# Multinational Home Use of Closed-Loop Control Is Safe and Effective

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## OBJECTIVE

**To evaluate the efficacy of a portable, wearable, wireless artificial pancreas system (the Diabetes Assistant [DiAs] running the Unified Safety System) on glucose control at home in overnight-only and 24/7 closed-loop control (CLC) modes in patients with type 1 diabetes.**

## RESEARCH DESIGN AND METHODS

**At six clinical centers in four countries, 30 participants 18–66 years old with type 1 diabetes (43% female, 96% non-Hispanic white, median type 1 diabetes duration 19 years, median A1C 7.3%) completed the study. The protocol included a 2-week baseline sensor-augmented pump (SAP) period followed by 2 weeks of overnight-only CLC and 2 weeks of 24/7 CLC at home. Glucose control during CLC was compared with the baseline SAP.**

## RESULTS

**Glycemic control parameters for overnight-only CLC were improved during the nighttime period compared with baseline for hypoglycemia (time <70 mg/dL, primary end point median 1.1% vs. 3.0%; $P < 0.001$), time in target (70–180 mg/dL: 75% vs. 61%; $P < 0.001$), and glucose variability (coefficient of variation: 30% vs. 36%; $P < 0.001$). Similar improvements for day/night combined were observed with 24/7 CLC compared with baseline: 1.7% vs. 4.1%, $P < 0.001$; 73% vs. 65%, $P < 0.001$; and 34% vs. 38%, $P < 0.001$, respectively.**

## CONCLUSIONS

**CLC running on a smartphone (DiAs) in the home environment was safe and effective. Overnight-only CLC reduced hypoglycemia and increased time in range overnight and increased time in range during the day; 24/7 CLC reduced hypoglycemia and increased time in range both overnight and during the day. Compared with overnight-only CLC, 24/7 CLC provided additional hypoglycemia protection during the day.**


In the past decade, the diabetes community has seen unprecedented advances in artificial pancreas (AP) technology, which moved from short-term inpatient studies to long-term trials at home using wireless, portable, wearable AP systems. A comprehensive review of the early developments in the AP field and of the first inpatient closed-loop control (CLC) studies can be found in a Perspectives in Diabetes article by Cobelli, Renard, and Kovatchev (1), and several recent reviews highlight additional progress in this field (2–6). A notable achievement in AP technology was the introduction of the first portable, wearable AP platform—the Diabetes Assistant (DiAs) (7)—developed by our group at the University of Virginia (UVA) and first tested in outpatient trials in Italy and in France in October 2011 (8). DiAs was built using an Android smart phone as a computational hub and included an AP graphical

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**A full listing of the members of the Control to Range Study Group is included in the APPENDIX.*



**See accompanying articles, pp. 1123, 1127, 1135, 1151, 1161, 1168, 1175, and 1180.**

user interface designed for the patient (9) and a web-based remote monitoring system for use by the study team (10). The defining characteristic of DiAs is its capability to switch between different modes of operation, depending on patient preference and signal availability (7,9).

Using DiAs as the medical platform, we previously tested and validated two modular closed-loop algorithms (the Unified Safety System [USS], developed at UVA, and the Modular Model Predictive Control, developed by the international AP study group) in gradually less structured and less monitored settings, following a pathway to achieve eventual regulatory approval (11). This pathway included several feasibility and safety trials in hotel settings (8,12,13), summer camp studies testing DiAs in children with diabetes (14,15), and the recently completed overnight (16) and 42-h dinner-overnight (17) trials of CLC at home. Here, we describe the first longer-term use of DiAs–USS Virginia at home using a completely wireless and portable, wearable AP system. The goal of this study was to provide safety and efficacy data for the DiAs–USS Virginia AP system in the home environment with the aim of supporting preliminary data for the next step in the development pathway—a large-scale clinical trial to establish CLC as a viable treatment modality for type 1 diabetes.

## RESEARCH DESIGN AND METHODS

The protocol, conducted at six clinical centers in the U.S., Italy, France, and Israel, was approved by each institutional or independent review board, and written informed consent was obtained from each participant. An independent Data and Safety Monitoring Board provided oversight. The study is listed on www.clinicaltrials.gov (clinical trial reg. no. NCT02137512). Details of the protocol are available online (http://www.clinicaltrials.gov/ct2/show/NCT02137512); key aspects are summarized herein.

Major eligibility criteria included age 18–69 years, type 1 diabetes duration of at least 1 year, use of an insulin pump for at least 6 months, A1C $<$10.0%, continuous access to internet, cell phone service, and a computer at home. Additional eligibility criteria included commitment from a companion living with the participant to take part in all training activities, to be knowledgeable of the participant's location at all times, and to be available to provide assistance when the system was used at night. Exclusions included diabetic ketoacidosis or severe hypoglycemia with seizure or loss of consciousness in the prior 12 months and hypoglycemia unawareness defined as a score of $\geq$3 on a 0–7 scale by a Clarke Hypoglycemia Unawareness Questionnaire. Other exclusions included the presence of one of a variety of medical conditions, laboratory abnormalities, or medications that were considered to affect study participation.

