A single-blind, randomised, crossover study to reduce hypoglycaemia risk during postprandial exercise with closed-loop insulin delivery in adults with type 1 diabetes: announced (with or without bolus reduction) vs unannounced exercise strategies.

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Closed loop insulin delivery in adults with type 1 diabetes in real life conditions: a multicentre, 12-week randomised crossover trial

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ABBREVIATIONS

AP, artificial pancreas

CGM, continuous glucose monitoring

CI, confidence interval

CL, closed loop

DBLG1, Diabeloop Generation 1 system

IQR, interquartile range

MDI, multiple daily injections

mITT, modified Intention-To-Treat

MPC, model predictive control

OL, open loop

SAP, sensor-assisted pump

LBGI, low blood glucose index

HBGI, high blood glucose index

BGRI, blood glucose risk index

T1D, type 1 diabetes mellitus

ABSTRACT

Background: Closed-loop insulin delivery systems are expected by patients with type 1 diabetes. Our objective was to assess whether the Diabeloop DBLG1 artificial pancreas system could improve glucose control compared to sensor-assisted pump therapy (SAP).

Methods: In this multicentre, open-label, randomised, crossover trial, we recruited adults with type 1 diabetes for ≥ 2 years, pump therapy for ≥ 6 months, HbA1c ≤ 10% (86 mmol/mol) and preserved hypoglycaemia awareness. After a 2-week run-in period, patients were randomised (1:1, web-based random blocks of two) to a hybrid monohormonal system featuring machine-learning-based algorithm and study-related remote monitoring or to SAP, for 12 weeks of free living, followed by a 8-week washout period and then the other intervention for 12 weeks. The primary outcome was the percentage of time spent in the 3·9 – 10·0 mmol/L glucose range for the 12-week study period. Statistical analysis was performed on modified intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT02987556 and is completed.

Findings: 68 patients were randomised, of whom 5 did not complete the trial (4 unavailability, 1 pregnancy). The percentage of time in the 3·9-10·0 mmol/L glucose range was 68·5% [66·1;71·0] (DBLG1) compared with 59·4% [56·9;61·8] (SAP) (p<0·0001). Five severe hypoglycaemia episodes occurred under DBLG1 due to pump dysfunction or human errors versus three under SAP.

Interpretation: The DBLG1 system improves glucose control. This supports the use of closed-loop technology combined with appropriate health care organisation in adults with type 1 diabetes.

FUNDING

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RESEARCH IN THE CONTEXT

Evidence before this study

We searched PubMed for articles published up to November 5, 2018, using the terms (« artificial pancreas » OR « closed-loop ») AND ("type 1 diabetes mellitus" OR "diabetes") AND ("outpatient" OR "home") AND ("randomised" OR "randomised controlled trial"), for reports of randomised controlled trials published in English only. We limited our analysis to home studies with single hormone systems conducted in adult patients with a minimum duration of four weeks. We identified five randomised controlled trials (Nimri et al, 2014, Thabit et al, 2015 ; Kropff et al, 2015 ; Bally et al, 2017 ; Tauschmann et al, 2018) that lasted 4, 6, 8 or 12 weeks. Three of these trials were performed with successive versions of the same algorithmic system. Three studies featured a day-and-night closed loop delivery and two studies proposed evening-and-night or night only automated delivery. All had a crossover design but one with a parallel group design. Three of these studies included patients with baseline HbA1c ranging from 8·1 to 8·5%, one study targeted patients with HbA1c < 7·5%, and one study included patients with mean baseline HbA1c of 7·5%. Closed-loop insulin delivery was associated with an increased proportion of time in 3·9 – 10·0 mmol/L glucose target range (from 8·6 to 12·2 percentage point in the overnight studies and from 10 to 11 percentage point in the day-and-night studies) and a reduction of time spent in hypoglycaemia. Three studies showed a reduction of HbA1c, from 0·25 to 0·36%. Remote monitoring was implemented in two of these studies, but its modality and its impact were not reported.

Added value of this study

To our knowledge, regarding pivotal trials leading to the CE marking and approval of a closed-loop system, our study is the first one that has a randomised, controlled design. This multicentric study is the largest randomised trial of a closed-loop system in an ambulatory setting with a crossover design, and the second largest trial when taking into account studies with parallel group design. So far, no controlled study has exceeded the 12-week, 24-hour per day duration of closed loop use that is described in this trial. It is the longest and largest trial testing tubeless, patch pumps. The DBLG1 system is an original, comprehensive solution integrating a patch-pump, a glucose sensor, a command module hosting a hybrid algorithm with customisation settings, that was combined, in this study, with real-time remote monitoring that is extensively described here. This original closed-loop system, as compared to sensor-assisted pump therapy, was associated with a significant improvement in the percentage of time spent in the glucose target range (3·9 – 10 mmol/L) and a significant reduction in the percentage of time spent in the hypoglycaemic range. Actually, we observed an improvement in every profile of included patients, with a longer time in target glucose range in patients with hyperglycemia concern, and a reduced time in low glucose range in patients with lower glucose values at baseline. This was achieved because we included an adult population of patients with type 1 diabetes featuring a broad range of initial HbA1c, ranging from 5·7 to 9·6% (mean 7·6%), recruited nationwide in France among 12 investigating centres (6 patients per centre), prefigurating what closed-loop therapy could be in real life.

Implications of all the available evidence

Hybrid closed-loop insulin delivery, combined with remote monitoring, improves glycaemic control and reduces hypoglycaemic risk in adult patients with type 1 diabetes, exempt from severe hypoglycaemia unawareness. Results from our study reinforce data reported by other groups and strongly support the use of closed-loop technology in routine practice.

