Original Article

Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial – interim analysis

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Background: Artificial pancreas (AP) systems have shown an improvement in glucose control and a reduced risk of nocturnal hypoglycemia under controlled conditions but remain to be evaluated under daily-life conditions.
Objective: To assess the feasibility, safety, and efficacy of the MD-Logic AP in controlling nocturnal glucose levels in the patient's home.
Methods: Two-arm study, each covering four consecutive nights comparing the MD-Logic AP ('closed-loop' arm) with sensor-augmented pump therapy ('control' arm). Fifteen patients (mean age 19 ± 10.4 yr, A1c $7.5 \pm 0.5\%$ or 58 ± 5.9 mmol/mol, diabetes duration 9.9 ± 8.2 yr) were randomly assigned either to 'Group A' (first 'closed-loop', then 'control' arm) or to 'Group B' (vice versa). Investigators were masked to treatment intervention. Primary endpoints were the time spent with glucose levels below 70 mg/dL and the percentage of nights in which the mean overnight glucose levels were within 90–140 mg/dL. Endpoint analyses were based on unmodified sensor glucose readings of the four study nights.
Results: Time of glucose levels spent below 70 mg/dL was significantly shorter on the closed-loop nights than on control nights, median and interquartile range 3.8 (0, 11.6) and 48.7 (0.6, 67.9) min, respectively; p = 0.0034. The percentage of individual nights in which mean overnight glucose level was within 90–140 mg/dL was 67 (33, 88), and 50 (25, 75), under closed-loop and control nights, respectively, with no statistical difference. Secondary endpoint analyses demonstrated significant improvements in hypoglycemia parameters. No serious adverse events were reported.
Conclusion: This interim analysis demonstrates the feasibility, safety, and efficiency of the MD-Logic AP system in home use, and demonstrates an improvement over sensor-augmented pump therapy. (Clinical Trials.gov identifier NCT01726829).

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The ultimate therapeutic target in type 1 diabetes mellitus (T1DM) is to maintain continuous near-normoglycemia, thus preventing the onset and progression of long-term complications (1). Any such remedy must be suitable, safe, and effective in home-care under normal life conditions, thus allowing patients to manage their diabetes with a sense of complete disease control.

The introduction of both continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion pump (CSII) portable devices constitutes marked progress toward this goal: (2) nevertheless, these have proved to have their limitations, with significant risks of hypoglycemia and the need for unfaltering attention by patients and caregivers. The overnight period is of particular concern. Hypoglycemia has been found to occur in 8.5% of nights (3), and furthermore most severe hypoglycemic events in children occur at night, accounting for 75% of all hypoglycemic seizures (4). Failure to respond to nocturnal hypoglycemia can result in coma or even death: 6% of deaths in patients with T1DM under the age of 40 yr have been attributed to 'death-in-bed' syndrome (5). Inevitably, this results in increasing anxiety and sleep disturbance among patients and their caregivers, with the subsequent adoption of hypoglycemia-avoidance strategies not compatible with good glycemic control (6). The implementation of CSII and CGM for the treatment of diabetes has been found to improve overall glycemic control but not during the night (7, 8), mainly because of inadequate response and intervention.

A promising strategy to challenge the risk of nocturnal hypoglycemia could be an automated closed-loop control, or artificial pancreas (9), which connects CGM with CSII via a closed-loop algorithm, mimicking the activity of functioning pancreatic beta cells, with strict control of blood glucose levels. Such an autonomous system could well lessen the burden imposed by management of the diabetic regimen (10).

A number of inpatient studies reported by different research groups (9, 11–16), including our DREAM consortium group (17–19), have indicated the superiority of the artificial pancreas over standard CSII therapy in terms of increased time within target glucose range, reduced incidence of hypoglycemia, and better overnight control. The major remaining challenge is the successful implementation of such a system in a daily-life situation in the home.

Very recently, we reported the effect of a closed-loop system applied in the outpatient setting of a camp for diabetic youngsters (20): this multicenter, randomized crossover trial demonstrated for the first time the safety and efficacy of the fully automated MD-Logic AP system (17), which achieved a lower rate of hypoglycemia and tight control of nocturnal glucose levels under the challenging conditions of the camp (20). Furthermore, the MD-Logic AP system provides a personalized treatment approach, with real time learning ability and safety algorithms for prevention of hypoglycemia and prolonged hyperglycemia (17, 21). In addition, a monitoring system designed for remote diabetes management was validated for its safety and efficacy in the camp setting. Thus, it appeared that the personalized MD-Logic system, together with the remote monitoring module, would be suitable for a home study.

Hereby presented is a one-center interim analysis of an on-going three-center, randomized, crossover, single-blinded trial designed to assess the safety and efficacy of the automated closed-loop MD-Logic AP for controlling overnight blood glucose in T1DM patients under regular conditions in the home setting.

