McAuley et al. Online Supplementary Material

Six-months of hybrid closed-loop versus manual insulin delivery with finger-prick blood glucose monitoring in adults with type 1 diabetes: a randomized, controlled trial

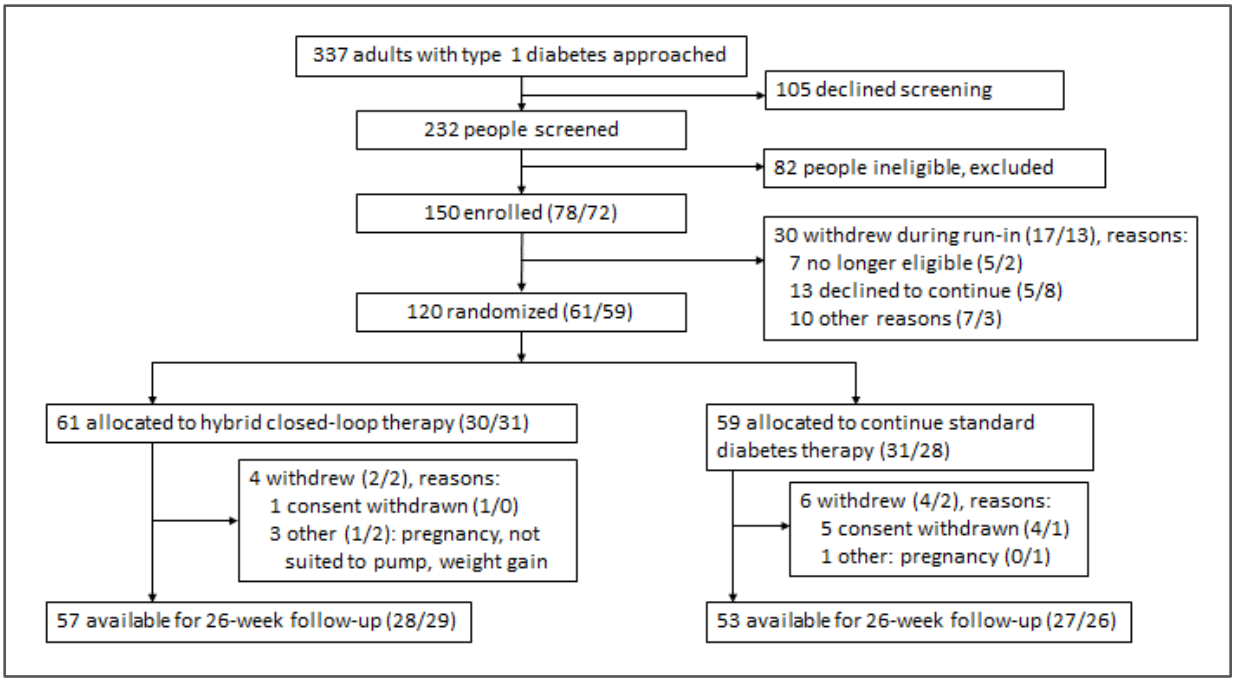

Figure S1: Trial profile. Overall numbers (baseline insulin delivery via multiple daily injections / pump).