INTRODUCTION

The availability of continuous glucose monitoring (CGM) at the turn of the 21st century has raised new hopes for better outcomes in the management of type 1 diabetes. Whereas CGM-assisted insulin pump therapy and multiple daily injections combined with CGM have become the standard regimen, they do not fulfil the expectations of professionals and patients, in terms of metabolic outcomes and quality of life.[1] For the past decade, remarkable achievements have been made in the field of automated insulin delivery devices, that led in 2017 to the approval of the first hybrid closed-loop system following a pivotal, non-randomised, safety trial.[2,3] Randomised trials were reviewed in two recent meta-analyses suggesting that artificial pancreas could increase time spent in optimal glucose range by 10 percentage point, reduce time in hypoglycaemia by half, and improve HbA1c by 0·3 percentage point.[4,5] However, only five trials lasted beyond four weeks, and these involved a cumulated number of 229 patients only.[6-10] Additional knowledge is needed regarding the metabolic and safety outcomes, the definition of optimal indications and responders, the organisation of health care delivery associated with artificial pancreas. The Diabeloop DBLG1 system features a hybrid, single hormone closed-loop device, that was reinforced by structured remote monitoring for the purpose of the study. The current WP7 study was a pivotal, multicentre, nationwide, randomised trial, which data were intended to file for CE-marking. The primary objective was to assess whether the DBLG1 system provides better glycaemic control than usual sensor-assisted insulin pump therapy over a 12-week period.

METHODS

Study Design and Participants

The study was a national, multicentre, interventional, controlled, randomized, open-label comparative crossover trial. It involved 12 university hospitals in France (see appendix for the full list of centres). Adult patients (age ≥ 18 years) were eligible if they had type 1 diabetes for 2 years or more, HbA1c ≤ 10% (86 mmol/mol), preserved hypoglycaemia awareness (Gold score ≤4),[11] insulin requirements ≤ 50 U per day, and had been using insulin pump therapy for ≥ 6 months. Patients prone to severe hypoglycaemia in the past 12 months were excluded (see appendix for the full list of inclusion and exclusion criteria).

The institutional review board approved the study (French Committee for the Protection of Persons participating in biomedical research « CPP Ile de France VI », CPP/68-16-ID RCB : 2016-A01198-43, October 4th, 2016), and Clinical Trial Authorisation was obtained from the French National Safety Authority (ANSM). All patients provided signed written informed consent.

RANDOMISATION

Participants were randomly assigned (1:1) to receive either treatment with DBLG1 system followed by sensor-assisted pump therapy, or vice versa. Following the run-in period, the order of the two periods was locally stratified and determined with an automated web-based program (ClinInfo, Lyon, France) with randomly permuted blocks of two. Investigators and participants were immediately informed of treatment allocation.

PROCEDURES

The study was conducted as a crossover trial, with two treatment sessions of 12 weeks separated by a wash-out lasting at least 8 weeks. Each session corresponded to a treatment period. According to the order of the draw, patients received either the treatment managed by the Diabeloop algorithm (closed-loop, DBLG1 group) or the treatment consisting of sensor-assisted pump therapy (open-loop, SAP group).

After screening and inclusion, patients entered a 2-week run-in period, intended for them to be trained to use the study insulin pump and the CGM device at home. After this period, compliant patients, that satisfied a competency and safety checklist, and willing to carry on the study were randomised. Patients assigned to the SAP group returned to their usual treatment with their own pump, combined with a Dexcom™ G5 CGM (Dexcom Inc, San Diego USA), which was not blinded. Participants were free to activate or shut off sensor alarms and there were no recommended thresholds for high- and low-glucose alarms.

Patients assigned to the DBLG1 group, in period 1 of the crossover, were equipped with the Cellnovo® insulin patch-pump driven by the Diabeloop application installed in a dedicated Motorola® android smartphone and connected to the Dexcom™ G5 CGM via "Bluetooth Low Energy" radio. These patients were initiated with closed-loop insulin delivery during a 48h stay in hospital research centre, requested by French National Safety Authority (ANSM), intended for them to be taught by a dedicated nurse how to use the various components of the system (sensor, pump, smartphone) and how to behave in case of an alarm. This nurse would later be in charge of remote monitoring and phone interaction with the given patient. Remote

monitoring had to be implemented, as a request by ANSM. Customisation of closed-loop required the system to be tuned through eight settings, which was done during this initial 48h stay. The DBLG1 (Regulation v2017.04.20, Diabeloop SA, Paris, France) system, combining an algorithm based upon machine-learning within a physiological framework with an expert system and self-learning algorithms, is currently an hybrid closed-loop device requiring the patient to declare carbohydrate intake in a semi-quantitative fashion, as well as intensity and duration of planned physical activities. Details on algorithm and customisation, remote monitoring and generation of automatic text messages (SMS) have been published[12] and are exposed in Appendix. Target glucose was set at 6.05 mmol/L (110 mg/dL). After 48h, patients were discharged and returned home, and followed-up remotely in their usual personal and professional activities, with the only limitation to remain under GSM phone coverage in France, for a period of 12 weeks. In both DBLG1 and SAP groups, hospital visits were scheduled at week 1, 3, 6, 9 and 12 in order to download data from the command terminal or Dexcom receiver, to check for adverse events and to deliver satisfaction questionnaires. After this first 12-week period of the crossover, patients started a washout period, initially planned to last at least eight weeks. During the washout period, patients returned to their usual pump treatment and stopped using Dexcom G5 CGM, but were free to use previous CGM or flash glucose monitoring if any. All participants used their usual, fast-acting insulin analog (lispro, aspart or glulisine), ultra-fast acting aspart (FiAsp®) was not allowed. Of note, during the period 1 of the crossover, we observed three severe hypoglycaemic events that were reviewed by the Data Safety and Monitoring Board (appendix). A failure in a safety sensor of the CellNovo® Generation 1 pump of 2017 was diagnosed. In agreement with regulation authority (ANSM), protocol was amended and patients in the period 2

of the crossover were equipped with the Kaleido® insulin patch-pump (Appendix, figure S1). Washout period had to be extended to 30 weeks in order to implement this modification.

