemia or ketoacidosis occurred.

Conclusions: The use of Fiasp in the CamAPS FX closed-loop system may reduce hypoglycaemia without compromising glucose control compared with standard insulin aspart in adults with T1D.

KEYWORDS

artificial pancreas, aspart, closed-loop insulin delivery, continuous glucose monitoring, faster insulin aspart, insulin pump therapy, type 1 diabetes

1 | INTRODUCTION

Hybrid closed-loop (HCL) systems are transforming the management of type 1 diabetes (T1D)[1–3] but their performance can be limited by the comparatively slow absorption of subcutaneously administered rapid-acting insulin analogues.[4] Faster-acting insulins have been developed that have the potential to further improve the efficacy and safety of closed-loop insulin delivery systems.

Fast-acting insulin aspart (Fiasp) is insulin aspart in a new formulation, to which two excipients have been added.[5] L-arginine serves as a stabilizing agent, while niacinamide is responsible for accelerated absorption after subcutaneous administration. Pharmacokinetic and pharmacodynamic studies have shown that administration of a Fiasp bolus, by either subcutaneous injection or continuous subcutaneous insulin infusion, is associated with earlier insulin exposure and action and earlier offset of exposure than standard insulin aspart.[5,6]

Short studies of 2-week duration investigating Fiasp and ultra-rapid lispro in the Minimed 670G hybrid closed-loop system did not show any significant differences in glucose control when compared with standard insulin.[7,8] Improved postprandial glucose control was reported with Fiasp compared with standard insulin aspart in the Medtronic advanced hybrid closed-loop system during a 6-week open-label study, although overall time in the target glucose range was not significantly different between interventions.[9] In a supervised inpatient study involving unannounced exercise and unannounced meals, time in the target glucose range was similar with Fiasp compared with standard insulin aspart in the GlucoSitter closed-loop system, although postprandial glucose control was superior with standard insulin aspart.[10]

We aimed to evaluate the use of Fiasp in the CamAPS FX hybrid closed-loop system in adult pump users with T1D over a longer time period. Based on available information, we hypothesized that closed-loop with Fiasp would provide similar efficacy as closed-loop with standard insulin aspart.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study participants

Inclusion criteria included T1D as defined by the World Health Organization, age 18 years or over, insulin pump therapy for at least 6 months (with or without Flash glucose monitoring or continuous glucose monitoring [CGM]) and an HbA1c of 10% or less (≤86 mmol/mol). Key exclusion criteria included pregnancy, a total daily insulin dose of 2.0 units/kg/day or higher and more than one episode of severe hypoglycaemia within the 12 months prior to enrolment.

Eligible adults were recruited from diabetes clinics at Addenbrooke's Hospital (Cambridge, UK), Manchester Royal Infirmary (Manchester, UK), Medical University of Graz (Austria) and Inselspital, University Hospital of Bern (Switzerland).

2.2 | Study oversight

Prior to study commencement, approval was received from independent research ethics committees in the UK, Austria and Switzerland, and regulatory authorities in the UK (Medicines and Healthcare Products Regulatory Agency), Austria (Austrian Agency for Health and Food Safety) and Switzerland (Swissmedic). Participants signed informed consent before any study-related activities were commenced. Participants were reimbursed for their participation in the study and travel expenses.

2.3 | Study design and procedures

The study (trial registration: NCT04055480) adopted a double-blind, multicentre, multinational, randomized, two-period, crossover design contrasting hybrid closed-loop glucose control using faster-acting insulin (Fiasp; Novo Nordisk, Bagsvaerd, Denmark) versus hybrid closed-loop using standard insulin aspart (Novo Nordisk) during unrestricted living. Each intervention lasted 8 weeks and the order of the two interventions was random. A 2–4-week run-in period preceded randomization, during which participants used the study insulin pump and CGM system.

At enrolment, blood samples were taken for analysis of HbA1c. At the start of the run-in period, participants received individual face-to-face training lasting 2–3 h regarding the use of the study insulin pump (Dana Diabecare RS; Sooil, South Korea) and CGM system (Dexcom G6; Dexcom, San Diego, CA, USA). Closed-loop (Auto Mode) functionality was disabled. At the end of the run-in period, compliance

in the use of study pump and continuous glucose monitoring was assessed.