Methods

Trial design

Presented is an interim analysis of a study carried out in one of the centers participating in an ongoing randomized, multinational, crossover, single-blinded trial. This was carried out as a two-arm study, each covering four consecutive nights, comparing the MD-Logic AP system with sensor-augmented pump (SAP) therapy. The study was conducted in compliance with the protocol, the Declaration of Helsinki and applicable regulatory and GCP requirements.

Participants and eligibility criteria

Recruited for the study in November and December 2012 were 15 eligible patients (6 males and 9 females) from the Schneider Children's Medical Center (Table 1). Inclusion criteria were: age above 10 and below 65 yr; a history of T1DM for at least 1 yr since diagnosis; use of an insulin pump for at least 3 months; previous experience using CGM; HbA1c of ≥ 7 and <10; Body Mass Index (BMI) for age below the 97th percentile of age; the presence in the home of at least one adult able to operate a computer-based system; an internet connection in the home; the ability to comply with all trial instructions. Main exclusion criteria were concomitant disease, participation in another study, pregnancy, a history of diabetic ketoacidosis or severe hypoglycemia within the last month, or any medications or other conditions that could influence metabolic control, compromise safety, or prevent subjects from

Table 1. Baseline patient characteristics

	Adults (n = 5)	Adolescents (n = 10)	All (n = 15)
Age (yr)	30.3 ± 11.3	13.3 ± 2.5	19.0 ± 10.4
Body mass index (kg/m^2)	27.1 ± 2.6	20.6 ± 2.7	22.8 ± 4.1
Body mass index	27.1 ± 2.6	0.5 ± 0.9*	—
A1c (%)	7.5 ± 0.5	7.6 ± 0.6	7.5 ± 0.5
A1c (mmol/mol, IFCC)	58.4 ± 5.4	59.1 ± 6.3	58.6 ± 5.9
Diabetes duration (yr)	18.6 ± 11.6	5.2 ± 3.8	9.9 ± 8.2
Pump therapy duration (yr)	10 ± 6.2	3.4 ± 2.7	5.2 ± 4.7
Daily insulin dose (total units)	56.3 ± 27	49 ± 22.2	51.4 ± 23.2
Daily insulin dose (units/kg)	0.7 ± 0.3	0.9 ± 0.3	0.9 ± 0.3

*BMI-SD score.

completing the study. All patients and parents provided a written informed consent prior to trial initiation.

Randomization

Using computer software and blocked randomization procedure, patients were randomly assigned to participate either as 'Group A' – first four consecutive overnights under MD-Logic AP ('closed-loop' arm), then four consecutive overnights under SAP therapy ('control' arm), or 'Group B' (vice versa), with a washout period of 10 ± 3 d between arms (Fig. 1). Randomization results were transferred automatically to patients' computers and were blinded to the assigned physician till the end of the study.

Interventions

The enrolled subject first participated in a training session on sensor use, calibration, technical issues, problem solving, safety, and data recording. Each patient then went through a 2-wk run-in period of sensor wear, and an additional 1-wk evaluation period. Used uniformly throughout were an insulin pump (Paradigm® Veo™, Medtronic, Northridge, CA, USA), a real-time sensor (Enlite® Sensor, Medtronic), and a glucose meter (CONTOUR® LINK meter, Bayer, Leverkusen, Germany). Sensor thresholds for high and low glucose alarms were activated and uniformly set at 350 and 75 mg/dL, respectively (except to low glucose suspension), and projected alarms were set to 20 min. The patients were allowed to modify or shut off these alarms according to their usual routine. Patients' profile data were collected and recorded (supplemental data). Prior to the initiation of closed-loop sessions, patients and their caregivers were given further training on the MD-Logic AP system and available safety measures.

Patients placed a new sensor and new pump tubing prior to the first of the four consecutive overnights of each arm. During study sessions, patients administered insulin boluses 10 min before each meal or snack. Fingerstick measurements were taken 30 min before dinner, at bedtime (23:00 hours), at 02:00 hours, and at wake-up time (07:00 hours), or when prompted by the sensor. No guidelines were given regarding meals, as patients were encouraged to continue their daily routine. Similarly, patients could take additional fingerstick measurements as desired or upon the physician's advice.