OUTCOMES

The primary outcome was the percentage of time spent in the 3·9–10·0 mmol/L (70-180 mg/dL) glucose target range measured continuously for 12 weeks with CGM.[13] The secondary efficacy outcomes were the percentage of time with sensor glucose concentration in the 4·4-7·8 mmol/L (80-140 mg/dL) range, then out of main target range, i.e., below 3·9 mmol/L, 3·3 mmol/L (60 mg/dL) and 2·8 mmol/L (50 mg/dL), and above 10·0 mmol/L (180 mg/dL), 13·9 mmol/L (250 mg/dL) and 16·7 mmol/L (300 mg/dL); the percentage of time spent in the different target ranges and under or above the different glucose thresholds mentioned above during the night period (defined as 0h00-6h00) ; the mean sensor glucose during each 12-week period (calculated by 24-hour intervals, then averaged) ; HbA1c (measured at the beginning and end of each treatment period) and delta of HbA1c ; glucose coefficient of variation (calculated by 24-hour intervals, then averaged), low and high blood glucose index (LBGI and HBGI) and blood glucose risk index (BGRI) on each 12-week period ; the total insulin intake ; the number and the amount of carbohydrate intakes during the last week of each period.

Safety outcomes were the number of severe hypoglycaemic events (requiring third party assistance), the number of severe hyperglycaemic episodes (capillary blood glucose ≥ 20·0 mmol/L (360 mg/dL)) including ketoacidosis, the number of technical incidents causing interruptions of the closed loop. We also measured a benefit outcome by assessing the percentage of time spent in closed-loop in functional mode.

Finally, qualitative outcomes were assessed by measurement of satisfaction (Diabetes Treatment Satisfaction Questionnaire or DTSQ) and through three visual analogical scales testing satisfaction, ease of use and pleasantness of the system.

STATISTICAL ANALYSIS

The statistical analysis plan was defined prior to the database lock. The analysis was performed by a contract research organization (RCTs company, Lyon, France) with the usual procedures of data management and database lock using SAS® 9.4 (SAS Institute, Cary, NC, USA). The analysis was performed on a modified intention-to-treat population, defined as all randomised patients who completed the two periods of the cross-over. We based our study on previous trials with the DBLG1 system[14] and calculated that a sample size of 50 evaluable patients would be sufficient to show, with a statistical power of 94%, a statistically significant difference on the mean time spent in the 3·9 – 10·0 mmol/L glucose target range between the CL period and the OL period, with the following assumptions: Type I error = 0·05 (two-sided) ; closed loop = 77·8% ; open loop = 71·5% ; standard deviation = 12·4% ; correlation = 0·5 (power calculations performed with SAS Power & Sample Size 3.1). Accounting for dropouts, we increased the target recruitment number to 71 patients.

Comparisons of continuous outcomes between the CL period and the OL period were performed using a mixed model for repeated measures. The model included the treatment group (CL/OL) and the period as fixed effects and the patient as a random effect. It was adjusted on the HbA1c level at the beginning of each period and the site number (as a stratification variable).

As distributions of percentage of time spent in the different target ranges were close enough to the parametric assumptions, the mixed model was used for the primary analyses.

Nevertheless, to evaluate the robustness of the results, sensitivity analyses using the same model with log-transformed data were performed, including on the percentage of time spent in hypoglycaemia, hyperglycaemia and in the different target ranges.

No adjustment for multiplicity was performed with regard to the number of secondary endpoints.

ROLE OF FUNDING SOURCE STATEMENT

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Diabeloop employees read the manuscript before submission as a courtesy. No changes were made in the manuscript following the review. No author has been paid to write this article, by any company or agency. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

From March 03 to June 19, 2017, 71 patients were screened; three patients unwilling to engage through the whole protocol withdrew before entering the run-in period; four participants with previous experience in the material used in the trial skipped the run-in period; overall, 68 patients were randomised. All investigating centres (n=12) randomised six patients each, except two centres that randomised five and three patients, respectively. Of the 68 randomised patients, five dropped out during washout period, because of pregnancy (n=1) or consent withdrawal for timetable conflict (n=4). The remaining 63 patients completed the study and their data were assessed in the mITT analysis. Trial was completed on August 28, 2018. Figure 1 shows the patients' flow chart. The median duration of the washout period was 30 weeks (IQR

25.9-31.7) and ranged from 16 to 45 weeks. A sensitivity analysis was performed by adding the treatment-by-period interaction in the primary model of the primary endpoint. The treatment-by-period interaction was not statistically significant (p=0.96) ; there was no carry-over effect. There was no period effect either (p=0.28) (table S1). P-values from sensitivity analyses were similar and confirmed the robustness of the primary model results.

Baseline characteristics of patients are summarised in table 1. Of note, baseline HbA1c was 7·6±0·9% (59·4±9·8 mmol/mol) and its distribution is shown in appendix table S2. All patients were free of macroangiopathy, 20/63 (31·7%) had retinopathy and 6/63 patients (9·5%) had permanent positive microalbuminuria (incipiens nephropathy). Experience in flexible insulin therapy and carbohydrate counting was reported for 58/63 patients (92·1%).

Efficacy

Primary and secondary outcomes are summarised in table 2 and 24-h sensor glucose profiles for the whole 12-week period in each group are shown in figure 2. The percentage of time with glucose within the target range of 3·9-10·0 mmol/L was 9·2% higher (95% CI 6·4 to 11·9, p<0·0001) in the DBLG1 group (68·5%, SE 1·2) than in the SAP group (59·4%, SE 1·3). Mean sensor glucose concentration was reduced by -0·4 mmol/L (-7·2 mg/dL) (-0·6 to -0·1, p=0·012) in the DBLG1 group. Patients in the DBLG1 sequence exhibited a reduction in the percentage of time in hypoglycaemia by more than 50% as compared with the SAP sequence : time below 3·9 mmol/L was 2·0% [1·4;2·5] (DBLG1) vs 4·3% [3·8;4·9] (SAP) (p<0·0001), time below 3·3 mmol/L was 0·8% [0·5 ;1·1] vs 2·0% [1·7 ;2·3] (p<0·0001), and time below 2·8 mmol/L was 0·2% [0·1 ;0·4] vs 0·7% [0·6 ;0·9] (p<0·0001) (table 2). HbA1c, prespecified secondary endpoint, was reduced by 0·29% [-0·43;-0·16] (DBLG1) and

0·14% [-0·27;-0·01] (SAP), difference -0·15% [-0·33;0·03] (p=0·098). It seems that the greatest improvements in time in target range were observed in patients with highest baseline HbA1c levels (appendix, table S5 and figure S2). A post-hoc analysis showed that patients with the highest CGM values during the control period had the best improvements in time in target range during the experimental sequence. On the other hand, patients with fair time in target range but longer time in low glucose range during the SAP sequence had the greatest reduction in time in hypoglycaemia during the DBLG1 period (appendix, figure S3).