### Closed-Loop System

The CLC system included the following components: *1*) DiAs, a smart-phone medical platform; *2*) Dexcom G4 Platinum connected to DiAs via continuous glucose monitor (CGM) receiver and USB-Bluetooth relay hardware (SmartLoop LLC; New York, NY); *3*) Roche Accu-Chek insulin pump connected to DiAs via wireless Bluetooth; *4*) remote monitoring server connected to DiAs via 3G or local Wi-Fi network; and *5*) modular CLC algorithm running on DiAs, which is of control-to-range class.

In this trial, DiAs operated in the following modes.

#### *Sensor-Only Mode*

This is the default mode any time the DiAs is connected with a CGM but has no connection with the insulin pump. In this mode, the pump operates in its standard open-loop (OL) manner while DiAs provides hypo- and hyperglycemia alerts implemented as traffic-light signals (green/yellow/red light) (9) and data transfer to a server for remote monitoring and diagnostics (10).

#### *Pump Mode or OL Control Mode*

In this mode, the DiAs control algorithms are not active, and the system delivers the normal basal rates as programmed in the DiAs insulin profile settings. Pump mode also tracks insulin on board and allows the user to issue meal and correction boluses. If DiAs loses communication with the pump, DiAs will revert to either sensor-only mode (if a CGM is connected) or stopped mode (if no CGM is connected) and the insulin pump will revert to the patient's preprogrammed basal rates within 30 min.

#### *CLC Mode*

The algorithms deployed in the USS Virginia use a modular architecture (18,19) composed of the safety supervision (20), hyperglycemia mitigation, and basal rate modules. Insulin corrections are administered by the hyperglycemia mitigation module if glucose levels are predicted to exceed the upper limit of a preset glucose range, e.g., 180 mg/dL, and the module is designed to maintain glucose between 70 and 180 mg/dL during the day. The basal rate module is designed to slide its glucose target from 160 mg/dL during the daytime down to 120 mg/dL by wake-up time in the morning (15,16). The system uses as a base the patient's underlying insulin pump parameters. Meals are announced using the DiAs meal screen (9), and upon meal announcement the system recommends premeal boluses.

#### *Safety Mode*

This is a variant of CLC mode in which only the safety supervision module (20) is active so that the system can reduce insulin to prevent hypoglycemia but cannot exceed OL basal insulin delivery. Per protocol, this mode was to be used whenever the participant was driving, exercising, or performing any potentially dangerous activity.

Participants were asked to remain in CLC whenever feasible and permitted by protocol but were able to switch to pump or sensor mode as needed. Participants were instructed to perform fingerstick blood glucose checks after hypo- or hyperglycemia red light alerts and to treat with carbohydrate or corrective insulin as specified in a participant user guide. Manual correction boluses in the absence of any traffic light alerts were permitted, but participants were encouraged to rely on automated insulin dosing whenever feasible. Home use of the system included all the activities of normal daily living, including eating, going to work, sleeping, exercising, etc.

### Study Protocol

Depending on the participant's current experience with CGM use (17 of the 30 enrolled were active CGM users at enrollment), the participant initially spent 0–3 weeks using CGM at home followed by a 2-week period at home using both the study pump and CGM. This 2-week period of sensor-augmented pump (SAP) therapy at home was considered the baseline period to be compared with the 2 weeks of overnight-only CLC system use and 2 weeks of a 24 h per day and 7 days per week (24/7) CLC system

use at home. After this baseline SAP period, participants and study companions completed a 12-h training session with the DiAs system in OL control (OLC) mode in either a clinical or transitional nonclinical setting. The participant proceeded to use the DiAs in OLC mode for a 1-week period at home. Upon completion, the participant and companion returned to the clinic or transitional nonclinical setting such as a hotel for a 48-h training session of use of the DiAs in CLC and safety modes. The participants then completed 3–5 days of trial use of DiAs in overnight-only CLC followed by 2 weeks of overnight-only CLC use at home, a 3- to 5-day trial period of DiAs in 24/7 CLC mode, and 2 weeks of 24/7 CLC use at home. During the periods of at-home CLC use, remote safety monitoring was available to clinical staff who followed specific guidelines for intervening and contacting a participant or companion should there be a technical issue or safety concern. As an additional safety precaution, participants also were contacted daily by study staff during the 3- to 5-day trial periods of CLC use at home.

Adverse event reporting included any untoward medical occurrence or unexpected occurrence in a study participant including severe hypoglycemia (which was defined as an event that required assistance of another person to administer oral carbohydrate, glucagon, or other resuscitative actions), hyperglycemia resulting in ketoacidosis, and any study or device-related event.