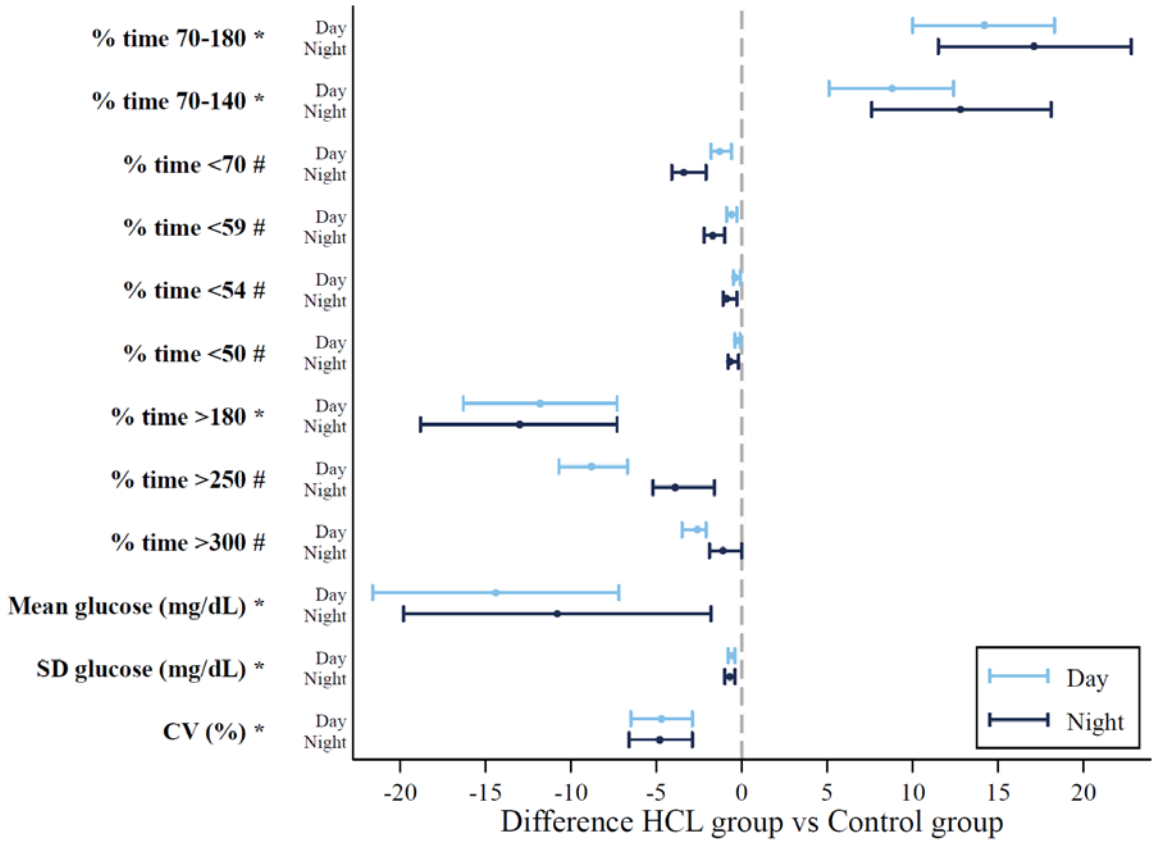

Figure S2: Sub-group analysis by Day (6am–midnight) vs Night (midnight–6am). Forest plot of differences in sensor glucose metrics at study-end between participants assigned to hybrid closed-loop (HCL) intervention versus control, presented by time of day (Day, light blue; Night, navy). Glucose levels are expressed in mg/dL. * Lines represent mean difference with adjustment for baseline values (95% CI). # Lines represent median difference (95% CI).