Safety

A total of 18 serious adverse events during both 12-week periods were reviewed by the Data Safety Monitoring Board, declared to the French National Safety Agency (ANSM), and summarised in table 3. None of these 18 events were related with inappropriate algorithmic recommendation. These events did not include ketoacidosis, but consisted of nine severe hyperglycaemic events in the DBLG1 group and, regarding severe hypoglycaemia, five events in the DBLG1 group and three in the SAP group. There was no admission to hospital during any of the two sequences. The nine severe hyperglycaemic events occurred in four different patients (five events in one patient) and were all related to a hardware origin (tubing, cannula or pump). Analysis of the five severe hypoglycaemic events in the DBLG1 group showed a mistake in a bolus dose by a patient overriding the system (n=1, period 2), an error in pairing the pump with the handset at initiation of closed-loop between two patients sharing the same room (n=1, period 2), and a dysfunction of the pump (n=3, period 1, see above). Every situation of severe metabolic event occurring outside hospital was detected by remote monitoring and properly addressed by the generation of automatic text messages followed by phone contact between nurse and patient/entourage.

Investigator was then informed by nurse. Data regarding insulin intakes, as well as ingested carbohydrates for prevention or treatment of hypoglycaemia will be analysed in a further report.

Usage

Insulin was delivered in functional closed-loop mode for a median of 83·8% (IQR 72·3 – 89·3) of the closed-loop 12-week period. A prespecified on treatment (« per-protocol ») analysis showed that primary endpoint was similar than in the mITT analysis (DBLG1 69·9% (SE 1·2) vs SAP 59·3% (SE 1·2), difference 10·6% [95% CI 7·9 - 13·3], p<0·0001) (Appendix, table S4).

We investigated the reasons why insulin was temporarily delivered in open-loop mode during the closed-loop sequence. We observed that a technical dysfunction of a single component (pump, sensor or handset) of the DBLG1 system (39·6%), a decision of the user (10·2%), or a combined explanation (50·2%) could be incriminated.

To analyse the potential impact of remote monitoring (post-hoc analysis), we separated the 12-week period into three periods of four weeks each. We also split the modifications in settings of the algorithm directly available in the patient user interface of the DBLG1 system according to their frequency into three categories. We first observed that the number of modifications in the eight settings of the algorithm per patient (mean of 10·6 (SD 0·8) adjustments per patient during the entire 12-week period) gradually decreased from period week 1-4 to period week 9-12 as well as the number of text messages leading to a phone call to the patient (mean of 4·2 (SD 3·5) text messages per patient received by nurses during the entire 12-week period) (Appendix, table S6). However, the proportion of time with glucose in a given range

was not different between the three time periods. There were also no clinically significant differences in metabolic outcomes related to the frequency of modifications in algorithm settings (Appendix, table S7).

The target glucose, set by default at 6.05 mmol/L (110 mg/dL), and adjusted throughout the 12-week period, manually by the user or automatically by the algorithm, was observed at a mean of 6.36 mmol/L (115.7 mg/dL), with a range per patient from 5.6 mmol/L (101.7 mg/dL) to 6.9 mmol/L (125.8 mg/dL).

Finally, teaching patients with the system was very straightforward (four hours training was sufficient, no early side effect), and all investigators and patients agreed that the 48h inpatient initiation stay was unnecessary.

Satisfaction

Differences between experimental group and control group regarding DTSQ outcome or the three visual analogical scales were not clinically relevant (Appendix, table S8).

DISCUSSION

This randomised pivotal trial established that the DBLG1 system can improve the proportion of time spent in the recommended glucose target range over a period of 12 weeks. The extent of this improvement (9·2 percentage point increase) is at least similar to what was reported by the other randomised home trials of same duration[8,10] or by the non-randomised trial of the other approved closed-loop device,[2,3] all using a single hormone approach.

This trial also evidenced a significant reduction of time spent in hypoglycaemia. Although the crossover design may have led to inappropriate estimation of the risk of

hypoglycaemia, [15] this bias was reduced by the long washout period of our trial. Of note, the absence of recommended thresholds for low-glucose alarms in the control group may have unfavourably influence the rate of hypoglycaemic events in this group. Other groups have chosen a dual hormone approach with results suggesting a higher efficacy on the reduction in incidence of hypoglycaemia,[16,17] but long term data are needed. Besides, further improvements may target the proportion of time in functional closed-loop mode, measured at 83.8% in our trial and ranging from 71 to 88% in other home studies. This goal will require to improve the reliability and integration of the technical components of the system, including pump and sensor. Of note, Diabeloop is the integrator of the system comprised of the handset manufactured by Diabeloop, the pump and the CGM. This means that future evolutions of the system could possibly integrate other pumps or even CGMs.

Our metabolic results were obtained with a sophisticated system combining a closed-loop device with remote monitoring that was requested by French regulatory authorities and that call for four different comments.