### Statistical Methods

The primary outcome was CGM sensor glucose percent time <70 mg/dL, which was computed separately for each of the three 2-week study phases. The two primary comparisons were the change from baseline in the percent time <70 mg/dL during overnight-only CLC and during 24/7 CLC. A sample size of $N = 30$ participants was estimated to provide ~85% power to detect a 33% reduction in the percent time <70 mg/dL during the 24/7 CLC compared with baseline SAP, assuming a two-tailed paired *t* test and a type I error of 5%.

Safety and basic system performance analyses included all participants. Efficacy glycemic analyses excluded one participant for whom baseline data were unavailable due to a broken CGM receiver, leaving $N = 29$ included in analysis. Similarly, insulin analyses excluded one participant for whom baseline pump data were lost, leaving $N = 29$ included in analysis. Downloaded CGM readings during times when DiAs was inactive or not receiving data during the overnight CLC (7% of the total data) and 24/7 CLC (4% of the total data) were excluded from the analysis (results were similar when using all CGM receiver data from the two CLC phases). Paired *t* tests for normally distributed metrics or the signed-rank test for skewed distributions were used to compare baseline versus overnight-only CLC and baseline SAP versus 24/7 CLC overall and separately by daytime (0700–2300 h) and nighttime (2300–0700 h). Paired *t* tests to compare overnight-only CLC versus 24/7 CLC were added as post hoc analyses.

No adjustment was made for multiple comparisons. All *P* values are two tailed, and analyses were performed using SAS 9.4 software.

## RESULTS

Characteristics of the 30 participants were as follows: median age 44 years (ranged 18–66), 57% male, 96% Caucasian, median BMI 25 kg/m$^2$ (interquartile range [IQR] 23, 27), median type 1 diabetes duration 19 years (IQR 13, 28), median total daily units of insulin per kg 0.57 (IQR 0.42, 0.72), and median A1C 7.3% (IQR 7.1, 7.7) (Supplementary Table 1). All participants completed the full 2 weeks of both the overnight-only and 24/7 phases.

Nighttime (2300–0700 h) sensor glucose metrics were significantly improved during overnight-only CLC compared with baseline. Median time <70 mg/dL dropped from 3.0% during baseline to 1.1% during overnight-only CLC ($P < 0.001$) (Table 1 and Fig. 1); median time in target, 70–180 mg/dL, increased from 61 to 75% ($P < 0.001$); median time >180 mg/dL dropped from 37 to 24% ($P < 0.001$); mean glucose dropped from 163 to 150 mg/dL ($P = 0.002$) (Fig. 2); and median coefficient of variation dropped from 36 to 30% ($P < 0.001$). Sensor glucose metrics (day and night pooled) also were improved during the 24/7 CLC phase compared with baseline SAP. Median time <70 mg/dL dropped from 4.1% during baseline SAP to 1.7% during 24/7 CLC ($P < 0.001$) (Table 1 and Figs. 1 and 3), median time in target 70–180 mg/dL increased from 65 to 73% ($P < 0.001$), median time >180 mg/dL dropped from 32 to 25% ($P = 0.001$), and median coefficient of variation dropped from 38 to 34% ($P < 0.001$). Mean glucose was not significantly different (157 vs. 153 mg/dL; $P = 0.14$). Daytime hypoglycemia, time in range, hyperglycemia, and coefficient of variation also were improved during 24/7 CLC ($P \leq 0.02$) (Table 1). Results for other glucose metrics are shown in Supplementary Table 2.

Similarly, nighttime sensor glucose metrics were significantly improved during the 24/7 CLC phase compared with baseline SAP. Nighttime median time <70 mg/dL dropped from 3.0% during baseline to 0.4% during 24/7 CLC ($P < 0.001$) (Table 1 and Fig. 1); median time in target, 70–180 mg/dL, increased from 61 to 72% ($P < 0.001$); median time >180 mg/dL dropped from 37 to 27% ($P < 0.001$); mean glucose dropped from 163 to 154 mg/dL ($P = 0.03$) (Fig. 2); and median coefficient of variation dropped from 36 to 32%; ($P < 0.001$).

Trends toward improved time in range 70–180 mg/dL were observed even for participants who already had good control (≥65% in range) at baseline (Fig. 3, Supplementary Table 3, and Supplementary Fig. 1). Among the 14 participants with baseline time in range ≥65%, the median improvement for overall daytime and nighttime was 5% during overnight-only CLC and 2% during 24/7 CLC. Corresponding median improvements for the 15 participants with baseline time in range <65% were 12% and 13%, respectively.