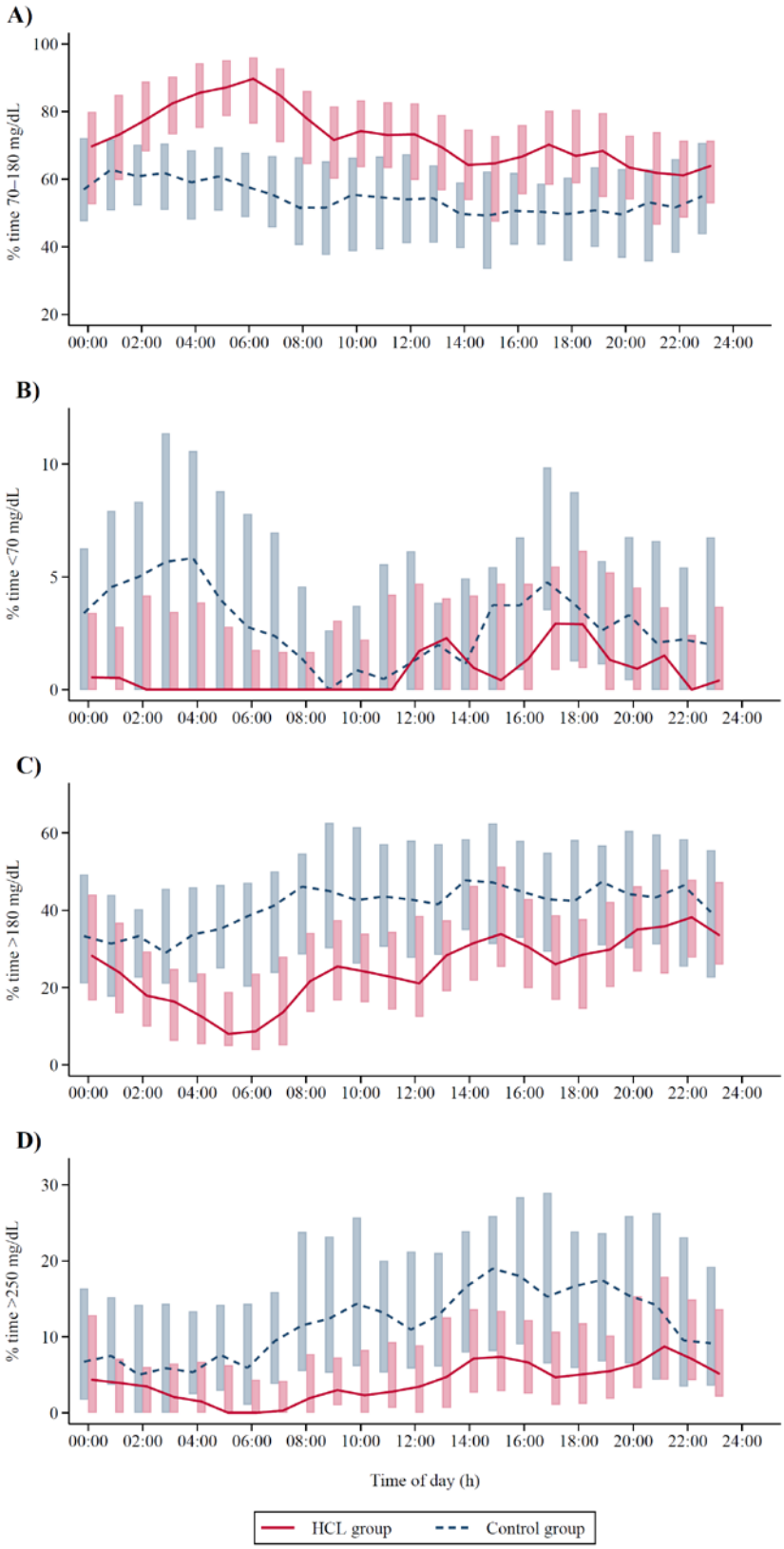

Figure S3: Proportion of continuous glucose monitoring time: in range 70–180 mg/dL (Panel A), below 70 mg/dL (Panel B), above 180 md/dL (Panel C), and above 250 mg/dL (Panel D). The time is shown in hourly blocks, by allocated group (hybrid closed-loop [HCL] group, red; control group, blue). Lines represent the medians, and the bottom and top of each box represent the 25th and 75th percentiles.