Participants were randomly assigned to receive either 8 weeks of hybrid closed-loop with standard insulin aspart followed by hybrid closed-loop with Fiasp or vice versa. Permuted block randomization was applied. Assignment was blinded to study participants and study personnel.

At the start of the first closed-loop period, participants attended for training on the hybrid closed-loop system. Competency in using the closed-loop system was assessed. Participants were provided with blinded insulin vials and thereafter participants continued the study intervention for the next 8 weeks in free-living settings without remote monitoring or supervision. No restrictions were imposed on food intake, travel or physical activity. Participants were advised to bolus 15 min prior to eating throughout the study as per standard clinical practice.

No pump settings were pre-emptively changed prior to the start of each study period as insulin type was unknown to the participants and study personnel. All participants were provided with a 24-h telephone helpline to contact the local study team in the event of study-related issues.

2.4 | Closed-loop system

The CamAPS FX app (CamDiab, Cambridge, UK) resides on an unlocked Android phone, receives sensor glucose data from the Dexcom G6 transmitter, and uses a Cambridge adaptive model predictive control algorithm to direct insulin delivery on the Dana Diabecare RS pump. The CamAPS FX app acts as a CGM receiver and includes a bolus calculator utilizing bolus settings downloaded from the insulin pump and controlling meal bolus delivery on the insulin pump. Every 8 to 12 min, the adaptive control algorithm residing on the app calculates the insulin infusion rate, which is communicated wirelessly to the study pump via a low-energy Bluetooth communication protocol. The control algorithm is initialized using the participant's weight and total daily insulin dose and, gradually, adapts its insulin dosing based on observed glucose patterns. The default glucose target is 5.8 mmol/L and can be adjusted by participants as required between 4.4 and 11 mmol/L. Further details are provided in Supplementary Appendix (Figure A1).

2.5 | Assays

HbA1c at recruitment was measured locally using an International Federation of Clinical Chemistry and Laboratory Medicine-aligned method and following National Glycohemoglobin Standardization Program standards.

2.6 | Study endpoints

The primary endpoint was the proportion of time when glucose was in the target range between 3.9 and 10.0 mmol/L during the study periods as recorded by sensor glucose measurements. Secondary endpoints included mean sensor glucose; glucose variability measured by the standard deviation and coefficient of variation; time spent at glucose levels of less than 3.9, less than 3.5, less than 3.0, less than 2.8, less than 10.0 and higher than 16.7 mmol/L; and insulin delivery (total, basal and bolus amounts). Hypoglycaemia burden was additionally assessed by the low blood glucose index. Secondary endpoints were calculated over the whole study periods, weekly and monthly in each intervention period and during daytime and night-time periods; daytime was classified as 6:00 AM to 9:59 PM and night-time as 10:00 PM to 5:59 AM.

2.7 | Statistical analysis

This was an exploratory non-inferiority analysis aiming for 24 participants completing the study. The statistical analysis plan was agreed by the investigators in advance. All analyses were carried out on an intention-to-treat basis. Non-inferiority was assessed by comparing the lower limit of 95% confidence interval for the mean difference in the percentage of time with glucose levels in the target range between 3.9 and 10.0 mmol/L to −5%. We analysed endpoints from participants with a minimum of 48 h of sensor data in at least one study period. The respective values obtained during the 8-week randomized interventions were compared using a linear mixed model adjusting for period as a fixed effect and site as a random effect. Baseline values from the run-in period were included in the model. For analyses conducted by time of day, a treatment by time of day interaction term was included in the model to assess whether the treatment effect differed by time of day. Rank normal transformation analyses were used for highly skewed endpoints. Endpoints are presented as mean ± SD for normally distributed values or as median (interquartile range [IQR]) for non-normally distributed values. Outcomes were calculated using GStat software, version 2.3 (University of Cambridge, Cambridge, UK), and statistical analyses were carried out using SAS software, version 9.4 (SAS Institute). A 5% significance level was used to determine statistical significance. For secondary analyses, the false discovery rate was controlled using the adaptive Benjamini-Hochberg procedure.[11] All p values are two-sided.