Safety measures

The remote monitoring system already tested under camp conditions (20) was exploited for continuous
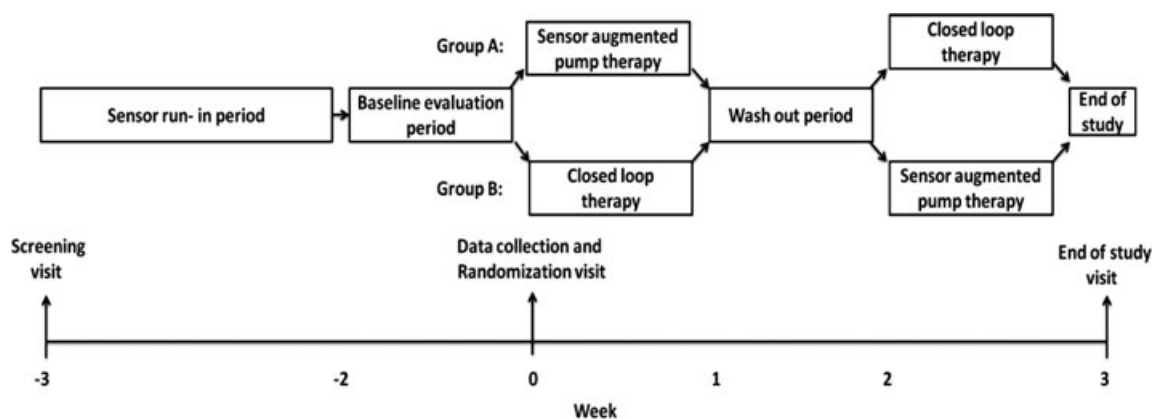

Fig. 1. Trail scheme with a randomization crossover design.

night-supervision of patients during the study. The overnight MD-Logic as well as the control arm nights were remotely monitored. This system enables real-time wireless transfer of glucose data to a control center, permitting the attendant physician to supervise an individual's glucose values but without knowing the related study arm and the insulin delivery data. For both arms, the remote monitoring system generated alarms for the attention of the supervising physician. These alarms were different from those used by the subjects. Participants also learned how to independently respond to an alarm or to calibrate the sensor when instructed by the system. In addition, all patients and caregivers were provided with a telephone hotline and 24-h SOS remote access to an on-call physician and technical support.

Outcomes

Primary endpoints were defined as the reduction in overall time spent in nocturnal hypoglycemia (glucose levels below 70 mg/dL), and the percentage of nights per patient, in which the mean overnight sensor glucose levels were within 90–140 mg/dL. A night period was the time between 23:00 hours until 7:00 hours the next morning.

Secondary endpoints included the number and frequency of hypoglycemic events, overnight glycemic control and glucose variability measures (22) (a detailed list is provided as supporting information). All endpoints were based on the glucose sensor measurements accumulated during the night sessions.

Setting and data collection

Individual baseline data (of the sensor, insulin pump and glucose meter) were downloaded using CARELINK™ software (Medtronic). These were used to automatically derive personalized settings for the pump and the MD-Logic system (e.g. new correction factor, carbohydrate ratio, and basal insulin plan), and were implemented after approval by the study physician.

During the trial, subjects and caregivers manually recorded (in a diary or in the internal pump memory) all physical activity, meals (carbohydrate count), and other events (e.g. technical errors and hypoglycemic episodes). At the end of the trial, recorded data were also downloaded using CARELINK™ software.

Statistical methods

The power of the nonparametric tests for the time below 70 mg/dL primary endpoint was estimated on the basis of the results of power simulations (MATLAB 2011b, Mathworks, Natick, MA, USA), which were performed prior to the trial using sensor data from 118 patients with the eligibility profile under standard treatment at home (see Appendix S1). On the basis of previous inpatient (18, 19) and outpatient studies (20), we calculated that enrollment of 45 participants in total (15 per center) would provide a power of 80% for detecting a 60% reduction in the time below 70 mg/dL at a 0.05 two-sided significant level, while assuming a withdrawal of seven participants. Analyses included all assigned patients who had at least two nights of valid data. MD-Logic nights were considered valid if closed-loop was active for at least 67% of the time. SAP nights were considered valid if the sensor was active for at least 67% of the time, similar to other studies (3).

All endpoints were analyzed per arm while for each endpoint, each patient provided just one value as average of up to four nights.

Comparisons between closed-loop and control nights were performed using the paired nonparametric Wilcoxon Sign Rank Test or the paired McNemar Test for categorical nonparametric comparison (exact method) when applicable. Multiple regression analysis was applied to compare personalized sensor values over time between study arms. An interim analysis was not initially planned. The method of Pocock (23) was used, with a p-value of 0.022 required to declare significance at the 5% level, corresponding to a maximum of two interim analyses (one after each center reported results).

Results

The 15 randomized patients all completed the study. Valid for analysis were 45 closed-loop nights and 54 open-loop nights (Fig. 2). The operation time of the MD-Logic in the closed-loop sessions was an average of 85%.