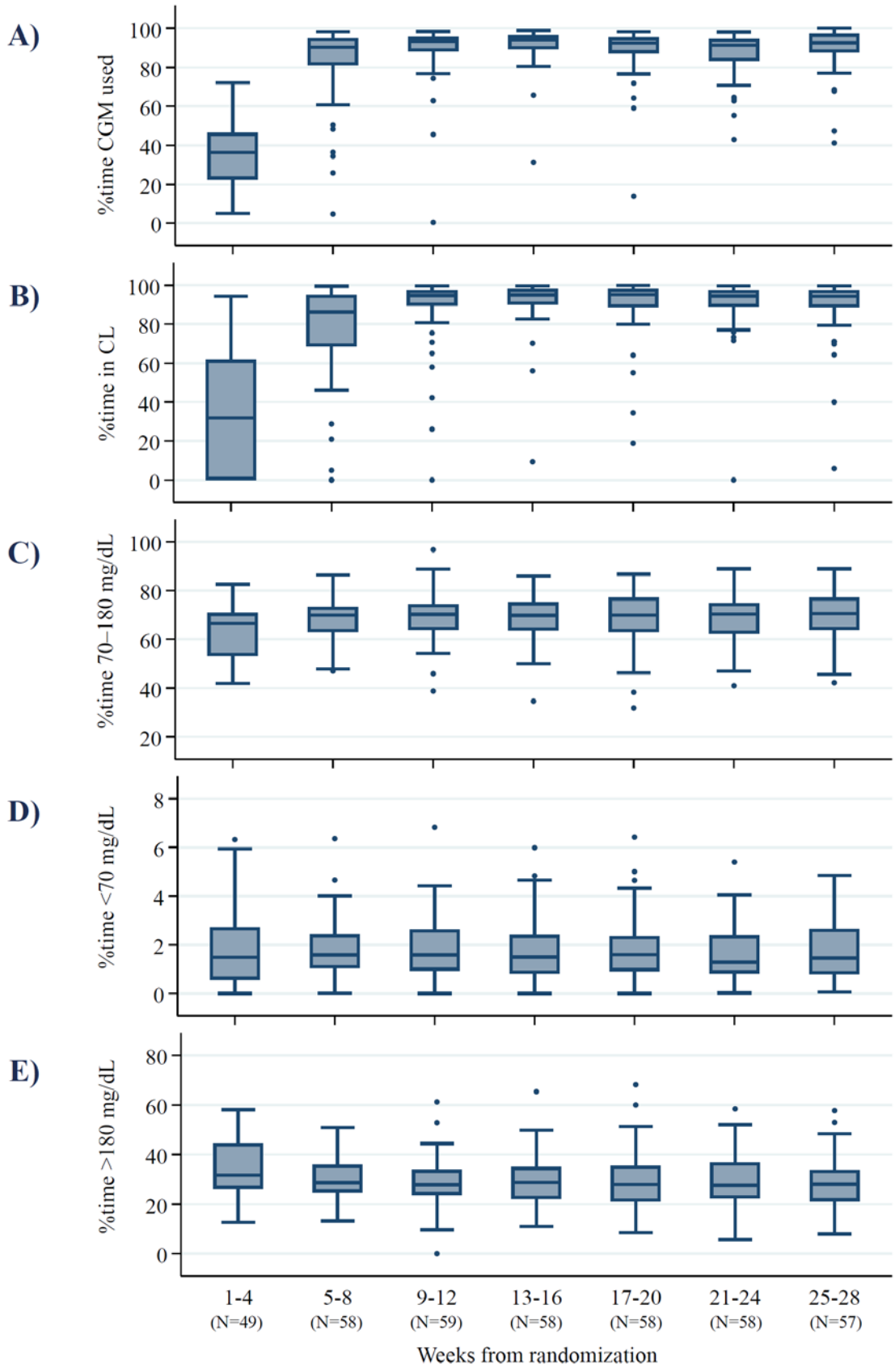

Figure S4: Intervention group – device wear and continuous glucose monitoring (CGM) metrics. Boxplots represent 4-week time blocks, starting from randomization. Glucose levels are expressed in mg/dL. CL, closed-loop.

Table S1: Eligibility criteria

Inclusion criteria

An individual is eligible for inclusion in the study if ALL the following criteria are met:

1. Type 1 diabetes (diagnosis consistent with American Diabetes Association Classification of Diabetes Mellitus) for at least 1 year, with fasting C-peptide <0.1 nmol/L (in the absence of hypoglycaemia)
2. Insulin regimen either:
    - Multiple daily injections (MDI) with ≥4 injections per day (including ≥3 rapid-acting insulin injections and ≥1 long-acting insulin injection); or
    - Insulin pump therapy (CSII) established for ≥3 months
3. Age 25–70 years inclusive at time of screening
4. HbA_{1c} ≤10.5%
5. Living in an area with internet and cellular phone coverage
6. English speaking

