CamAPS FX hybrid closed-loop with ultra-rapid lispro compared with standard lispro in adults with type 1 diabetes: a double-blind, randomized, crossover study.

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ABSTRACT

Introduction: To evaluate hybrid closed-loop with ultra-rapid insulin lispro (Lyumjev) compared with hybrid closed-loop with standard insulin lispro in adults with type 1 diabetes.

Materials and methods: In a single-center, double-blind, randomized, crossover study, 28 adults with type 1 diabetes (mean±SD: age 44.5±10.7, HbA1c 7.1±0.9% [54±10mmol/mol]) underwent two 8-week periods comparing hybrid closed-loop with ultra-rapid insulin lispro and hybrid closed-loop with standard insulin lispro in random order. The same CamAPS FX closed-loop algorithm was used in both periods.

Results: In an intention-to-treat analysis, the proportion of time sensor glucose was in target range (3.9 to 10mmol/L [70-180mg/dL]; primary endpoint) was greater with ultra-rapid lispro compared with standard insulin lispro (mean±SD: 78.7±9.8% vs. 76.2±9.6%; mean difference 2.5 percentage points [95%CI 0.8 to 4.2]; p=0.005). Mean sensor glucose was lower with ultra-rapid lispro compared with standard insulin lispro (7.9±0.8mmol/L [142±14mg/dL] vs. 8.1±0.9mmol/L [146±16mg/dl]; p=0.048). The proportion of time with sensor glucose <3.9mmol/L [70mg/dl] was similar between interventions (median [IQR] ultra-rapid lispro 2.3% [1.3–2.7%] vs. standard insulin lispro 2.1% [1.4–3.3%]; p=0.33). No severe hypoglycemia or ketoacidosis occurred.

Conclusions: The use of ultra-rapid lispro with CamAPS FX hybrid closed-loop increases time in range and reduces mean glucose with no difference in hypoglycemia compared with standard insulin lispro in adults with type 1 diabetes.

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INTRODUCTION

Hybrid closed-loop systems, combining an insulin pump, a continuous glucose monitor and a control algorithm, improve glycemic outcomes for people living with type 1 diabetes[1-3]. Rapid-acting insulin analogues are used to good effect in closed-loop systems[1] but limit closed-loop efficacy due to relatively slow absorption compared to physiological insulin secretion[4,5].

Outside closed-loop use, novel ultra-rapid acting insulin analogues have been shown to reduce postprandial hyperglycemia without increasing hypoglycemia risk[6-10]. When used with hybrid closed-loop systems, the findings have been inconsistent. Randomized clinical studies of the Medtronic hybrid closed-loop system have demonstrated greater time in range and reduction in hypoglycemia (<3.9mmol/L [70mg/dL]) with faster acting insulin aspart when compared to standard insulin aspart[11,12]. In a study utilizing the CamAPS FX closed-loop system we found that faster aspart reduced hypoglycemia (<3.9mmol/L [70mg/dL] and <3.0mmol/L [54mg/dL]) versus standard insulin aspart with comparable time in range and mean glucose[13].

Ultra-rapid lispro (Lyumjev, Eli Lilly, Indianapolis, IN, USA) combines standard insulin lispro with treprostinil and sodium citrate, excipients which facilitate faster insulin absorption, earlier glucose-lowering and shorter duration of action. In a randomized study of the Medtronic 670G hybrid closed-loop system, ultra-rapid lispro significantly reduced time spent below 3.9mmol/L [70mg/dL], however no significant difference was seen in time in range[14].

The present study aimed to expand the limited evidence and evaluate the efficacy of ultra-rapid lispro compared with standard insulin lispro in the CamAPS FX hybrid closed-loop system in adults with type 1 diabetes.

MATERIALS AND METHODS

Study participants and study design

Adults aged 18 years and above with type 1 diabetes on insulin pump for at least 6 months and HbA1c of 10% or less (≤86 mmol/mol) were recruited. Exclusion criteria included more

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than one episode of severe hypoglycemia in the preceding 12 months, a total daily insulin dose of 2.0units/kg/day or higher and pregnancy. Eligible adults were recruited from diabetes clinics at Addenbrooke's Hospital (Cambridge, UK). Ethical approvals were obtained from an independent research ethics committee. Participants signed informed consent before any study-related activity. Trial registration NCT05257460.