3 | RESULTS

From August 2019 to February 2020, 25 participants were recruited and randomized (12 males, mean ± SD age 38 ± 9 years, duration of diabetes 22 ± 12 years, HbA1c 7.4% ± 0.8% [57 ± 8 mmol/mol], and total daily insulin 46 ± 13 units/day [46% basal, 54% bolus]) (Table 1). The flow of participants through the trial is shown in Figure S2A. All 25 randomized participants completed the trial with at least 48 h of sensor data in both periods.

Primary and secondary endpoints calculated using data from all randomized participants are presented in Table 2. The primary endpoint, the proportion of time sensor glucose was in the target range between 3.9

TABLE 1 Characteristics of study participants at baseline

	Overall (n = 25)	Fiasp first (n = 13)	Standard insulin aspart first (n = 12)
Age (years)	38 ± 9	37 ± 10	39 ± 8
Male, n (%)	12 (48)	5 (38)	7 (58)
Race/ethnicity, n (%)			
White	23 (92)	12 (92)	11 (92)
Other	2 (8)	1 (8)	1 (8)
BMI (kg/m^2)	26.0 (23.6, 28.5)	26.0 (23.6, 28.3)	26.0 (23.7, 31.6)
Duration of diabetes (years)	22 ± 12	18 ± 10	26 ± 13
HbA1c (%)	7.4 ± 0.8	7.6 ± 0.8	7.1 ± 0.7
HbA1c (mmol/Mol)	57 ± 8	59 ± 8	55 ± 8
Percent of time with sensor glucose level			
3.9 to 10.0 mmol/L	61 ± 13	59 ± 10	64 ± 15
>10.0 mmol/L	35 ± 15	39 ± 12	32 ± 17
>16.7 mmol/L	2.8 (1.0, 4.3)	2.8 (1.3, 4.1)	2.3 (0.6, 5.8)
<3.9 mmol/L	2.4 (1.0, 4.6)	1.9 (0.6, 4.6)	2.8 (1.4%, 4.6)
<3.0 mmol/L	0.2 (0.1, 0.7)	0.2 (0.1, 0.4)	0.3 (0.2, 0.8)
Mean glucose (mmol/L)	9.1 ± 1.3	9.4 ± 1.2	8.8 ± 1.4
Glucose SD (mmol/L)	3.3 ± 0.6	3.4 ± 0.5	3.2 ± 0.8
Total daily insulin (units/day)	46 ± 13	45 ± 12	48 ± 16
Total daily basal insulin (units/day)	21 ± 7	21 ± 6	21 ± 9
Total daily bolus insulin (units/day)	25 ± 8	24 ± 8	26 ± 9

Abbreviation: BMI, body mass index.
Data are presented as mean ± SD or median (Q1, Q3) unless otherwise indicated. Glucose data are based on sensor glucose measurements.

TABLE 2 Glucose control and insulin delivery over 8 weeks of closed-loop with faster-acting insulin (Fiasp) and closed-loop with standard insulin aspart