The time of glucose levels spent below 70 mg/dL was significantly smaller on the closed-loop nights than on the control nights (p = 0.0034, Table 2). The percentage of nights in which mean overnight glucose level was within 90–140 mg/dL did not differ significantly (Table 2). Pre-specified secondary endpoint analyses of closed-loop vs. control nights demonstrated a significant improvement in all tested parameters of hypoglycemia (Table 3). In addition, the percentage of time spent within 70–180 mg/dL was significantly higher on the closed- loop nights [87, (75.2, 94.1)] than on control nights [65.4, (55.9, 77.2)], (p = 0.005). The two study arms showed no difference in blood glucose fluctuations, as measured by glucose standard deviation and coefficient of variation (Table 3). However, converging glucose levels over time demonstrated a significant narrowing in the interquartile range (multiple regression analysis, p = 0.002) only on the closed-loop nights (Fig. 3, upper
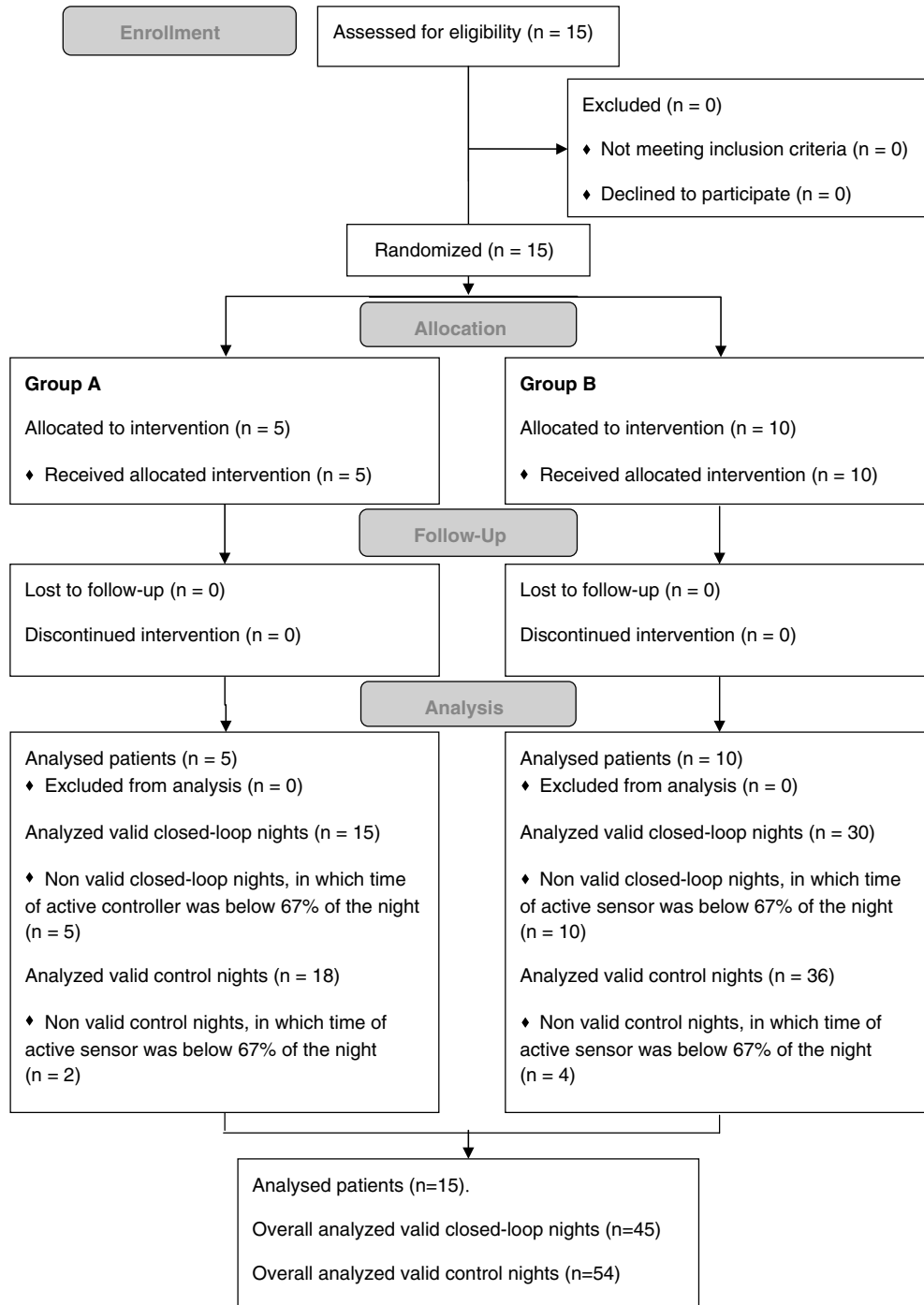
Fig. 2. Study flow diagram.

panels). The total overnight insulin doses per individual were similar during closed-loop (8 ± 3.3 units) to those during control nights (9.2 ± 3.9 units) ($p = 0.19$), although significantly more insulin boluses were delivered on the closed-loop nights (3.6 ± 1.8 vs. 2 ± 1.7 units, respectively; $p = 0.02$) (Fig. 3, lower panels).