Exclusion criteria

An individual will be excluded from the study if ANY of the following criteria are met:

1. Chronic kidney disease (eGFR <45mL/min/1.73m^2)
2. Current use of real-time CGM (defined as real-time CGM use >25% of the time for the past 3 months)
3. Use of any non-insulin glucose-lowering agent within the past 3 months
4. Oral or injected steroid use within the past 3 months
5. Pregnancy, or planned pregnancy within study period
6. Uncontrolled coeliac disease (not following a gluten free diet), or other untreated malabsorption
7. Uncontrolled thyroid disease
8. Clinically-significant gastroparesis
9. Uncontrolled hypertension (diastolic BP >100 mmHg and/or systolic BP >160 mmHg)
10. History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischaemic attack, stroke, or thromboembolic disease in the past 3 months
11. Poor visual acuity precluding use of the investigational technology
12. Inability or unwillingness to meet protocol requirements (such as carbohydrate-counting, frequency of blood glucose monitoring, CGM wear as per allocated study group only)
13. Severe or unstable medical or psychological condition which, in the opinion of the investigator, would compromise the ability to meet protocol requirements

Table S2: Missing data for study outcomes

	Overall missing	**HCL group (MDI/Pump) *n*=61 (30/31)**	**Control group (MDI/Pump) *n*=59 (31/28)**
CGM mid-study	11	4 (1/3)	7 (5/2)
CGM study-end	20	6 (3/3)	14 (9/5)
HbA_{1c} mid-study	8	3 (0/3)	5 (4/1)
HbA_{1c} study-end	9	2 (1/1)	7 (5/2)
ICR mid-study	11	3 (0/3)	8 (5/3)
ICR study-end	16	3 (2/1)	13 (8/5)
Weight mid-study	14	4 (0/4)	10 (5/5)
Weight study-end	12	3 (2/1)	9 (4/5)
Total daily insulin mid-study	11	3 (0/3)	8 (5/3)
Proportions daily insulin mid-study	11	3 (0/3)	8 (5/3)
Total daily insulin study-end	14	3 (2/1)	11 (6/5)
Proportions daily insulin study-end	14	3 (2/1)	11 (6/5)
1,5-anhydroglucitol study-end	10	2 (1/1)	8 (5/3)
Psychosocial study-end	13	3 (1/2)	10 (6/4)

MDI, multiple daily injections. CGM, continuous glucose monitoring. HCL, hybrid closed loop. ICR, insulin-to-carbohydrate ratio.

Table S3: Glucose outcomes 24 hours/day at mid-study

	HCL group (*n*=61)	Control group (*n*=59)	Difference HCL minus control	p value
%time glucose 70–180 *	67.8 (10.9)	54.9 (14.4)	12.4 (8.5, 16.3)	<0.001
%time glucose 70–140 *	44.3 (8.2)	33.7 (12.1)	9.1 (5.8, 12.4)	<0.001
%time glucose <70 †	1.7 (1.0, 2.9)	4.0 (2.8, 6.0)	-2.2 (-2.8, -1.3)	<0.001
%time glucose <59 †	0.5 (0.3, 1.2)	1.9 (0.6, 2.8)	-1.2 (-1.6, -0.6)	<0.001
%time glucose <54 †	0.3 (0.1, 0.6)	1.0 (0.3, 1.9)	-0.7 (-1.0, -0.3)	<0.001
%time glucose <50 †	0.2 (0.0, 0.5)	0.8 (0.2, 1.4)	-0.5 (-0.7, -0.2)	<0.001
%time glucose >180 *	30.0 (11.2)	39.9 (16.4)	-9.0 (-13.1, -4.9)	<0.001
%time glucose >200 †	6.1 (4.5, 9.6)	15.3 (7.1, 18.9)	-7.1 (-9.8, -3.8)	<0.001
%time glucose >250 †	1.9 (0.6, 3.8)	4.9 (0.9, 7.1)	-2.0 (-3.5, -0.6)	0.001
Mean glucose *	157 (14)	171 (23)	-11 (-16, -4)	0.003
SD *	54(11)	67 (13)	-9.0 (-13, -5)	<0.001
CV *	34.7 (4.5)	39.3 (5.3)	-3.2 (-5.0, -1.4)	0.001
HbA_{1c} (%) *	7.0 (0.5)	7.5 (0.8)	-0.4 (-0.6, -0.2)	<0.001
HbA_{1c} (mmol/mol) *	53 (6)	58 (9)	−4 (−7, −2)	<0.001

Glucose levels are expressed in mg/dL. HCL, hybrid closed loop.