	Fiasp (n = 25)	Standard insulin aspart (n = 25)	*p* value	95% CI for treatment difference
% of time with sensor glucose level				
3.9 to 10.0 mmol/L*	75 ± 8	75 ± 8	<.001**	−0.6 (−1.8, 0.7)
<3.9 mmol/L	2.4 (1.2, 3.2)	2.9 (1.7, 4.0)	.01	−0.3 (−0.5, −0.1)
<3.5 mmol/L	1.2 (0.5, 1.9)	1.7 (0.7, 2.3)	.02	−0.3 (−0.5, −0.1)
<3.0 mmol/L	0.4 (0.2, 0.7)	0.7 (0.2, 0.9)	.03	−0.3 (−0.6, −0.1)
<2.8 mmol/L	0.2 (0.1, 0.4)	0.4 (0.1, 0.5)	.01	−0.4 (−0.6, −0.1)
>10.0 mmol/L	22 ± 9	21 ± 9	.13	1.2 (−0.2, 2.5)
>16.7 mmol/L	1.4 (0.4, 2.1)	1.2 (0.5, 1.6)	.94	0.0 (−0.2, 0.2)
Mean glucose (mmol/L)	8.1 ± 0.8	8.0 ± 0.8	.13	0.10 (−0.02, 0.22)
Glucose SD (mmol/L)	2.9 ± 0.5	2.9 ± 0.5	.90	−0.00 (−0.08, 0.07)
Glucose CV (%)	36 ± 4	36 ± 4	.18	−0.5 (−1.3, 0.2)
Low blood glucose index	0.7 (0.5, 1.0)	0.9 (0.5, 1.1)	.01	−0.3 (−0.5, −0.1)
Total daily insulin (units/day)	49 ± 15	49 ± 15	.45	0.6 (−1.0, 2.3)
Total daily basal insulin (units/day)	30 ± 13	29 ± 13	.14	1.3 (−0.3, 2.8)
Total daily bolus insulin (units/day)	19 ± 7	19 ± 6	.93	0.1 (−1.2, 1.3)
% time using closed-loop	95 (94, 97)	96 (92, 97)	.98	0.1 (−0.6, 0.6)
% time using CGM	97 (96, 98)	97 (95, 98)	—	—

Abbreviation: CGM, continuous glucose monitoring; CV, coefficient of variation.
Data presented are mean ± SD or median (Q1, Q3) throughout the 8-week study periods. Glucose data are based on sensor glucose measurements. The prespecified analysis plan did not include analyses of CGM use.
*Primary endpoint.
***p* value is for non-inferiority; the non-inferiority margin is 5%.

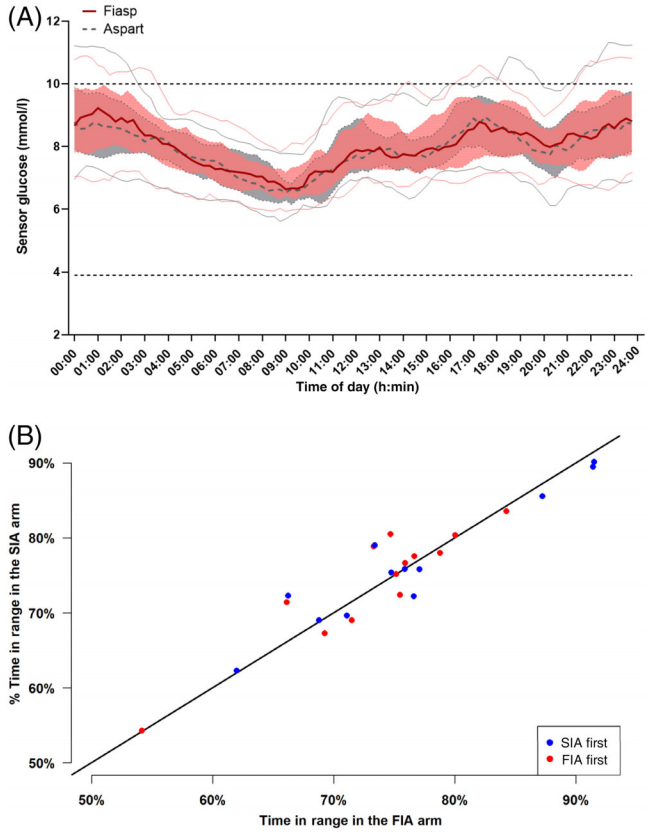

FIGURE 1 (A) Sensor glucose levels (median, IQRs) during closed-loop with Fiasp (n = 25; solid red line and red shaded area) and during closed-loop with standard insulin aspart (n = 25; dashed black line and grey shaded area). Dashed horizontal lines indicate the target glucose range between 3.9 and 10 mmol/L. (B) Percentage of time spent in target glucose range using Fiasp (FIA) compared with standard insulin aspart (SIA; n = 25)

and 10.0 mmol/L, was not different between interventions (75% ± 8% vs. 75% ± 8% for hybrid closed-loop with Fiasp vs. hybrid closed-loop with standard insulin aspart, respectively; $p < .001$ for non-inferiority), with a mean adjusted difference of −0.6 percentage points (95% CI −1.8 to 0.7). Figure 1A shows 24-h sensor glucose profiles.