The study adopted a double-blind, single center randomized, two-period crossover design comparing hybrid closed-loop insulin delivery using ultra-rapid insulin lispro (Lyumjev) and hybrid closed-loop using standard insulin lispro. A 2-to-4-week run-in period during which the participants used the study insulin pump (Dana Diabecare RS or Dana I; Sooil, Seoul, South Korea) and continuous glucose monitor Dexcom G6; Dexcom, San Diego, CA, USA) in open-loop preceded the intervention period.

At the initial visit blood samples were taken for analysis of HbA1c using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)-aligned method and following NGSP standards. Participants received training on the use of the study insulin pump and the study continuous glucose monitoring system (. At the end of the run-in period appropriate use of the devices was assessed.

Participants were randomly assigned to receive either 8 weeks of hybrid closed-loop with standard insulin lispro followed by hybrid closed-loop with ultra-rapid insulin lispro 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 training on the CamAPS FX hybrid closed-loop app (CamDiab, Cambridge, UK) and competency was assessed. At the start of each study period, participants were provided with blinded insulin vials and thereafter participants continued the study interventions, each lasting 8 weeks. There was no washout period separating the two interventions. No restrictions were imposed on food intake, physical activity or travel. Participants were advised to bolus 15 minutes before eating and adjust as required in both treatment periods, as per standard clinical practice. All participants were provided with a 24-hour telephone helpline to contact the study team for study-related support.

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Psychosocial metrics were assessed using the Hypoglycemia Confidence Scale[15], Problem Areas In Diabetes questionnaire[16], and INSPIRE measure (Insulin delivery Systems: Perceptions, Ideas, Reflections and Expectations)[17].

Hybrid closed-loop system

The CamAPS FX interoperable app resided on an unlocked Android phone (Galaxy S8, Samsung, South Korea) and used the Cambridge adaptive model predictive control algorithm to direct insulin delivery by insulin pump based on sensor glucose levels. The app includes a bolus calculator for app-initiated meal bolus insulin delivery. Every 8 to 12 minutes, the adaptive control algorithm calculates the insulin infusion rate, which is communicated wirelessly to the insulin pump. The control algorithm is initialized using participant weight and total daily insulin dose and gradually adapts its insulin dosing based on glucose patterns. The algorithm adapts to duration of insulin action to optimize compatibility with faster acting insulins. The default glucose target is 5.8 mmol/L [105mg/dL] and can be adjusted by participants as required between 4.4 and 11.0 mmol/L [79 and 198 mg/dL][2]. The same algorithm was used in both study periods,

Study endpoints

The primary endpoint was the proportion of time when glucose was in the target range between 3.9mmol/L [70mg/dL] and 10.0mmol/L [180mg/dL] 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 concentrations of <3.9mmol/L [70mg/dL], <3.0mmol/L [54mg/dL], >10.0mmol/L [180mg/dL] and >16.7mmol/L [300mg/dL], and insulin delivery (total, basal and bolus amounts). Endpoints were calculated over the whole of each study period and during daytime and night-time periods; daytime was classified as 06:00 to 23:59 and night-time as midnight to 05:59.

Statistical analysis

This was an exploratory analysis aiming for 24 participants completing the study. The statistical analysis plan was agreed by the investigators in advance. The sample was chosen

to match the sample size of a study in adults comparing faster insulin aspart to standard insulin aspart using the CamAPS FX closed-loop algorithm[13]. All analyses were performed on an intention-to-treat basis. Mean±SD or summary statistics appropriate to the distribution were calculated for the primary and secondary outcomes over the 8-week period by treatment intervention. The treatment interventions were compared using a linear mixed model adjusting for period as a fixed effect. The analysis dataset were three records per subject (one for baseline and one for each period). Inclusion of the pre-randomisation baseline value as a third observation for each subject in the model gave a variance reduction analogous to adjusting for it as a covariate. The model accounted for correlated data from the same subject. Analyses of secondary endpoints were considered exploratory thus no formal corrections for multiple comparisons were performed.