* Results presented as mean (SD), mean difference (95% CI), analysis using ANCOVA with adjustment for baseline value

† Results presented as median (IQR), median difference (95% CI), analysis using rank sum test.

Table S4: Intervention group continuous glucose monitoring metrics, before and after the initial HCL activation

	Before closed-loop activation *	After closed-loop activation					
		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6 †
Number of participants ‡	60	60	59	58	58	56	49
% time glucose 70–180	62 (49, 69)	71 (64, 74)	69 (65, 74)	70 (63, 76)	69 (63, 77)	71 (63, 76)	73 (65, 78)
% time glucose 70–140	34 (26, 43)	42 (39, 49)	43 (39, 47)	43 (39, 50)	43 (37, 52)	45 (37, 49)	46 (40, 52)
% time glucose <70	1.5 (0.7, 2.9)	1.3 (0.9, 2.4)	1.6 (1.1, 2.5)	1.4 (0.8, 2.4)	1.5 (0.9, 2.5)	1.4 (0.8, 2.6)	1.4 (0.8, 3.0)
% time glucose <59	0.3 (0.0, 0.8)	0.4 (0.2, 0.7)	0.5 (0.2, 1.0)	0.4 (0.2, 0.8)	0.4 (0.2, 0.8)	0.4 (0.2, 0.8)	0.4 (0.2, 1.0)
% time glucose <54	0.1 (0.0, 0.5)	0.2 (0.1, 0.4)	0.3 (0.1, 0.6)	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)
% time glucose <50	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)
% time glucose >180	37 (28, 49)	28 (23, 35)	29 (23, 33)	28 (21, 36)	29 (20, 35)	27 (21, 36)	25 (19, 33)
% time glucose >250	9 (5, 15)	6 (4, 9)	6 (4, 9)	6 (4, 10)	6 (3, 10)	6 (3, 9)	6 (3, 8)
Mean glucose	165 (157, 180)	157 (150, 165)	156 (150, 164)	157 (147, 168)	156 (146, 168)	154 (147, 166)	151 (145, 164)
Glucose SD	56 (50, 64)	52 (48, 60)	54 (48, 58)	54 (47, 59)	54 (47, 58)	53 (47, 57)	51 (45, 59)
Glucose CV	34 (31, 38)	34 (32, 36)	34 (32, 36)	34 (32, 36)	34 (31, 37)	34 (31, 35)	33 (31, 36)
% time in closed-loop when using CGM	0.0 (0.0, 0.0)	95 (92, 98)	95 (91, 98)	95 (89, 98)	94 (88, 99)	94 (87, 98)	94 (89, 97)
% time in closed-loop as proportion of total time	0.0 (0.0, 0.0)	88 (82, 92)	87 (80, 92)	88 (78, 92)	85 (74, 91)	85 (74, 91)	84 (78, 89)
CGM use (%)	39 (26, 67) §	94 (90, 97)	93 (87, 95)	93 (88, 95)	91 (84, 95)	94 (84, 97)	91 (86, 93)

Results presented as median (IQR). Glucose level are expressed in mg/dL. CGM, continuous glucose monitoring.

* Median duration of this period: 17.5 days (IQR: 10.5, 28).

† Trial duration was 26 weeks post randomization, irrespective of time to closed-loop activation. Some participants had longer duration due to insufficient masked CGM readings

‡ One participant was excluded from analysis due to withdrawal prior to closed loop activation

§ CGM use between date of randomization and HCL activation.