In a post hoc analysis, daytime median time <70 mg/dL, which was 3.2% during overnight-only CLC, was further reduced to 2.3% during 24/7 CLC ($P < 0.001$) (Table 1 and Figs. 1 and 2). Daytime mean glucose; median time in target, 70–180 mg/dL; and median time >180 mg/dL were not significantly different ($P = 0.07$, 0.49, and 0.61 respectively) comparing 24/7 CLC and overnight-only CLC.

For nighttime only, the median total delivered insulin was 1.26 units/h (IQR 1.04, 1.61) during baseline SAP, 1.28 units/h (IQR 0.95, 1.59) during overnight-only CLC, and 1.23 units/h (IQR 0.94, 1.75) during 24/7 CLC. For overall daytime and nighttime, the median total delivered insulin was 1.78 units/h (IQR 1.56, 2.07), 1.74 units/h (IQR 1.53, 2.22), and 1.83 units/h (IQR 1.46, 2.38), respectively (Supplementary Fig. 2).

**Table 1—Efficacy and safety outcomes ($N$ = 29 participants*)**

| | Overall (day and night) | | | Night only (2300–0700 h) | | | Day only (0700–2300 h) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Overnight-only CLC | 24/7 CLC | Baseline | Overnight-only CLC | 24/7 CLC | Baseline | Overnight-only CLC | 24/7 CLC |
| Total sensor hours, median* | 335 | 336 | 336 | 115 | 113 | 112 | 217 | 219 | 218 |
| Time spent <70 mg/dL, %, median (IQR) | 4.1 (2.0, 7.8) | 2.6 (1.6, 3.6) | 1.7 (1.1, 2.7) | 3.0 (1.1, 6.3) | 1.1 (0.2, 1.6) | 0.4 (0.2, 1.7) | 4.6 (2.0, 7.0) | 3.2 (2.1, 4.6) | 2.3 (1.3, 3.0) |
| *P* vs. baseline | NA | 0.002 | <0.001 | NA | <0.001 | <0.001 | NA | 0.10 | <0.001 |
| *P* vs. night CLC† | NA | NA | <0.001 | NA | NA | 0.31 | NA | NA | <0.001 |
| Time in range 70–180 mg/dL, %, median (IQR) | 65 (59, 69) | 73 (65, 78) | 73 (68, 76) | 61 (53, 73) | 75 (69, 80) | 72 (65, 80) | 65 (61, 71) | 70 (65, 77) | 72 (69, 78) |
| *P* vs. baseline | NA | <0.001 | <0.001 | NA | <0.001 | <0.001 | NA | 0.001 | <0.001 |
| *P* vs. night CLC† | NA | NA | 0.91 | NA | NA | 0.20 | NA | NA | 0.49 |
| Sensor glucose, mg/dL, mean ± SD | 157 ± 18 | 149 ± 12 | 153 ± 12 | 163 ± 23 | 150 ± 12 | 154 ± 13 | 154 ± 19 | 148 ± 15 | 152 ± 14 |
| *P* vs. baseline | NA | 0.009 | 0.14 | NA | 0.002 | 0.03 | NA | 0.07 | 0.54 |
| *P* vs. night CLC† | NA | NA | 0.06 | NA | NA | 0.18 | NA | NA | 0.07 |
| Glucose coefficient of variation, %, median (IQR) | 38 (34, 41) | 35 (33, 37) | 34 (31, 37) | 36 (32, 40) | 30 (29, 34) | 32 (27, 36) | 38 (34, 42) | 37 (34, 39) | 35 (31, 37) |
| *P* vs. baseline | NA | 0.005 | <0.001 | NA | <0.001 | <0.001 | NA | 0.13 | <0.001 |
| *P* vs. night CLC† | NA | NA | 0.02 | NA | NA | 0.52 | NA | NA | <0.001 |
| SD, mg/dL, median (IQR) | 61 (53, 69) | 52 (48, 58) | 51 (47, 55) | 61 (50, 69) | 47 (42, 51) | 48 (40, 58) | 58 (53, 65) | 55 (49, 60) | 53 (47, 54) |
| *P* vs. baseline | NA | <0.001 | <0.001 | NA | <0.001 | <0.001 | NA | 0.02 | <0.001 |
| *P* vs. night CLC† | NA | NA | 0.41 | NA | NA | 0.12 | NA | NA | 0.06 |
| Time spent >180 mg/dL, %, median (IQR) | 32 (25, 36) | 24 (20, 31) | 25 (22, 28) | 37 (24, 45) | 24 (19, 28) | 27 (19, 34) | 31 (23, 35) | 23 (19, 32) | 25 (21, 29) |
| *P* vs. baseline | NA | <0.001 | 0.001 | NA | <0.001 | <0.001 | NA | 0.02 | 0.02 |
| *P* vs. night CLC† | NA | NA | 0.26 | NA | NA | 0.11 | NA | NA | 0.61 |

NA, not applicable. *One participant was excluded due to missing baseline CGM data. †Post hoc comparison of overnight-only CLC vs. 24/7 CLC.