There was no difference in mean glucose (8.1 ± 0.8 vs. 8.0 ± 0.8 mmol/L; $p = .13$) or glucose variability (SD of sensor glucose 2.9 ± 0.5 vs. 2.9 ± 0.5 mmol/L; $p = .90$) between study interventions (Table 2). The proportion of time sensor glucose was less than 3.9 mmol/L was reduced with Fiasp versus standard insulin aspart (median 2.4 [IQR 1.2%–3.2%] vs. 2.9 [IQR 1.7%–4.0%]; $p = .01$), with a mean adjusted difference of −0.3 percentage points in favour of Fiasp (95% CI −0.5 to −0.1). The time spent with sensor glucose readings below 3.5, 3.0 and 2.8 mmol/L, and the relative burden of hypoglycaemia as measured by the low blood glucose index, were all reduced with Fiasp compared with standard insulin aspart (Table 2). There was high correlation of the time in the target glucose range between hybrid closed-loop with Fiasp and hybrid closed-loop with standard insulin aspart (Figure 1B).

Total daily insulin delivery was similar between interventions (49 ± 15 vs. 49 ± 15 units/day for closed-loop with Fiasp vs. closed-loop with standard insulin aspart, respectively; $p = .45$). There was no difference in basal or bolus insulin delivery between study interventions (Table 2). Approximately 60% of insulin was delivered as basal insulin and 40% through user-initiated boluses during each intervention.

Glucose sensor use and closed-loop use were high. Closed-loop was in use for a median of 95% (IQR 94%–97%) of the time with Fiasp and 96% (92%–97%) with standard insulin aspart (Table 2).

Secondary endpoints calculated for daytime and night-time are shown in Table 3. There was no evidence that the effect of treatment depended on the period of the day (daytime vs. night-time). Sensor glucose measures and insulin measures remained stable from week 1 of each intervention period and between months of each intervention period (data not shown). There was no evidence of a carryover effect between interventions when a period by treatment interaction term was included in the model ($p = .85$).

3.1 | Adverse events

No severe hypoglycaemia or diabetic ketoacidosis or other severe adverse events were reported during the study. Four adverse events were reported; two occurred during run-in, one during hybrid closed-loop with Fiasp, and one during hybrid closed-loop with standard insulin aspart. One event related to the study pump, which consisted of a malfunctioning of the pump refill mechanism during a set change, and which required pump replacement. All participants recovered fully without clinical sequelae.

There were nine unscheduled contacts throughout the study that occurred in five participants. Seven contacts were related to device issues.

4 | DISCUSSION

This double-blind, multicentre, randomized, controlled trial investigated the application of Fiasp in a hybrid closed-loop system in adults with T1D over an 8-week period of unrestricted living. Our findings show that use of Fiasp in the CamAPS FX hybrid closed-loop system may offer additional benefit with a reduction in hypoglycaemia compared with standard insulin aspart, without compromising overall glycaemic control as measured by time in target glucose range, mean glucose and glucose variability.

The results of the current study are consistent with observations in shorter studies using the Minimed 670G hybrid closed-loop system in terms of the lack of an effect of currently available faster-acting insulins on overall measures of glucose control. However, our study shows reduced hypoglycaemia with Fiasp and supports the application of Fiasp in hybrid closed-loop systems in adults with T1D.[7,8] It is unclear if similar benefits can be obtained with other closed-loop systems and further longer studies with other closed-loop systems are warranted.