Endpoints from participants with a minimum of 48h of sensor data in at least one study period were analysed. A 95% confidence interval was reported for the difference between interventions and p values <0.05 were considered significant. Non-normally distributed data were winsorized. Missing data were not imputed for the primary analysis. Outcomes were calculated using GStat software, version 2.3 (University of Cambridge, Cambridge, UK), and statistical analyses carried out using SPSS Statistics software, version 28 (IBM Software, Hampshire, UK).

RESULTS

From January 2022 to August 2022, 28 participants were recruited (18 males, mean±SD age 44.5±10.7 years, HbA1c 7.1±0.9% [54±10mmol/mol], and total daily insulin 39.7 units per day) (Table 1). One participant withdrew prior to randomization due to Covid-19. Twenty-seven participants were randomized and 14 participants were allocated to hybrid closed-loop with standard insulin lispro first. One participant from this group withdrew during the first study period due to device issues. Twenty-six participants completed both study periods. All randomized participants had at least 48 hours of sensor data in at least one study period.

Primary and secondary endpoints calculated using data from all randomized participants are presented in Table 2. Hybrid closed-loop with ultra-rapid lispro demonstrated superiority to

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hybrid closed-loop with standard insulin lispro for the primary endpoint, the proportion of time sensor glucose was in target range between 3.9mmol/L [70mg/dL] and 10.0mmol/L [180mg/dL] (ultra-rapid insulin lispro vs. standard insulin lispro; 78.7±9.8% vs. 76.2±9.6%; p=0.005 with a mean difference of 2.52 percentage points [95% CI 0.82 to 4.23]). Figure 1 shows 24-hour sensor glucose profiles and individual participant's percentage of time spent in target glucose by treatment period.

Mean glucose was significantly lower with ultra-rapid insulin lispro (ultra-rapid insulin lispro vs. standard insulin lispro; 7.9±0.8mmol/L [142±14mg/dL] vs. 8.1±0.9mmol/L [146±16mg/dL]; p=0.048 with a mean difference of -0.17mmol/L [95% CI -0.33 to 0.00] or -3.1mg/dL [95% CI -5.9 to 0.0]) (Table 2). The time spent with the sensor glucose reading above 10mmol/L [180mg/dL] was significantly reduced with ultra-rapid lispro (ultra-rapid insulin lispro vs. standard insulin lispro; 19.2±9.9% vs. 21.5±10.1%; p=0.011 with a mean difference of -2.38 percentage points [95% CI -4.18 to 0.59]) (Table 2). There was no significant difference in the proportion of time sensor glucose was less than 3.9mmol/L [70mg/dL] (median[IQR] ultra-rapid insulin lispro vs. standard insulin lispro; 2.3% [1.3 to 2.7] vs. 2.1% [1.4 to 3.3]; p=0.327), less than 3.0mmol/L [54mg/dL] (0.30% [0.15 to 0.46] vs. 0.30% [0.16 to 0.46]; p=0.650) or more than 16.7mmol/L [300mg/dL] (0.8% [0.2 to 2.0] vs. 1.1% [0.3 to 3.5]; p=0.083). There was no significant difference in measures of glucose variability (standard deviation or coefficient of variation of sensor glucose); ultra-rapid insulin lispro vs. standard insulin lispro; SD: 2.8±0.7mmol/L [50±13mg/dL] vs. 2.9±0.6mmol/L [52±11mg/dL]; p=0.098, CV 34.7±5.0% vs. 35.5±4.6%; p = 0.279.

Total daily insulin delivery was similar between interventions (median [IQR] ultra-rapid insulin lispro vs. standard insulin lispro; 41.7 units per day [32.6 to 54.7] vs. 42.8 units per day [31.3 to 53.4] p=0.502). There was no difference in basal or bolus insulin delivery between study interventions (Table 2).

Closed-loop use and glucose sensor use were high (Table 2). Closed-loop was in use for a median of 96.8% [IQR 95.4 to 97.6] with ultra-rapid lispro and 96.5% [IQR 94.7 to 98.0] for standard insulin lispro, p=0.714 (Table 2).