There were no cases of severe hypoglycemia, diabetic ketoacidosis, or other serious adverse events during the trial.

The system performed well in terms of connectivity with the CGM sensor and delivery of recommended amounts of insulin (Supplementary Table 4), although participants were instructed on how to reconnect devices to the DiAs, as this was needed on some occasions.

At the conclusion of the study, participants completed a questionnaire regarding their experience with the DiAs–USS Virginia. In general, the experience was reported as positive. Suggestions for improvements or enhancements in the system are summarized in Supplementary Appendix A.

## CONCLUSIONS

In this study, we demonstrated that glucose control was significantly improved during both overnight-only and 24/7 CLC compared with baseline SAP. In the overnight period, this included both an increased time in range and a reduction in hypoglycemia. The control strategy of tightening the glucose target overnight from a starting point of 160 mg/dL down to 120 mg/dL 3 h later ensures that the algorithm is less aggressive when the effect of insulin is anticipated to be greatest overnight and more aggressive once steady state is achieved and the insulin resistance associated with the dawn phenomenon is occurring (16). Hence, even though participants received more insulin between 0100 and 0500 h during CLC relative to baseline SAP, it was dosed in a manner that reduced hyperglycemia but did not significantly contribute to hypoglycemia.

The inclusion of 2 weeks each of overnight-only CLC and 24/7 CLC interventions allowed us to assess whether there was an incremental benefit to using the closed-loop system 24/7 versus during the overnight period alone. Despite the challenges of normal daily living, overnight-only and 24/7 CLC were both superior to SAP in terms of glucose time in range during the day and over 24 h. While many early adopters of a closed-loop system will use the system 24/7, we envision that there will be others who will prefer to use the system only at night. Hence, it is clinically relevant that overnight-only CLC provided benefit in overall glycemia, not only in the overnight period when algorithmic

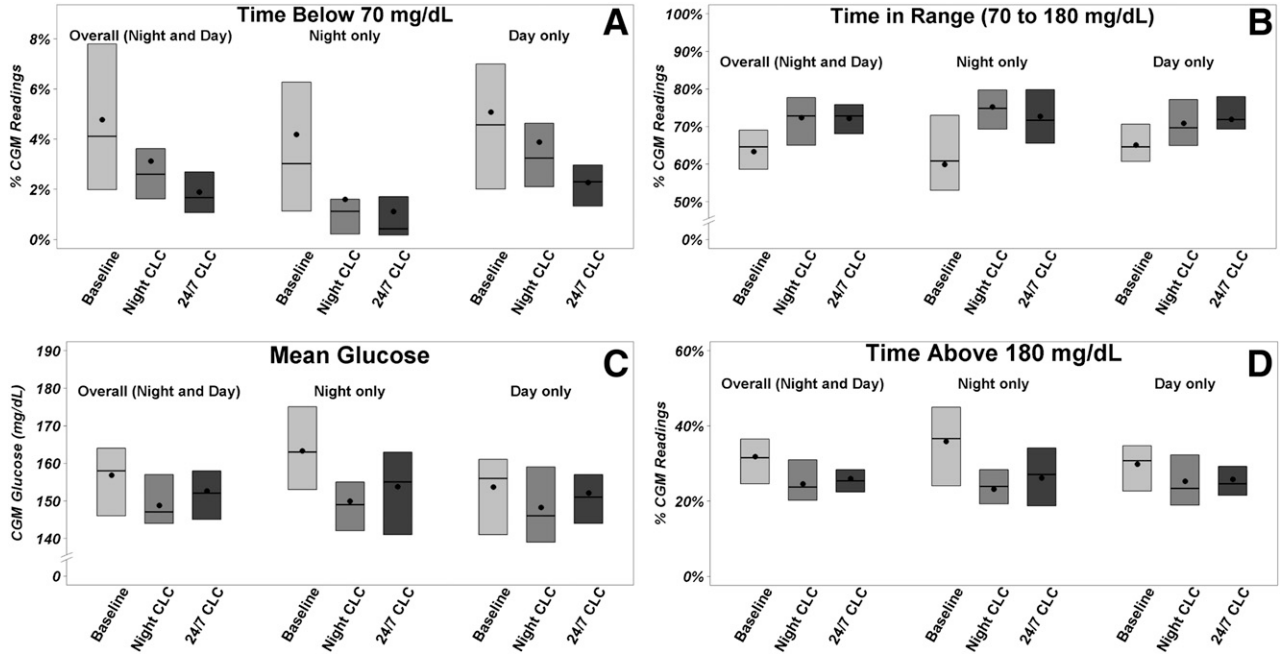


**Figure 1—**Time <70 mg/dL (*A*), between 70 and 180 mg/dL (*B*), and >180 mg/dL (*D*) and mean glucose (*C*) by study phase. Bottom and top of each box denote the 25th and 75th percentile, respectively; the horizontal line inside each box denotes the median, and the dot denotes the mean. *N* = 29 participants; 1 participant was excluded owing to missing baseline CGM data. Night CLC, overnight-only CLC.