First, other closed-loop trials have included remote monitoring. [3,6,7,18] In the six-week overnight trial of the MD-Logic system, remote monitoring led to 86 phone calls to the patients, mostly linked with safety issues.[6] The DiAs system developed by the University of Virginia allows remote monitoring that was reported in a trial studying intense outdoor exercise.[18] To the best of our knowledge, this monitoring only had a safety purpose and was not associated with modifications in algorithm settings. In a recently reported closed-loop trial, though automated monitoring was not implemented, contacts (visit, phone, mail) with investigators were 4-fold more frequent in experimental group than in control patients.[10] In the recent pivotal trial of

the Medtronic 670G system, remote monitoring helped to tune some settings of the algorithm, mostly during the first month or especially the first week, which could have impacted whether closed loop was active or not.[19]

Second, from the design of our trial, we cannot rule out that remote monitoring could have been partly involved in the improved outcome. Indeed, telemonitoring of adult patients with T1D was shown to be associated with reduced HbA1c.[20] Our remote monitoring was centralised and devoted to safety, technical support and adaptation of algorithm settings available to the patient in the user interface of the DBLG1 system. No motivational or behavioural support was provided. Most of the modifications of command settings were done during the first four weeks of our trial. Although improvement in metabolic outcomes was observed at the very early stages following initiation of closed-loop, one can speculate that system setting adjustments could have contributed to the outcomes. On the other hand, results did not improve, with time, or in patients with more frequent adjustments.

Third, modifications of command settings, which are part of the design of the system, contributes to its originality and adaptability to various metabolic phenotypes. Whether adjustments are conducted through remote monitoring or during face-to-face visits is a matter of health care organisation. In the near future, tuning some settings of the algorithm may be performed automatically, with the aid of deep-learning long-term algorithms. Thus, a recent uncontrolled trial has shown that automated, cloud-based algorithmic adaptation of basal rate (every week) and carbohydrate ratios (every month) was safe and feasible.[21] Finally, human factors should be taken into account. A recent paediatric study reported that CGM with remote monitoring could reduce fear of hypoglycaemia and improve other psychosocial metrics including quality of life in parents of children with T1D, whereas these qualitative outcomes

were not improved in previous CGM studies without remote monitoring.[22, 23] Besides, remote monitoring raises ethical issues related with confidentiality that should not be neglected. [24]

Our trial was among the largest multicentre studies, involving 12 centres throughout France each recruiting 6 patients, and without experience in closed-loop therapy for the most. In this respect, centralised remote monitoring was a useful adjunct to the necessary technical and educational training of patients. Although the regulation algorithm and the command software were found to be safe and reliable in our trial, we observed severe metabolic events that were either linked to human errors or to hardware issues. We observed that five out of nine pump-related adverse events occurred in a single patient. Cannula and tubing-related issues stand as the Achille's heel of pump therapy and may expose future patients that are naive to pump treatment to some initial metabolic hazards, without appropriate support and education. Of note, it has been suggested that fault detection algorithms could efficiently detect insulin infusion set failures[25] and these will be implemented in the DBLG1 system.

Overall, these reports and our data suggest that a professional and human support is needed by some patients in the early phase of CL initiation, which can be provided by transient remote monitoring, whereas the tuning of the algorithm may become automatic through autolearning technologies in the near future. Additional studies are needed to confirm whether or not remote monitoring is useful to implementation of closed-loop therapy and, if so, to define its optimal modalities (short/long duration, local/centralised, all/selected patients).

The next challenge is to file for medical insurance coverage and to propose practical settings for implementing closed-loop in real life. For this purpose, medico-economic

data will be needed. Implications of our findings are important in this perspective. Improvement in time in range was recently validated using the DCCT data set and shown to be strongly associated with the risk of microvascular complications.[26,27] It was shown that the hazard rate of development of retinopathy and microalbuminuria was increased by 64% and 40%, respectively, for each 10 percentage points lower time in range. Additionally, another frontier is to address satisfaction outcomes. Whereas our study was unable to discriminate groups regarding satisfaction, it may be meaningful to develop specific clinimetric tools. [28]

Improvement in HbA1c though was not statistically significant in our study. The four other home trials that lasted 12 weeks showed a reduction in HbA1c ranging from 0·30 to 0·50%. [3,8,10,21] Our results may be linked with a baseline A1c (7·6%) that was lower than in the two other controlled trials (8·3 to 8·5%), [8,10] although the two other 12-week long trial, that were uncontrolled, started at a baseline A1c of 7·0% (53 mmol/mol).[3,21] Indeed 69·9% of our patients had a baseline HbA1c below 8% (64 mmol/mol). The most recently reported closed-loop trial showed that reduction in HbA1c was higher in patients with higher baseline value.[10] Our data also evidenced a positive correlation between improvement in outcome and baseline HbA1c. Actually, we observed an improvement in every profile of included patients, with a longer time in target glucose range in patients with hyperglycemia concern, and a reduced time in low glucose range in patients with lower glucose values at baseline.

Overall, the main limitations of our study, to be addressed in further trials, are a) the lack of an appropriate control for a proper assessment of the impact of remote monitoring ; b) a thorough evaluation of psychosocial and human factors ; c) a better

picture of the impact on HbA1c, that should be more appropriately adressed with a parallel-group design. Further studies will also address the roles of carbohydrate, protein and fat intakes, and physical activity, with their respective algorithmic management.

In conclusion, we observed that the use of the DBLG1 system, featuring a patch-pump, a glucose sensor, a hybrid closed-loop regulation algorithm and combined with a remote monitoring improved glucose control in real life conditions for 12 weeks in adult patients with T1D over a large spectrum of HbA1c. These clinically relevant findings support the use of closed-loop technology combined with appropriate health care organisation in adults with T1D.

DATA SHARING

The Diabeloop study group agrees to share de-identified individual participant data, as well as study protocol and statistical analysis plan, 3 months following publication, with academic reseachers who provide a methodological sound proposal. Proposals should be directed to the last author of the current paper (kerbonac@free.fr).