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There was no evidence of a carryover effect between interventions when a period by treatment interaction term was included in the model (p=0.282).

No severe hypoglycemia or diabetic ketoacidosis occurred during the study. There was one non-study related severe adverse event prior to randomization. Twenty-two other adverse events were reported; two occurred during run-in (all non-study related), six occurred during the standard insulin lispro period (all non-study related) and fourteen occurred during the ultra-rapid lispro period (four non-study related, ten study-related). All participants recovered fully without clinical sequelae. The ten-study related adverse events occurred during the ultra-rapid lispro period and were all due to stinging at the infusion site. In all cases this was mild and did not result in any of the participants withdrawing from the study. There were ten device deficiencies reported by seven participants in the study, eight were pump related, one was sensor related and one was due to the smartphone.

There were no differences in psychosocial outcomes as measured by the Hypoglycemia Confidence Scale, Problem Areas in Diabetes questionnaire, and INSPIRE measure (results not shown).

DISCUSSION

The present study demonstrated that ultra-rapid lispro with CamAPS FX hybrid closed-loop significantly increased time in range by 2.5 percentage points (36 minutes per day) when compared to standard insulin lispro. Additionally, significant reductions in time above range and mean glucose were observed. Use of ultra-rapid lispro may offer additional benefits without increased risk of hypoglycemia.

Time in range is a clinically significant glucose metric[18], endorsed by international consensus and associated with a meaningful reduction in microvascular and macrovascular complication risk and HbA1c[19,20]. Although previous guidelines suggest a 5 percentage point change in TIR is clinically significant, this is in relation to a technology change rather than an insulin change within existing technology[18]. We suggest that a 2.5 percentage point improvement is a significant clinical benefit, as changing insulin involves no additional user burden or training.

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In contrast, a shorter 4-week study of the hybrid closed-loop system Medtronic 670G comparing ultra-rapid lispro with standard insulin lispro found no difference in time in range, with a small but significant increase in mean glucose and significant reduction in time spent below 3.9mmol/L[70mg/dL][14]. The differences between the studies may be attributable to the hybrid closed-loop control algorithms. The CamAPS FX algorithm adapts to the duration of insulin action, day-to-day prandial and diurnal glucose patterns[1], optimizing compatibility with faster-acting insulin profiles. Bolus dose timing may also be a contributing factor. In the present study participants were advised to bolus 15 minutes before meals and adjust as necessary. In the 670G hybrid closed-loop study, bolus doses were administered 0 to 2 minutes before food; time in range was no different, however a reduction in time spent in hypoglycemia was seen[14] Further studies are warranted to examine the optimal timing of faster-acting insulin bolus dosing in the context of hybrid closed-loop systems[4].

Time spent in hypoglycemia below 3.9mmol/L [70mg/dL] or 3.0mmol/L [54mg/dL] and total daily dose of insulin between ultra-rapid lispro and standard insulin lispro were comparable. Increase in time in range did not come at the expense of increased hypoglycemia risk or excess insulin use. Previous hybrid closed-loop studies have demonstrated small but significant hypoglycemia reduction with faster aspart in comparison to standard insulin aspart[11-13], and with ultra-rapid lispro versus standard lispro[14]. Time spent in hypoglycemia in the present study was low for both ultra-rapid lispro and standard lispro, and within the ranges recommended by international consensus guidance on time in range[21] during closed-loop study periods.

The CamAPS FX hybrid closed-loop system performed well with an increase in time in target glucose range from 63.2% at baseline to 78.7% for ultra-rapid lispro and 76.2% for standard insulin lispro, consistent with previous CamAPS FX studies[13]. Time spent in hypoglycemia and total daily insulin were comparable between baseline and closed-loop periods. High use of closed-loop and CGM during the study (median >96%) demonstrates the usability of the CamAPS FX hybrid closed-loop system, an important factor in realizing the benefits of advanced diabetes technology[22].