During control nights, 11 of the 15 patients decided to activate glucose sensor alarms. Overall, there were 8 and 34 hypoglycemia alarms during the closed-loop and control nights, respectively, with 8 and 12 subsequent carbohydrate interventions, respectively ($p = 0.78$). The assigned physician contacted patients during 2 of the 45 closed-loop nights and 12 of the 54 control nights ($p = 0.21$).

No severe adverse events occurred in any of the study arms. Adverse events during night sessions and daytime hypoglycemia on the day after the night session study are presented in Table 4.

Table 2. Primary endpoints analysis, N = 15

Variable	Closed-loop*	Control*	p Value
Time glucose level spent below 70 mg/dL (min)	3.8 (0, 11.6)†	48.7 (0.6, 67.9)†	0.0034
Percent of nights in which mean glucose levels were within 90–140 (mg/dl)‡	67.0 (30.0, 88.0)	50.0 (25.0, 75.0)	0.5692

*Median values with the interquartile range in brackets.
†Significant differences of p < 0.022 between closed-loop and control night.
‡The percentage out of the four consecutive nights of each patient.

Table 3. Secondary endpoints analysis, N = 15

Variable	Closed-loop*	Control*	p Value
Glucose control			
Time within 70–140 mg/dL (h)	4.4 (3.8, 5.2)	3.1 (2.6, 4.1)	0.0479
Median CGM readings (mg/dL)	133.5 (123.9, 145.8)	130 (113.1, 152.4)	0.8148
Sensor levels at night session start	182 (147.3, 212.6)	178.5 (127.4, 207.8)	0.6
Sensor levels at 23:00 hours (mg/dL)	135.3 (109.4, 168.2)	166 (148.2, 188.2)	0.03
Sensor levels at 07:00 hours (mg/dL)	127 (118, 144)	140 (114, 145)	0.52
Glucose variability			
Standard deviation (mg/dL)	33.4 (28.7, 36.9)	35.8 (26.2, 40.8)	0.4212
% Coefficient variable (CV)	23 (20, 26)	26 (18, 33)	0.1688
Hypoglycemia			
Total events <70 mg/dL	0.0 (0.0, 0.3)	0.5 (0.0, 0.5)	0.0156†
Total events <63 mg/dL	0.0 (0.0, 0.0)	0.2 (0.0, 0.6)	0.0078†
Area below 70 mg/dL (mg/dl)	0.0 (0.0, 0.1)	0.9 (0.0, 1.5)	0.0034†
Area below 63 mg/dL (mg/dl)	0.0 (0.0, 0.0)	0.3 (0.0, 0.8)	0.0019†
LBGI‡	0.4 (0.1, 0.9)	1.9 (0.4, 2.3)	0.0043†
Hyperglycemia			
Time > 140 mg/dL (min)	183.2 (156.2, 236.6)	223.3 (134.3, 306.7)	0.4543
Time > 180 mg/dL (min)	56.6 (20.9, 108.8)	73.7 (52.2, 161.0)	0.1688
Area above 140 mg/dL (mg/dl)	12.9 (8.3, 20.3)	15.4 (9.3, 29.1)	0.4542
Area above 180 mg/dL (mg/dl)	3.4 (0.6, 8.9)	5.7 (2.0, 11.8)	0.3302
HBGI§	2.7 (1.7, 4.1)	3.3 (2.3, 6.0)	0.3591

*Median values with the interquartile range in brackets.
†Significant differences of p < 0.022 between closed-loop and control night.
‡Kovatchev's low blood glucose index (LBGI) to measure glucose variability (22).
§Kovatchev's High Blood Glucose Index (HBGI) to measure glucose variability (22).

Two non-symptomatic hypoglycemia events (i.e. blood glucose below 70 mg/dL with no symptoms of hypoglycemia) occurred in a closed-loop arm, both occurred within half an hour from closed-loop initiation. Seven symptomatic (i.e. blood glucose level below 70 mg/dL with symptoms of hypoglycemia) and four non-symptomatic events occurred during control sessions.

Discussion

The present interim analysis has demonstrated the feasibility, safety, and efficacy of the automated closed-loop MD-Logic system in controlling nocturnal blood glucose in patients with T1DM under normal daily conditions in the patient's home. The significant reduction of nocturnal hypoglycemia with this system was achieved by the frequent automated boluses and prediction of hypoglycemia by analysis of previous glucose and insulin tracings. Thus, although this ongoing multicenter study is still ongoing, these interim findings may be considered an important step forward in the search for better means for the management of T1DM, and the possible implementation of the closed-loop as standard overnight treatment.