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AUTHOR'S CONTRIBUTION

PYB: study design, patients enrolment and follow-up, data interpretation, manuscript writing

SF: study design, patient enrolment and follow-up, data interpretation, manuscript editing

YR: study design, patient enrolment and follow-up, data interpretation, manuscript editing

CT: study design, patient enrolment and follow-up, data interpretation, manuscript editing

PS: study design, patient enrolment and follow-up, data interpretation, manuscript editing

ER: study design, patient enrolment and follow-up, data interpretation, manuscript editing

BG: study design, patient enrolment and follow-up, data interpretation, manuscript editing

LC: study design, patient enrolment and follow-up, data interpretation, manuscript editing

CLC: patient enrolment and follow-up

NJ: study design, patient enrolment and follow-up, data interpretation, manuscript editing

HH: study design, patient enrolment and follow-up, data interpretation, manuscript editing

SB: study design, patient enrolment and follow-up, data interpretation, manuscript editing

MD: algorithm engineering

PJ: algorithm engineering

IX: study design, protocol writing, relation with regulation authorities, data monitoring

VM: patient enrolment and follow-up

LM: patient enrolment and follow-up

BD: study design, patient enrolment

MG: patient enrolment and follow-up

LSL: patient enrolment and follow-up

AF: patient enrolment and follow-up

DR: study design, patient enrolment

SL: patient follow-up, manuscript editing

MJ: patient enrolment and follow-up, manuscript editing

AP: study design, patient enrolment and follow-up, data interpretation, manuscript editing

GC: study design, protocol writing, relation with regulation authorities, patient follow-up, data interpretation, manuscript editing

DECLARATION OF INTERESTS

PYB has received speaker honoraria from Abbott, Roche, Eli Lilly, Novo Nordisk, Sanofi and served on advisory board panels for Abbott, Roche, Medtronic, Dexcom, Insulet, Lifescan, Eli Lilly, Novo Nordisk and Sanofi.

SF declares congress invitations from Sanofi, Eli Lilly, MSD, Novo Nordisk, Roche, Abbott and Boehringer; she has received speaker honoraria from Lilly, Novo Nordisk and served on advisory board panels for Novo Nordisk, Roche, Sanofi, Janssen and Lifescan. She owns shares in Diabeloop SA.

YR discloses congress invitations, honoraria and consultancies from Medtronic, Insulet, Novo Nordisk, Sanofi and Eli Lilly.

CT has received speaker honoraria from Abbott, Eli Lilly, Sanofi and served on advisory board panels for Abbott, Roche, Medtronic.

PS declares congress invitations, honoraria and consultancies from Roche.

ER has received research support from Abbott, Dexcom Inc., Insulet Inc., Roche, Tandem, and has been a consultant for Menarini Diagnostics, Abbott, Air Liquide SI, Becton-Dickinson, Cellnovo, Dexcom Inc., Eli-Lilly, Insulet Inc., Johnson & Johnson (Animas, LifeScan), Medtronic, Novo-Nordisk, Roche, Sanofi-Aventis.

BG reports congress invitations, honoraria and consultancies from Abbott, Medtronic, Eli Lilly, Dexcom and Roche.

LC reports congress invitations, honoraria and consultancies from Abbott, Medtronic, Eli Lilly, Novo Nordisk and Sanofi.

CLC declares congress invitations, honoraria and consultancies from Abbott, Insulet, Eli Lilly, Medtronic, NovoNordisk, Vitalaire.

NJ discloses congress invitations, speaker honoraria and consultancies from Lilly, Sandoz, Roche and advisory board panels for Sanofi.

HH has received congress invitations, honoraria and consultancy fees from Abbott, Animas / Johnson & Johnson, Medtronic, Roche.

SB discloses congress invitations, honoraria and consultancies from Abbott, Animas / Johnson & Johnson, Medtronic, Roche.

MD has no personal disclosures

PJ has no personal disclosures

IX has no personal disclosures

VM received speaker honoraria from Abbott, Novo-Nordisk

LM discloses congress invitations, honoraria and consultancies from Novo Nordisk, Abbott, MSD and Eli Lilly.

BD reports congress invitations from Novo Nordisk, Sanofi, Eli Lilly, Novartis, and board fees or speaker honoraria from Sanofi, Eli Lilly, Novo Nordisk, Abbott.

MG declares congress invitations from Eli Lilly, Novo Nordisk, LVL medical, Sanofi.

LSL discloses congress invitations from Sanofi, Novo Nordisk, Eli Lilly, Abbott, Servier, has received speaker honoraria from Eli Lilly, and takes part to clinical trials as co-investigator for Roche and Sanofi.

AF declares congress invitations from Novo Nordisk.

DR declares congress invitations, honoraria and consultancy fees from AstraZeneca, Janssen, Lilly, Novartis, NovoNordisk, Sanofi.

SL has received speaker honoraria from Abbott, Novo Nordisk, Sanofi, Eli Lilly, Insulet and served on advisory board panels for Medtronic.

MJ discloses congress accomodations, honoraria and consultancy fees from Abbott, Medtronic, Sanofi, Lilly, Novo Nordisk, Astra Zeneca, MSD, BMS, Boehringer-Ingelheim, Amgen, Air Liquide SI, Lifescan.

AP discloses congress invitations, speaker honoraria and consultancies from Abbott, Eli Lilly, Lifescan, Medtronic, Novo Nordisk, Sanofi, and served on advisory board panels for Abbott, Insulet, Novo Nordisk and Sanofi.

GC has received congress invitations, honoraria and consultancy fees from Abbott, Dexcom, Medtronic, and owns shares in Diabeloop SA.

LEGENDS

Table 1: Characteristics of Patients at Baseline

Table 2: 24-h glucose control during closed-loop and control periods based on sensor glucose measurements (modified intention-to-treat analysis)

Table 3: Serious adverse events

Figure 1: Consort DIAGRAM and design study

The median duration of the washout period was 30 weeks (IQR 25.9-31.7) and ranged from 16 to 45 weeks.

Figure 2: Median 24-h sensor glucose profile

The median (IQR) sensor glucose concentration is shown during closed-loop period (solid red line and red shaded area) and control period (solid dark grey line and grey shaded area) over the 24-hour period.