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Ultra-rapid lispro was acceptable despite ten participants reporting stinging at infusion site, all of whom completed the study. Infusion site discomfort is a recognized side-effect of ultra-rapid lispro, seen in similar studies[14], likely due to the treprostinil and citrate additives. No participant had previous experience of ultra-rapid lispro (Table 1) and participants and investigators remained blind to the insulin throughout the study.

The strengths of our study include the double-blind, randomized, crossover design with each participant acting as their own control, with data collected over a longer duration than similar studies evaluating ultra-rapid lispro. Participants used the study insulin pump and glucose sensor during the run-in period (in open-loop) and intervention periods, so that any differences between the closed-loop periods could be attributed to the insulin rather than the component hardware. Limitations include a small study population with good baseline glycemic control (mean HbA1c 7.1%). This limits generalizability and may have contributed to the significant but small improvement in time in range. The study participants were solely of white ethnicity, also limiting generalizability. The group randomized to receive ultra-rapid lispro first had higher time in range at baseline, but this was unlikely to have impacted on study outcomes due to the cross-over study design with each participant acting as their own control and lack of period effect for primary outcome.

It would be interesting to analyse the effect of ultra-rapid insulin lispro specifically in the post-prandial period. Future studies evaluating closed-loop and ultra-rapid lispro in populations with suboptimal glucose levels at baseline are warranted as increased time in range would be of significant clinical benefit. Ultra-rapid lispro use in fully automated closed-loop systems warrants investigation as the glucodynamic and pharmacokinetic properties of this faster-acting insulin may result in additional benefit.

CONCLUSION

In conclusion, the CamAPS FX hybrid closed-loop system with ultra-rapid insulin lispro increases time in range and reduces mean glucose, without compromise of hypoglycemic risk. This advanced therapy is safe and effective in adults with type 1 diabetes.

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AUTHOR CONTRIBUTIONS

CKB and RH co-designed the study. MN, RL, CKB, HA and SH were responsible for screening and enrolment of participants, arranged informed consent from the participants, and provided patient care. JW and JMA supported study monitoring and randomization. RH designed and implemented the glucose controller. RL, CKB, MEW and RH undertook data analysis. MN, RL, CKB, and RH contributed to the interpretation of the results. MN wrote the report. All authors critically reviewed the manuscript. MN, RL, CKB 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 and analyses and for the adherence of the trial to the protocol.

CONFLICT OF INTEREST

MN has received travel grant support from Sanofi, Janssen and Eli Lilly and was previously chair of the Young Diabetologists' and Endocrinologists' Forum in the UK, which uses unrestricted sponsorship from industry partners to deliver educational programs for health care professionals. CKB has received consultancy fees from CamDiab and speaker honoraria from Ypsomed. SH reports speaker & advisory board fees from Dexcom, Medtronic, Sanofi & Ypsomed; being director at ASK Diabetes Ltd and receiving consulting / training fees from CamDiab. JW reports receiving speaker honoraria from Ypsomed and Novo Nordisk. JMA reports training fees from CamDiab. MEW reports receiving license fees from Bbraun, patents related to closed-loop, and being a consultant at CamDiab. MLE has been a member of advisory panels and/or received speaker fees from NovoNordisk, Eli Lilly, Abbott Diabetes Care, Medtronic, Ypsomed, Pila Pharma and Zucara. The University of Cambridge has received salary support for MLE through the National Health Service in the East of England through the Clinical Academic Reserve. RH reports having received speaker honoraria from

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Eli Lilly, Dexcom and Novo Nordisk, receiving license fees from Bbraun; patents related to closed-loop, and being director at CamDiab. HA is a consultant at CamDiab. RL declares no duality of interest associated with the present manuscript.

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Table 1. Characteristics of study participants at baseline.