TABLE 3 Daytime and night-time glucose control and insulin delivery during hybrid closed-loop with faster-acting insulin (Fiasp) and standard insulin aspart

	Daytime 6:00 AM to 9:59 PM		Night-time 10:00 PM to 5:59 AM		
	Fiasp (n = 25)	Standard insulin aspart (n = 25)	Fiasp (n = 25)	Standard insulin aspart (n = 25)	*p* value*
% of time with sensor glucose level					
3.9 to 10.0 mmol/L	75 ± 8	75 ± 8	75 ± 11	76 ± 9	.98
<3.9 mmol/L	2.6 (1.2, 3.7)	3.1 (1.7, 4.8)	2.0 (1.2, 2.8)	2.2 (1.3, 3.1)	.98
<3.5 mmol/L	1.2 (0.5, 1.8)	1.6 (0.8, 2.6)	1.0 (0.6, 1.4)	1.1 (0.6, 1.7)	.98
<3.0 mmol/L	0.4 (0.1, 0.7)	0.6 (0.2, 0.9)	0.3 (0.1, 0.6)	0.4 (0.2, 0.9)	.98
<2.8 mmol/L	0.2 (0.1, 0.3)	0.4 (0.1, 0.5)	0.2 (0.1, 0.4)	0.3 (0.1, 0.6)	.98
>10.0 mmol/L	22 ± 9	22 ± 9	22 ± 11	21 ± 10	.88
>16.7 mmol/L	1.1 (0.4, 2.4)	1.2 (0.5, 1.8)	1.3 (0.4, 2.4)	0.9 (0.2, 1.7)	.79
Mean glucose (mmol/L)	8.0 ± 0.8	8.0 ± 0.8	8.1 ± 0.9	8.0 ± 0.9	.57
Glucose SD (mmol/L)	2.9 ± 0.5	2.9 ± 0.5	2.9 ± 0.6	2.9 ± 0.6	.98
Glucose CV (%)	36 ± 4	36 ± 3	35 ± 5	36 ± 5	.98
Low blood glucose index	0.8 (0.5, 1.1)	0.9 (0.5, 1.2)	0.6 (0.5, 0.9)	0.7 (0.6, 1.0)	.98
Total daily insulin (units/day)	38 ± 11	37 ± 11	12 ± 5	11 ± 5	.98
Total daily basal insulin (units/day)	20 ± 9	19 ± 9	10 ± 4	10 ± 4	.57
Total daily bolus insulin (units/day)	18 ± 6	18 ± 5	1 ± 1	1 ± 1	.98

Abbreviation: CV, coefficient of variation.
Data presented are mean ± SD or median (Q1, Q3) throughout the 8-week study periods. Glucose data are based on sensor glucose measurements.
*p value for treatment-by-time of day interaction.

Hypoglycaemia is a major concern for people with T1D, an important cause of stress and anxiety and the main barrier to therapy intensification and optimal glucose control.[12] The reduction in time in hypoglycaemia below 3.9 mmol/L with Fiasp equates to approximately 5 min/day. This effect size was observed at a very low glucose threshold of 2.8 mmol/L, indicating that Fiasp reduces the exposure to the lowest glucose levels which is then propagated to hypoglycaemia exposure across higher glucose thresholds. A nominally greater reduction of hypoglycaemia with Fiasp was observed during the daytime period, suggesting the benefits may be attributable to faster offset of insulin action around mealtime boluses. The use of the highly adaptable Cambridge closed-loop algorithm and the longer study duration may be reasons why this effect was observed in our study compared with the study conducted by Hsu et al.[7] The frequency of clinically significant hypoglycaemia is often comparatively low in clinical trial settings, and it is probable that hypoglycaemia occurs less frequently in study cohorts than in real-world populations. Therefore, we consider the difference we observed to be clinically important when interpreting the outcomes of this study in the context of real-world clinical practice.

The performance of the CamAPS FX hybrid closed-loop system was notable with an increase in the time in the target glucose range from 61% during the run-in period to 75% during the study intervention period, an improvement observed within the first week after commencement of hybrid closed-loop irrespective of insulin type (data not shown). Time spent in hypoglycaemia was comparable between baseline (2.4%) and closed-loop study periods (2.4% and 2.9%). A similar time in the target glucose range (75%–78%) was reported with the Minimed 670G Fiasp study although this was over a shorter duration in a cohort with tighter glycaemic control at baseline (median HbA1c 7.1%).[7]

There was no difference in glycaemic control between daytime and night-time in our study; however, this was probably because of the definition of night-time (10:00 PM), when postprandial hyperglycaemia may still be encountered, and this is supported by the 24-h sensor glucose profiles (Figure 1).