insulin modulation and predictive alerts were active, but also the following day when the user was back in OLC mode. The majority of this effect occurred in the morning hours (i.e., 0700–1100 h), likely the result of an improved fasting glucose value prior to breakfast insulin dosing and perhaps also improved control of hepatic glucose output after overnight CLC use. Alternatively, some of the improvement might have come from the user being more engaged with DiAs than with SAP—i.e., monitoring DiAs more closely than traditional SAP sensor and pump. In the current study for the overnight-only CLC arm, DiAs was manually switched to CLC at bedtime and the system automatically reverted to OLC mode at 0700 h for OL therapy during the day. This contrasts with the methodology of Brown et al. (16) and Kropff et al. (21) who used DiAs–USS Virginia for overnight-only CLC and then transitioned to the Accu-Chek Spirit Combo plus Dexcom G4 Platinum (without DiAs) for OLC during the day. These investigators also observed improved daytime and 24-h glucose control with the overnight-only CLC system compared with SAP despite the absence of DiAs for OLC during the day, suggesting that there may be beneficial physiologic effects imparted by overnight CLC that are independent from any additional benefit of the DiAs platform. Indeed, other investigators using overnight-only CLC have reported similar results. Thabit et al. (22) reported a beneficial effect from overnight-only CLC use in children and adolescents that extended over the full 24-h period, and Hovorka et al. (23) found that overnight-only CLC resulted in lower glucose levels for 3.5 h after stopping CLC. The longest home study that demonstrated this carryover effect was performed by Nimri et al. (24) using MD-Logic overnight-only CLC for 6 weeks and showing a 10 mg/dL reduction in the average daytime glucose levels with significantly lower insulin levels compared with SAP.

Similar to our results, other groups using overnight-only CLC compared with SAP at home have demonstrated increased time in range and reduced time in hypoglycemia in the overnight period (16,21–24). In contrast to the adult-only population of the current study, three of these investigations included both adolescents and adults with type 1 diabetes (22–24). Bihormonal 24/7 CLC was evaluated in an inpatient facility as well as a diabetes camp setting for three consecutive nights where participants were randomized to different sequences of single-hormone CLC, bihormonal CLC, and conventional insulin pump therapy (i.e., OLC) (25–27). Bihormonal CLC resulted in comparable time in euglycemia compared with single-hormone CLC and less time spent in hypoglycemia (<4.0 mmol/L or 72 mg/dL) compared with OL and single-hormone CLC (25–27). Leelarathna et al. (28) evaluated 8 days of SAP or CLC insulin delivery in random order in 17 adults with type 1 diabetes. During the home phase, the percentage of time with glucose in the target range was significantly higher during CLC compared with SAP. However, contrary to the current study, time spent below target was comparable between 24/7 CLC and SAP. Possible differences likely come from the algorithm design—in our case, the algorithm is equipped with a dedicated safety system specifically responsible for the prevention of hypoglycemia.

In the current study, hypoglycemia <70 mg/dL was reduced in the overnight period by overnight-only CLC and in both the day and night periods by 24/7 CLC compared with SAP. However, overnight-only CLC did not reduce hypoglycemia <70 mg/dL during the day when the control algorithms were inactive. Hence, 24/7 closed loop offers an