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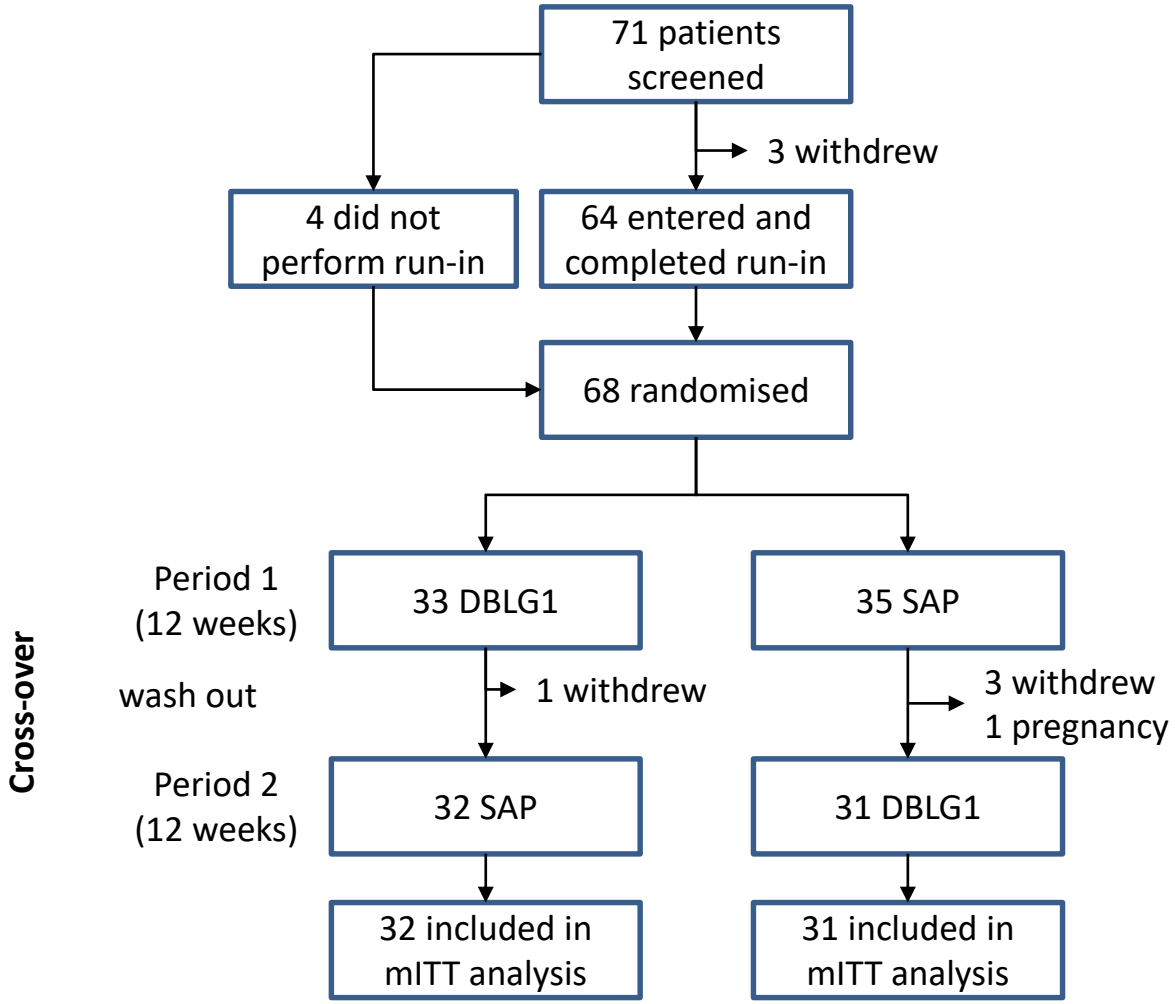
71 patients screened
3 withdrew
4 did not perform run-in
64 entered and completed run-in
68 randomised
Cross-over
Period 1 (12 weeks)
33 DBLG1
35 SAP
wash out
1 withdrew
3 withdrew
1 pregnancy
Period 2 (12 weeks)
32 SAP
31 DBLG1
32 included in mITT analysis
31 included in mITT analysis

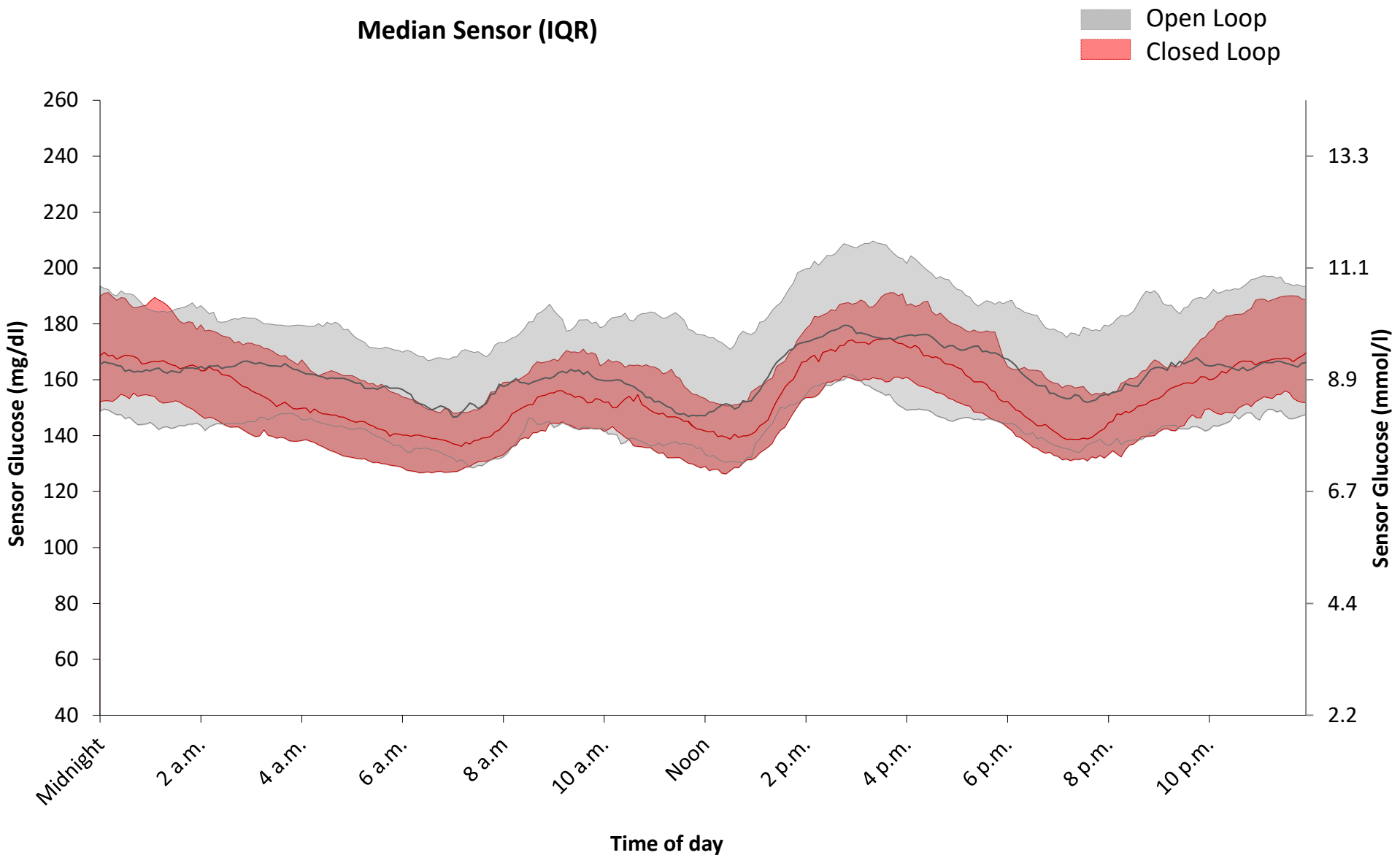
Median Sensor (IQR)
Open Loop
Closed Loop
Sensor Glucose (mg/dl)
260
240
220
200
180
160
140
120
100
80
60
40
Sensor Glucose (mmol/l)
13.3
11.1
8.9
6.7
4.4
2.2
Midnight
2 a.m.
4 a.m.
6 a.m.
8 a.m
10 a.m.
Noon
2 p.m.
4 p.m.
6 p.m.
8 p.m.
10 p.m.
Time of day