	Overall (n=28)	Ultra-rapid insulin lispro first (n=13)	Standard insulin lispro first (n=14)
Age (years)	44 ± 11	42 ± 12	46 ± 9
Gender – Male *n (%)*	18 (64)	8 (62)	9 (64)
Race/ethnicity *n (%)*			
White	28 (100)	13 (100)	14 (100)
Other	0 (0)	0 (0)	0 (0)
Insulin used at baseline *n (%)*			
Novorapid	23 (82)	11 (85)	11 (79)
Humalog	3 (11)	2 (15)	1 (7)
Fiasp	2 (7)	0 (0)	2 (14)
CGM used at baseline *n (%)*			
Freestyle Libre 2	17 (61)	9 (69)	8 (57)
Dexcom G6	6 (21)	2 (15)	3 (21)
None	5 (18)	2 (15)	3 (21)
BMI (kg/m^2)	29.6 ± 3.9	27.7 ± 4.5	28.6 ± 3.3
Duration of diabetes (years)	29.6 ± 12.1	30.3 ± 12	28.4 ± 13.0
HbA1c (%)	7.1 ± 0.9	7.3 ± 1.0	6.9 ± 0.8
HbA1c (mmol/mol)	54 ± 10	56 ± 11	52 ± 9

Percentage of time with sensor glucose level			
3.9 to 10.0 mmol/L [70-180mg/dL]	63.2 ± 16.8	58.8 ± 18.8	68.3 ± 13.9
> 10.0 mmol/L [>180mg/dL]	33.7 ± 18.0	38.9 ± 19.9	27.6 ± 14.7
>16.7 mmol/L [>300mg/dL]	1.6 (0.4, 6.4)	4.2 (0.5, 7.7)	1.3 (0.2, 2.8)
<3.9 mmol/L [<70mg/dL]	2.7 (1.3, 5.0)	1.5 (0.8, 3.4)	3.8 (1.6, 7.2)
<3.0 mmol/L [54mg/dL]	0.5 (0.2, 0.9)	0.4 (0.1, 0.6)	0.6 (0.1, 1.0)
Mean glucose (mmol/L)	9.1 ± 1.9	9.7 ± 2.1	8.5 ± 1.4
Mean glucose (mg/dL)	164 ± 34	175 ± 38	153± 25
Glucose SD (mmol/L)	3.3 ± 0.9	3.4 ± 0.7	3.1 ± 0.9
Glucose SD (mg/dL)	59 ± 16	61 ± 13	56 ± 16
Glucose Coefficient of Variation (%)	36.2 ± 5.5	35.5 ± 3.3	36.3 ± 6.8
Total daily insulin (units/day)	39.7 (30.9, 51.7)	39.9 (32.8, 56.9)	39.4 (30.6, 49.0)
Total daily basal insulin (units/day)	21.0 (15.3, 24.0)	21.4 (17.1, 23.6)	19.5 (14.4, 26.7)
Total daily bolus insulin (units/day)	21.0 (13.4, 26.2)	21.5 (17.6, 34.8)	19.9 (12.8, 26.1)

Data are presented as mean±SD or median (Q1, Q3) unless otherwise indicated.

Glucose data are based on sensor glucose measurements during the run-in period.

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Table 2. Glucose control and insulin delivery over 8 weeks of closed-loop with faster-acting insulin lispro and closed-loop with standard insulin lispro.

	Ultra-rapid insulin lispro (n=26)	Standard insulin lispro (n=27)	P value[b]	95% CI for treatment difference[b]
Percent of time with sensor glucose level				
3.9 to 10.0 mmol/L[a] [70-180mg/dL]	78.7 ± 9.8	76.2 ± 9.6	**0.005**	2.52 (0.82, 4.23)
<3.9 mmol/L [<70mg/dL]	2.3 (1.3, 2.7)	2.1 (1.4, 3.3)	0.327	-0.11 (-0.34, 0.12)
<3.0 mmol/L [<54mg/dL]	0.30 (0.15, 0.46)	0.30 (0.16, 0.46)	0.650	-0.01 (-0.06, 0.04)
>10.0 mmol/L [>180mg/dL]	19.2 ± 9.9	21.5 ± 10.1	0.011	-2.38 (-4.18, -0.59)
>16.7 mmol/L [>300mg/dL]	0.8 (0.2, 2.0)	1.1 (0.3, 3.5)	0.083	-0.43 (-0.93, 0.06)
Mean glucose (mmol/L)	7.9 ± 0.8	8.1 ± 0.9	0.048	-0.17 (-0.33, -0.00)
Mean glucose (mg/dL)	142±14	146±16		-3.1 (-5.9, -0.0)