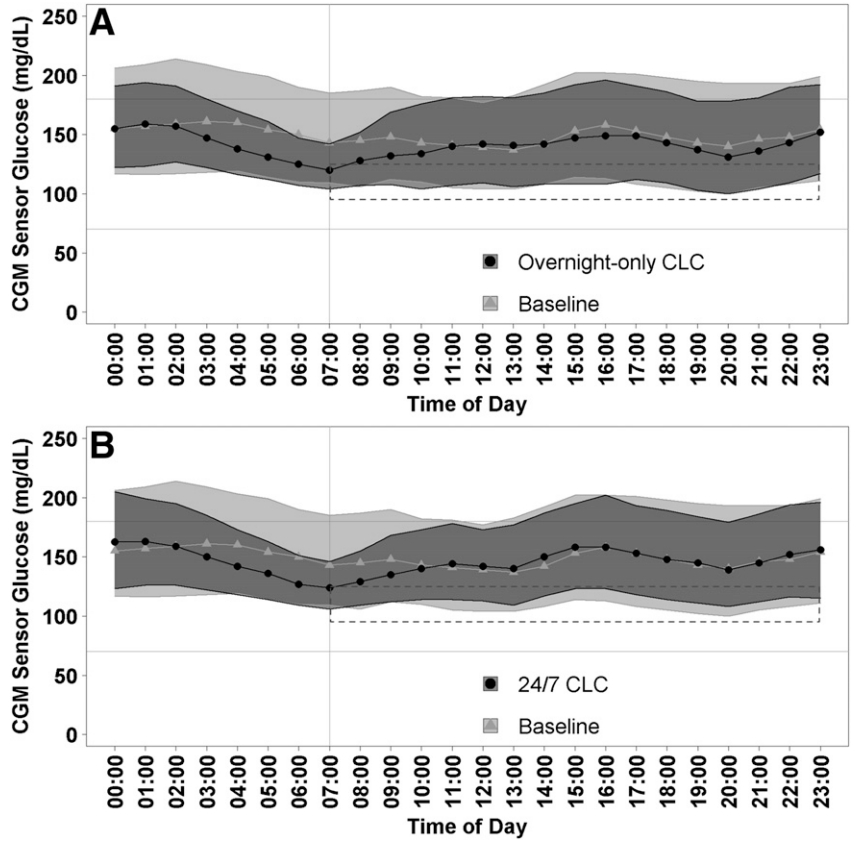


**Figure 2**—Twenty-four-hour CGM sensor glucose comparing baseline with overnight-only CLC (*A*) and 24/7 CLC (*B*). *N* = 29 participants; 1 participant was excluded owing to missing baseline CGM data. Bottom and top curves denote the 25th and 75th percentile, respectively, and the curves with dots or triangles denote the median. As seen in the two dashed-line rectangles, 24/7 CLC (*B*) consistently improved daytime hypoglycemia from baseline compared with overnight-only CLC (*B* compared with *A*).

additional benefit of hypoglycemia protection during times of system use during the day. Hyperglycemia defined as time spent >180 mg/dL was reduced both at night and during the day by both overnight-only and 24/7 CLC compared with SAP. Although a significant reduction in daytime hyperglycemia was seen with CLC, daytime meal challenges continue to be an obstacle for tight daytime glucose control with CLC. This is not unexpected given the mismatch in insulin activity and meal carbohydrate absorption with the current insulin analogs.

The home environment provided typical daily challenges of real-life. Some of the predicted distractions included work and school schedules, children, travel, and a variety of meal and exercise schedules. However, certain aspects of the functionality and performance of the system in the home environment were not predictable at the outset, such as how the system would perform when changing from Wi-Fi to 3G, during daylight saving time, or when system anomalies caused unexpected date and time changes. In the case of the DiAs–USS Virginia, fail-safe modes allowed the insulin pump to independently resume preprogrammed basal rates in the event of any failure of the DiAs or the control modules and an alert was sent to a physician.

One of the major differences between this trial and many previous outpatient investigations of CLC is that the system used was completely portable and wireless, giving participants freedom to carry on their normal activities. Full wireless connectivity will continue to be an important feature of CLC, as the equipment burden without it would be much more cumbersome to the user and may limit applications of use. Fortunately, additional rapid advancements in the CGM field have occurred in the past year and the Dexcom G5 transmitter will be able to directly communicate with a cell phone for future iterations of DiAs-AP systems.

As part of a multinational, multicenter study, we tested our system in a diverse group of patients with type 1 diabetes over a wide range of ages, duration of diabetes, baseline A1C, BMI, total daily insulin, and eating schedules (e.g., European vs. American mealtimes) and demonstrated that the system is safe and effective across borders. Baseline A1C was reasonably good (median 7.3%); hence, extrapolation of these results to populations with suboptimal control is not possible. Since our hybrid AP system is initialized with the participant's baseline pump parameters, only participants who were actively using predefined pump parameters were eligible. By design, participants with A1C ≥10% were excluded, as poor baseline diabetes control may be indicative of either noncompliance with the present insulin pump therapy or problematic pump settings at baseline. Adaptive AP systems and AP systems using an initial optimization of the pump parameters may be less dependent on baseline pump parameters and allow for participation of individuals with initial A1C >10%. For those people with baseline A1C of ~7%, a threefold reduction in hypoglycemia offers a safety layer and reassurance, while automated insulin delivery may alleviate the psychological burden of intensive treatment. In general, patients in good control would be one of the subgroups to benefit most from CLC owing to its power to reduce hypoglycemia without compromising A1C. For those with higher baseline A1C values, the AP system should aim to reduce A1C without increasing the occurrence of hypoglycemia. Both of these populations are being studied in an upcoming large trial.