The very high time spent in closed-loop during the study (≥95%) reflects the usability of the system and is a key factor to realizing the glycaemic benefits of closed-loop insulin delivery.[13]

The strengths of our study include the multinational, double-blind, crossover design with each participant acting as their own control, undertaken over a longer duration than previous studies investigating closed-loop with faster-acting insulin. This is the only study that has shown a reduction in hypoglycaemia with Fiasp in a hybrid closed-loop system. The study was performed without remote monitoring or close supervision, thereby assessing real-world use and supporting generalizability of findings. The limitations include a comparatively small total number of participants, and a study population with good glycaemic control at baseline (mean HbA1c 7.4%). The group randomized to receive standard insulin aspart first had superior glucose control and more time in hypoglycaemia at baseline, but given the crossover study design with each participant acting as their own control, this

was unlikely to have impacted on study outcomes, particularly as no carryover effect between the two intervention periods was observed.

Future studies evaluating hybrid closed-loop with Fiasp in young children, where hypoglycaemia is a major concern, are warranted. Furthermore, studies contrasting hybrid closed-loop with Fiasp to hybrid closed-loop with other faster-acting insulins including ultra-rapid lispro and insulin analogues under development may show additional benefits.[14]

In conclusion, hybrid closed-loop glucose control using the CamAPS FX app with Fiasp is effective and safe in adults with T1D, and may offer additional benefit in terms of hypoglycaemia reduction compared with standard insulin aspart without compromising overall glucose control.

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CONFLICT OF INTEREST

SH serves as a member of Sigma (Dexcom) and Medtronic advisory boards, is a director of Ask Diabetes Ltd providing training and research support in health care settings, and reports having received training honoraria from Medtronic and Sanofi. HT reports having received research support and speaker honoraria from Dexcom. MEW reports receiving license fees from B. Braun, patents related to closed-loop, and being a consultant at CamDiab. NLA reports being a consultant at CamDiab. JKM is a member in the advisory board of Becton-Dickinson, Boehringer Ingelheim, Capillary Biomedical, Eli Lilly, Medtronic, Prediktor SA and Sanofi, has received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Eli Lilly, Dexcom, Medtronic, Novo Nordisk, Roche Diabetes Care, Sanofi, Servier and Takeda, and is a shareholder at decide Clinical Software GmbH. ME reports having received speakers/writers' fees, acted on advisory board and/or had research collaborations with/acted as a trialist for Eli Lilly, NovoNordisk, Sanofi, Medtronic, Dexcom, Roche, Astra Zeneca, Zucara, Boehringer Ingelheim, Abbott Diabetes Care, NGM Pharma, Imcyse and Ypsomed. LL reports having received speaker honoraria from Animas, Abbott, Insulet, Medtronic, Novo Nordisk, Roche and Sanofi; acting on an advisory panel for Animas, Abbott, Novo Nordisk, Dexcom, Medtronic, Sanofi and Roche; and receiving research support from Novo Nordisk and Dexcom. RH reports having received speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving license fees from B. Braun and Medtronic; patents related to closed-loop, and being director at CamDiab. CKB, TP, DH, JS, NC, PC and LB declare no duality of interest associated with this manuscript.

AUTHOR CONTRIBUTIONS

RH, CKB, LL, HT, JKM, LB, MEW and ME co-designed the study. CKB, SH, LL, HT, JKM, TP, DH and LB were responsible for the screening and enrolment of participants, arranged informed consent from the participants, and provided patient care. CKB and RH wrote the report. CKB, MEW and RH contributed to data analysis. Statistical analyses were undertaken by NC and PC. RH designed and implemented the glucose controller. RH, CKB, SH, LL, HT, JS, JKM, LB and ME contributed to the interpretation of the results. All the authors critically reviewed the report. CKB, MEW, NC and RH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14355.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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