Hypoglycemia has decisive effect on diabetes care and the patient's quality of life, especially at night. Nocturnal hypoglycemia is hard to predict (24) and therefore is a true concern for all patients with diabetes and their caregivers. Up to now even the most advanced technology (pumps and sensors) and insulin analogs have led to only partial improvement in the occurrence of nocturnal hypoglycemia (25). This study provides the first demonstration of the effectiveness of the MD-Logic reducing the rate, magnitude and duration of nocturnal hypoglycemia in the home-setting. It should be noted that although the significant reduction in hypoglycemia was not associated with a concomitant increase in glucose levels, no change was found in time spent at hyperglycemia. These findings may be
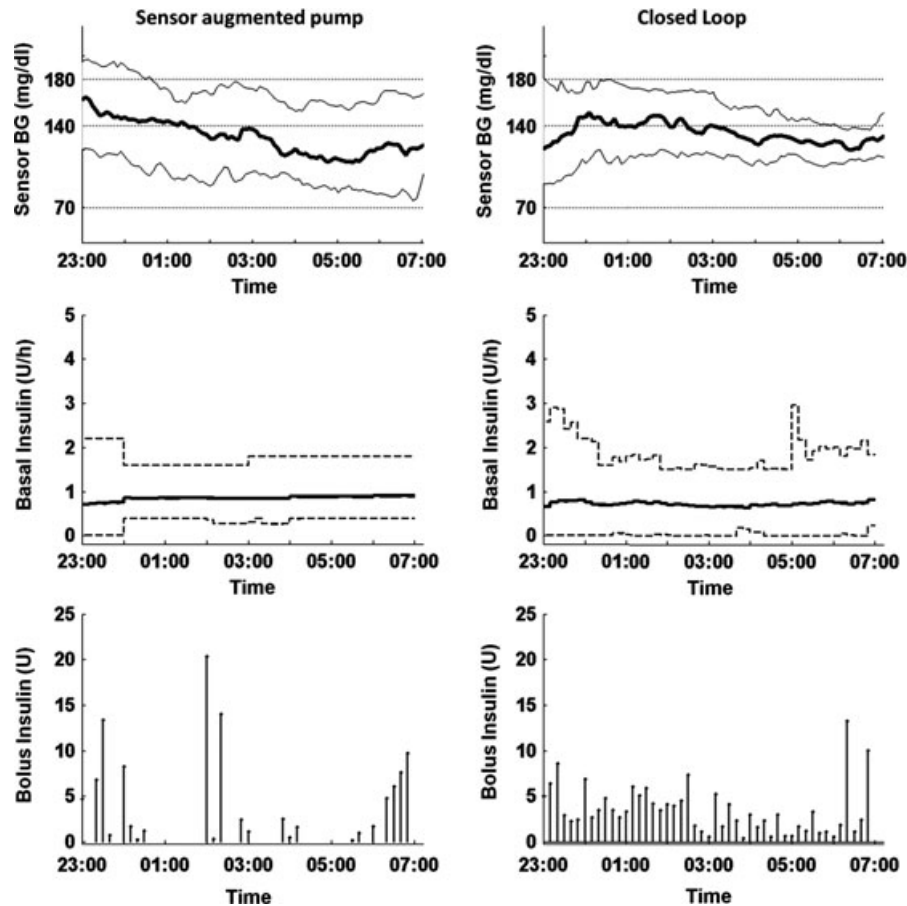
Fig. 3. Glycemic control overview of the studied arms. Presented are overview profiles of sensor blood-glucose (BG) levels (upper panels), basal insulin infusion (middle panels), and insulin boluses infusion (lower panels). Results of closed-loop and control nights are presented in the right and left panels respectively. In the upper panels, the thick black lines indicate median glucose levels and the two thin gray lines define the interquartile range. The dashed lines mark glucose measurements of 70, 140, and 180 mg/dL. In the middle panels, solid black lines indicate mean basal insulin infusion rate with ranges marked by dashed lines. In the bottom panels, vertical black lines indicate the total bolus insulin doses delivered over time.

Table 4. Numbers of adverse events and serious adverse events, N = 15

Variable	Closed-loop*	Control*
Adverse events		
Daytime hypoglycemia (<70 mg/dL)*	8	16
Nighttime Hypoglycemia (<70 mg/dL)	2	11
Ketosis	0	0
Pump canula occlusion	2	0
Other	2†	2‡
Serious adverse events		
Severe hypoglycemia§	0	0
Diabetes ketoacidosis	0	0

*The day that followed the relevant overnight arm.
†Mild asthma, allergic reaction to sensor.
‡Mild viral infection.
§An event that required assistance from another person to administer oral carbohydrate, glucagon, or other resuscitative actions.

related to better basal insulin control of an oncoming hypoglycemia and the provision of more insulin boluses in cases of hyperglycemia.

It should be noted that sensor glucose levels at start of night session and at bedtime (i.e. 23:00) were not statistically different, with a slight trend toward lower glucose levels with MD-Logic treatment as compared to SAP. This may be as a result of the pre bedtime treatment of the closed-loop.