Since this was the first use of DiAs–USS Virginia outside of a research setting, safety measures included self-monitoring of blood glucose (SMBG) testing seven times daily and the inclusion of only those participants with preserved hypoglycemia awareness. The imposed fingerstick schedule may have resulted in increased postprandial insulin correction dosing above baseline, although this would be anticipated to be similar in both the control and experimental arms, as the fingerstick schedule was similar in each. Future studies should not impose this type of monitoring schedule, as current CGM technology is

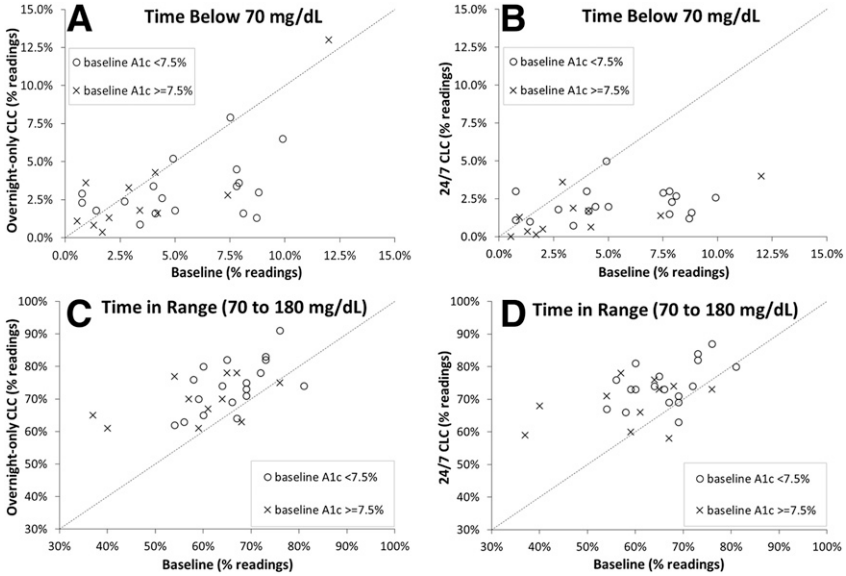


**Figure 3—**Participant-level overall (day and night) time <70 mg/dL and time in range (70–180 mg/dL) by baseline and study phase. *N* = 29 participants; 1 participant was excluded owing to missing baseline CGM data. *A*: Time <70 mg/dL during overnight-only CLC by baseline. *B*: Time <70 mg/dL during 24/7 CLC by baseline. *C*: Time in range during overnight-only CLC by baseline. *D*: Time in range during 24/7 CLC by baseline.

sufficiently accurate to catch impending hypo- and hyperglycemia events, and the Dexcom G5 Mobile has already achieved a replacement claim in Europe. Additionally, patients using AP systems at home are not likely to continue with this degree of SMBG testing in the long run. AP systems should be evaluated for performance using the minimum number of SMBG tests required to maintain CGM calibration, as this will likely be the fewest SMBG tests employed by users of commercial AP systems at home.

A limitation of the current study is the lack of a randomized crossover design of SAP, overnight-only CLC, and 24/7 CLC. However, the primary goal was to provide evidence of the safety and efficacy of such a wireless and portable system in the home environment. The future planned large-scale trial will use a randomized parallel-group design powered for A1C reduction.

In conclusion, use of a completely portable and wireless hybrid AP system in the home environment increases time in range and reduces hypoglycemia when the closed-loop system is active. Longer studies are needed to further establish safety, clinical outcomes over time, usability, and system adaptation. Additional studies in children, those with hypoglycemia unawareness, and those with suboptimal control are presently ongoing.

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**Author Contributions.** The Jaeb Center for Health Research had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The study was designed and conducted by the Control to Range Study Group. The authors (writing group) collectively wrote the manuscript and vouch for the data. S.M.A. was the protocol chair for the study; wrote the abstract, introduction, and discussion; and contributed to the editing of the entire manuscript. J.E.P., F.B., E.R., B.A.B., R.N., S.A.B., D.C., W.C.B.,

P.K.B., D.B., S.D.F., R.C., C.C., A.A., A.F., J.P., T.T.L., and S.S. researched data, contributed to discussion, and reviewed and edited the manuscript. F.J.D. III, P.K.-H., M.D.B., M.P., E.D., I.S.D., and C.K. contributed to discussion and reviewed and edited the manuscript. S.M.A., D.R., J.W.L., R.W.B., and B.K. wrote the manuscript, contributed to discussion, and reviewed and edited the manuscript. P.K.-H. was the chief engineer of the DiAs AP platform. M.D.B. and B.K. designed the CLC algorithm. S.M.A. 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.

## Appendix

The Control to Range Study Group is as follows.

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**Coordinating Center.** Jaeb Center for Health Research: Roy W. Beck (site PI), John Lum (I), Craig Kollman (biostatistician [B]), Dan Raghinaru (B), Judy Sibayan (C), Nelly M. Njeru (C), Barvan Alvarado (O), Denny Figuerres (E), and Carlos Murphy (O).

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