Table 1. Characteristics of Patients at Baseline

	modified Intention-To-Treat population (n=63)
Gender	
Female	39 (62%)
Male	24 (38%)
Age (years)	48·2 (13·4)
Body weight (kg)	70·8 (11·0)
BMI (kg/m^2)	24·8 (3·5)
Duration of diabetes (years)	28·0 (13·6)
HbA1c (%)	7·6 (0·9)
HbA1c (mmol/mol)	59·4 (9·8)
Total Daily Insulin (U/d)	36·3 (8·9)

Data are mean (SD) or n (%).

Table 2. 24-h glucose control during closed-loop and control periods based on sensor glucose measurements (modified intention-to-treat analysis)

	Closed-loop period (n=63)	Control period (n=63)	Paired difference (CI 95%) *	p value	p value **
Day and night (24h)					
Proportion of time with glucose concentration in range (%)					
3·9 – 10·0 mmol/L †	68·5 (1·2)	59·4 (1·3)	9·2 (6·4 to 11·9)	<0·0001	<0·0001
4·4 – 7·8 mmol/L	39·3 (1·0)	33·5 (1·0)	5·8 (3·7 to 7·9)	<0·0001	<0·0001
> 10·0 mmol/L	29·5 (1·3)	36·3 (1·3)	-6·8 (-9·7 to -3·9)	<0·0001	<0·001
> 13·9 mmol/L	7·4 (0·8)	11·7 (0·8)	-4·3 (-6·2 to -2·4)	<0·0001	<0·001
> 16·7 mmol/L	2·4 (0·4)	4·3 (0·4)	-2·0 (-3·0 to -1·0)	<0·001	<0·0001
< 3·9 mmol/L	2·0 (0·3)	4·3 (0·3)	-2·4 (-3·0 to -1·7)	<0·0001	<0·0001
< 3·3 mmol/L	0·8 (0·1)	2·0 (0·2)	-1·3 (-1·6 to -0·9)	<0·0001	<0·0001
< 2·8 mmol/L	0·2 (0·1)	0·7 (0·1)	-0·5 (-0·7 to -0·3)	<0·0001	<0·0001
HbA1c change (%)	-0·29 (0·07)	-0·14 (0·07)	-0·15 (-0·33 to 0·03)	0·098	
HbA1c change (mmol/mol)	-3·20 (0·73)	-1·57 (0·71)	-1·63 (-3·57 to 0·31)	0·098	
Glucose concentration (mmol/L)	8·7 (0·1)	9·1 (0·1)	-0·4 (-0·6 to -0·1)	0·012	
Coefficient of variation of glucose (%)	31·0 (0·5)	33·3 (0·5)	-2·3 (-3·1 to -1·5)	<0·0001	
LBGI	0·6 (0·1)	1·1 (0·1)	-0·5 (-0·6 to -0·4)	<0·0001	
HBGI	6·7 (0·3)	8·4 (0·3)	-1·7 (-2·6 to -0·9)	<0·001	
BGRI	7·3 (0·3)	9·5 (0·3)	-2·2 (-3·0 to -1·4)	<0·0001	

Data are mean (SE) or mean (95% CI). No significant period effect was observed. * Model adjusted for baseline HbA1c and site. Difference is closed-loop period minus open-loop period. ** p-value of the log-transformed sensitivity analysis. † Primary endpoint.

Table 3. Serious adverse events (safety set)

SAE : number of events (number of patients)	Closed-loop period (n=68)	Control period (n=68)
Diabetic ketoacidosis	0	0
Severe hyperglycaemia *	9 (4)	0
Severe hypoglycaemia †	5 (5)‡	3 (3)‡

Data are n. * Defined as capillary blood glucose of more than 20 mmol/L.

† Defined as intervention of a third party for correction of hypoglycemia.

‡ During closed-loop period, 3 episodes of severe hypoglycaemia occurred during period 1 due to hardware dysfunction and 2 episodes during period 2 due to human errors. During open-loop period, 2 episodes of severe hypoglycaemia occurred during period 1 and 1 episode during period 2.