Glucose SD (mmol/L)	2.8 ± 0.7	2.9 ± 0.6	0.098	-0.10 (-0.22, 0.02)
Glucose SD (mg/dL)	50 ±13	52 ± 11		-1.8 (-4.0, 0.4)
Glucose CV (%)	34.7 ± 5.0	35.5 ± 4.6	0.279	-0.56 (-1.61, 0.48)
Total daily insulin (units/day)	41.7 (32.6, 54.7)	42.8 (31.3, 53.4)	0.502	-0.57 (-2.28, 1.15)
Total daily basal Insulin (units/day)	26.4 (20.2, 38.5)	28.6 (16.9, 34.6)	0.814	-0.19 (-1.85, 1.47)
Total daily bolus Insulin (units/day)	15.0 (11.3, 19.3)	15.3 (10.3, 20.7)	0.822	0.11 (-0.86, 1.08)
% time using closed-loop	96.8 (95.4, 97.6)	96.5 (94.7, 98.0)	0.714	0.11 (-0.49, 0.70)
% time using CGM	98.5 (98.1, 98.9)	98.6 (98.2, 98.9)	0.451	-0.09 (-0.35, 0.16)

Data are mean±SD for normally distributed values, or median (IQR) for non-normally distributed values. Transformation (winsorisation) was applied to highly skewed secondary endpoints prior to statistical analysis. CV, coefficient of variation.

[a]Primary endpoint.

[b]Based on linear mixed model adjusting for repeated participant measures, period as fixed effect. Baseline values from the run-in period were included in the model

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Table 3. Daytime and night-time glucose control and insulin delivery during hybrid closed-loop with ultra-rapid insulin lispro (Lyumjev) and standard insulin lispro.
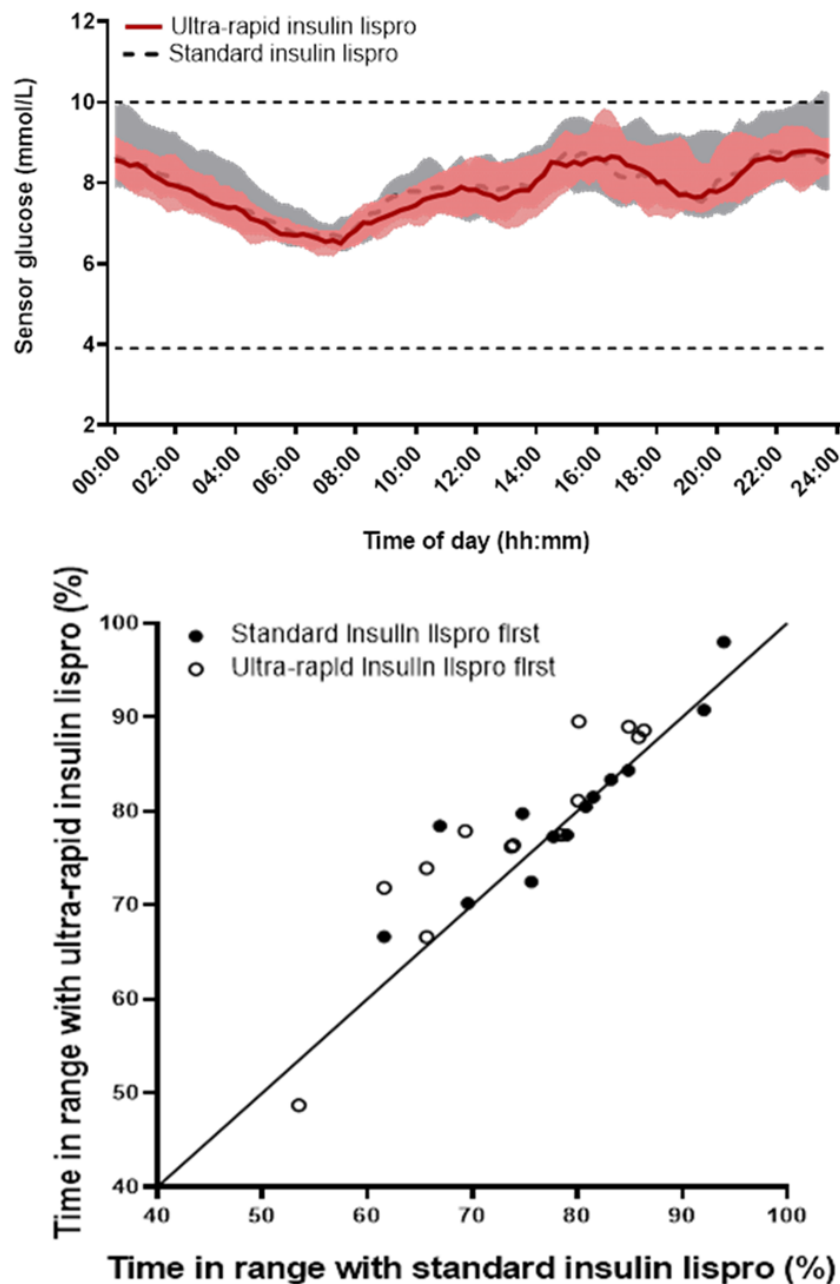
| | Daytime 0600 to 2359 | | Night-time 0000 to 0559 | |
	Ultra-rapid insulin lispro (n=26)	Standard insulin lispro (n=27)	Ultra-rapid insulin lispro (n=26)	Standard insulin lispro (n=27)
Percent of time with sensor glucose level				
3.9 to 10.0 mmol/L [70 to 180 mg/dL]	77.1 ± 10.3	75.0 ± 9.9	83.4 ± 9.5	79.8 ± 10.3
<3.9 mmol/L [<70mg/dL]	2.3 (1.5, 3.2)	2.6 (1.3, 3.6)	1.4 (0.5, 2.4)	1.7 (1.2, 2.0)
<3.0 mmol/L [<54mg/dL]	0.30 (0.14, 0.41)	0.27 (0.12, 0.59)	0.18 (0.03, 0.46)	0.23 (0.10, 0.38)
>10.0 mmol/L [>180mg/dL]	20.6 ± 10.5	22.5 ±10.4	15.2 ± 9.2	18.5 ± 10.4
>16.7 mmol/L [>300 mg/dL]	0.8 (0.3, 2.1)	1.0 (0.3, 3.2)	0.6 (0.1, 1.7)	0.9 (0.0, 3.9)
Mean glucose (mmol/L)	8.0 ± 0.9	8.1 ± 0.9	7.7 ± 0.8	7.9 ± 0.9
Mean glucose (mg/dL)	144±16	146±16	139±14	142±16