Under MD-Logic control, the time within the glucose range of 70–180 mg/dL improved as compared to SAP therapy. Moreover, during closed-loop nights there were fewer overall alarms and carbohydrate interventions. This was in accordance with our previous study results at the diabetes camp (20) and may reflect a high specificity and sensitivity of the MD-Logic hypoglycemia alarm module, which coordinates accumulated insulin delivery data and expected glucose dynamics. This approach was found to be superior to the conventional glucose sensor alarms using only the glucose data (26). The availability of reliable alarms should encourage adoption of the closed-loop system as false alarms reduce the patient's confidence, cooperation, and response (27).

The study endpoints were based on subcutaneous interstitial glucose sensor measurements. Analysis of glucose control by unmodified sensor data was recently accepted for evaluation of our closed-loop system at diabetes camp (20). Hovorka et al. in their manuscript (28) raised the concern that using unmodified sensor data may overestimate the magnitude of the benefit of closed-loop when evaluating time in target and below target. Taking this into account, we accepted the stochastic transformation as proposed by Hovorka as a method to evaluate our results in addition to the unmodified CGM data (see supplementary appendix for details about the method and Table S1). This analysis confirmed the reported results with respect to the treatment effect of the MD-Logic in significantly reducing the time duration of glucose levels below 70 mg/dL.

The study cohort comprised different age groups, including adults, and both genders, thus meeting the regulatory demands for testing of the system, closed-loop glycemic control in adults tends to be better than that achieved in adolescents, but the difference is less prominent during the nighttime (29) and it was therefore reasonable to include them as one group in the analysis. It must be noted that the current interim evaluation was limited as to sub-group analyses (e.g. per age and gender) because of the small size of the study cohort.

The most notable achievement of this study is its demonstration of the safe transfer of the closed-loop procedure from the protected environment of the hospital and even the diabetes camp to the daily routine of the home-setting as it was tested under uncontrolled real-life conditions (e.g. physical activities, different meals, and various system connection times). The study design was intended as a challenge by closed-loop control to the most advanced therapy currently available. The patients were all familiar with SAP therapy and 73% of the patients used the alarms during the control arm of the study. In addition, the pump settings were optimized for all patients before the overnight sessions. Patients were highly motivated and fairly well controlled due to additional boluses given during control nights. This is probably not the daily routine of most patients with diabetes, especially as only 2–5% of patients have been reported to use the sensor (30). It might therefore be assumed that the use of the closed-loop holds even greater potential for less controlled or motivated patients.

In conclusion, this interim analysis of a four-night crossover study in the home-setting demonstrated that the artificial pancreas system could be safe and efficient for home use. The MD-Logic may safely integrate into the lives of people with diabetes, providing a potent tool to lower the rate of nocturnal hypoglycemia.

Conflict of interest

MP is a member of the Advisory Board of AstraZeneca, Sanofi, Animas, Medtronic, Bayer Health Care and Board Member of C.G.M.3 Ltd., Consultant of Bristol-Myers Squibb, D-medical, Ferring Pharmaceuticals, Andromeda Biotech. The Institute headed by M.P received research support from Medtronic, Novo Nordisk, Abbott Diabetes Care, Eli Lilly, Roche, Dexcom, Sanofi, Insulet Corporation, Animas, Andromeda, Macrogenics. MP has been paid lecture fees by Sanofi, Novo Nordisk, Roche, Pfizer. He is a Stock/Shareholder of C.G.M.3 Ltd and D-Medical. M.P reports two patent applications. EA has been paid lecture fees by Medtronic Diabetes.

TB is a board member of Novo Nordisk, Sanofi, Medtronic and Bayer Health Care; Consultant of Spring. TB's Institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. T. TB received honoraria for participating on the speaker's bureaux of Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi and Roch. TB, NB and MAS. were supported in part by the Slovenian National Research Agency grant # P3-0343.

TD received honoraria for consulting, speaking engagements from Sanofi, NovoNordisk, Eli Lilly, Medtronic, Roche, Abbott, DexCom, GSK, Cellnovo, Bayer Diabetes Care, Johnson&Johnson.

OK received honoraria for scientific lectures from PriMedia, consulting fees and travel reimbursement from Sanofi and Roche Diagnostics.

There are no other potential conflicts of interest relevant to this article.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary Appendix.

Table S1. Stochastic evaluation of sensor data for study endpoints analysis, N = 15.