Glucose SD (mmol/L)	2.8 ± 0.6	2.9 ± 0.6	2.5 ± 0.8	2.8 ± 0.8
Glucose SD (mg/dL)	50±11	52±11	45±14	50±14
Glucose CV (%)	35.2 ± 4.7	35.5 ± 4.2	32.1 ± 7.2	34.5 ± 7.3
Total daily insulin (units/day)	37.4 (29.4, 52.8)	38.9 (30.7, 53.1)	6.6 (5.0, 8.4)	6.7 (4.7, 9.7)
Total daily basal insulin (units/day)	20.0 (15.4, 28.8)	22.0 (12.6, 26.0)	6.5 (4.7, 8.1)	6.6 (4.5, 8.5)
Total daily bolus insulin (units/day)	14.9 (11.3, 19.2)	14.7 (10.2, 20.6)	0.2 (0.0, 0.4)	0.2 (0.0, 0.5)

Data are mean±SD for normally distributed values, or median (IQR) for non-normally distributed values. Glucose data are based on sensor glucose measurements.

CV, coefficient of variation.

Figure Legend

Figure 1. Top panel Sensor glucose levels (median, IQR) during closed-loop with ultra-rapid insulin lispro (n = 26; solid red line and red shaded area) and during closed-loop with standard insulin lispro (n = 27; dashed black line and grey shaded area). Dashed horizontal lines indicate the target glucose range between 3.9 and 10.0 mmol/L. **Bottom panel** Percentage of time spent in target glucose range using ultra-rapid insulin lispro compared with standard insulin lispro (n=26).