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993: 329: 977–986.
2. BODE BW. Clinical utility of the continuous glucose monitoring system. Diabetes Technol Ther 2000: 2 (Suppl. 1): S35–S41.
3. JDRF CGM Study Group. Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. Diabetes Care 2010: 33: 1004–1008.
4. DAVIS EA, KEATING B, BYRNE GC, RUSSELL M, JONES TW. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 1997: 20: 22–25.
5. SOVIK O, THORDARSON H. Dead-in-bed syndrome in young diabetic patients. Diabetes Care 1999: 22 (Suppl. 2): B40–B42.
6. BARNARD K, THOMAS S, ROYLE P, NOYES K, WAUGH N. Fear of hypoglycemia in parents of young children with type 1 diabetes: a systematic review. BMC Pediatr 2010: 10: 50.
7. MONAGHAN MC, HILLIARD ME, COGEN FR, STREISAND R. Nighttime caregiving behaviors among parents of young children with Type 1 diabetes: associations with illness characteristics and parent functioning. Fam Syst Health 2009: 27: 28–38.
8. DEISS D, HARTMANN R, HOEFFE J, KORDONOURI O. Assessment of glycemic control by continuous glucose monitoring system in 50 children with type 1 diabetes starting on insulin pump therapy. Pediatr Diabetes 2004: 5: 117–121.
9. COBELLI C, RENARD E, KOVATCHEV B. Artificial pancreas: past, present, future. Diabetes 2011: 60: 2672–2682.
10. ELLERI D, ACERINI CL, ALLEN JM et al. Parental attitudes towards overnight closed-loop glucose control in children with type 1 diabetes. Diabetes Technol Ther 2010: 12: 35–39.
11. STEIL G, REBRIN K, DARWIN C, HARIRI F, SAAD M. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes 2006: 55: 3344–3350.
12. WEINZIMER S, STEIL G, SWAN K, DZIURA J, KURTZ N, TAMBORLANE W. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008: 31: 934–939.
13. HOVORKA R, ALLEN J, ELLERI D et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010: 375: 743–751.
14. EL-KHATIB F, RUSSELL S, NATHAN D, SUTHERLIN R, DAMIANO E. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010: 2: 27ra.
15. KOVATCHEV B, COBELLI C, RENARD E et al. Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of the results. J Diabetes Sci Technol 2010: 4: 1374–1381.
16. DASSAU E, ZISSER H, HARVEY RA et al. Clinical evaluation of a personalized artificial pancreas. Diabetes Care 2012: 36: 801–809.
17. ATLAS E, NIMRI R, MILLER S, GRUNBERG E, PHILLIP M. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. Diabetes Care 2010: 33: 1072–1076.
18. NIMRI R, ATLAS E, AJZENSZTEJN M, MILLER S, ORON T, PHILLIP M. Feasibility study of automated overnight closed-loop glucose control under MD-logic artificial pancreas in patients with type 1 diabetes: the DREAM Project. Diabetes Technol Ther 2012: 14: 728–735.
19. NIMRI R, DANNE T, KORDONOURI O et al. The "Glucositter" overnight automated closed loop system for type 1 diabetes: a randomized crossover trial. Pediatr Diabetes 2013: 14: 159–167.
20. PHILLIP M, BATTELINO T, ATLAS E et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 2013: 368: 824–833.
21. MILLER S, NIMRI R, ATLAS E, GRUNBERG EA, PHILLIP M. Automatic learning algorithm for the MD-logic artificial pancreas system. Diabetes Technol Ther 2011: 13: 983–990.
22. KOVATCHEV B, OTTO E, COX D, GONDER-FREDERICK L, CLARKE W. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care 2006: 29: 2433–2438.
23. POCOCK SJ. Group sequential methods in the design and analysis of clinical trials. Biometrika 1977: 64: 191–199.
24. GALE EA, TATTERSALL RB. Unrecognised nocturnal hypoglycaemia in insulin-treated diabetics. Lancet 1979: 1: 1049–1052.
25. KATZ ML, VOLKENING LK, ANDERSON BJ, LAFFEL LM. Contemporary rates of severe hypoglycemia in youth with type 1 diabetes: variability by insulin regimen. Diabet Med 2012: 29: 926–932.
26. HUGHES CS, PATEK SD, BRETON MD, KOVATCHEV BP. Hypoglycemia prevention via pump attenuation and red-yellow-green "traffic" lights using continuous glucose monitoring and insulin pump data. J Diabetes Sci Technol 2010: 4: 1146–1155.
27. BUCKINGHAM B, BLOCK J, BURDICK J et al. Response to nocturnal alarms using a real-time glucose sensor. Diabetes Technol Ther 2005: 7: 440–447.
28. HOVORKA R, NODALE M, HAIDAR A, WILINSKA ME. Assessing performance of closed-loop insulin delivery systems by continuous glucose monitoring: drawbacks and way forward. Diabetes Technol Ther 2013: 15: 4–12.
29. KUMARESWARAN K, ELLERI D, ALLEN JM et al. Meta-analysis of overnight closed-loop randomized studies in children and adults with type 1 diabetes: the Cambridge cohort. J Diabetes Sci Technol 2011: 5: 1352–1362.
30. LUDWIG-SEIBOLD CU, HOLDER M, RAMI B et al. Continuous glucose monitoring in children, adolescents, and adults with type 1 diabetes mellitus: analysis from the prospective DPV diabetes documentation and quality management system from Germany and Austria. Pediatr Diabetes 2012: 13: 12–14.