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



Pierre-Yves Benhamou, Sylvia Franc, Yves Reznik, Charles Thivolet, Pauline Schaepelynck, Eric Renard, Bruno Guerci, Lucy Chaillous, Celine Lukas-Croisier, Nathalie Jeandidier, Helene Hanaire, Sophie Borot, Maeva Doron, Pierre Jallon, Ilham Xhaard, Vincent Melki, Laurent Meyer, Brigitte Delemer, Marie Guillouche, Laurene Schoumacker-Ley, Anne Farret, Denis Raccah, Sandrine Lablanche, Michael Joubert, Alfred Penforinis, Guillaume Charpentier, on behalf of the DIABELOOP WP7 Trial Investigators*



Summary

Background Closed-loop insulin delivery systems are expected to become a standard treatment for patients with type 1 diabetes. We aimed to assess whether the Diabeloop Generation 1 (DBLG1) hybrid closed-loop artificial pancreas system improved glucose control compared with sensor-assisted pump therapy.

Methods In this multicentre, open-label, randomised, crossover trial, we recruited adults (aged ≥ 18 years) with at least a 2 year history of type 1 diabetes, who had been treated with external insulin pump therapy for at least 6 months, had glycated haemoglobin (HbA_{1c}) of 10% or less (86 mmol/mol), and preserved hypoglycaemia awareness. After a 2-week run-in period, patients were randomly assigned (1:1) with a web-based system in randomly permuted blocks of two, to receive insulin via the hybrid closed-loop system (DBLG1; using a machine-learning-based algorithm) or sensor-assisted pump therapy over 12 weeks of free living, followed by an 8-week washout period and then the other intervention for 12 weeks. The primary outcome was the proportion of time that the sensor glucose concentration was within the target range (3.9–10.0 mmol/L) during the 12 week study period. Efficacy analyses were done in the modified intention-to-treat population, which included all randomly assigned patients who completed both 12 week treatment periods. Safety analyses were done in all patients who were exposed to either of the two treatments at least once during the study. This trial is registered with ClinicalTrials.gov, number NCT02987556.

Findings Between March 3, 2017, and June 19, 2017, 71 patients were screened, and 68 eligible patients were randomly assigned to the DBLG1 group (n=33) or the sensor-assisted pump therapy group (n=35), of whom five dropped out in the washout period (n=1 pregnancy; n=4 withdrew consent). 63 patients completed both 12 week treatment periods and were included in the modified intention-to-treat analysis. The proportion of time that the glucose concentration was within the target range was significantly higher in the DBLG1 group (68.5% [SD 9.4]) than the sensor-assisted pump group (59.4% [10.2]; mean difference 9.2% [95% CI 6.4 to 11.9]; p<0.0001). Five severe hypoglycaemic episodes occurred in the DBLG1 group and three episodes occurred in the sensor-assisted pump therapy group, which were associated with hardware malfunctions or human error.

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

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Introduction

The development of continuous glucose monitoring at the start of the 21st century provided new hope for better outcomes in the management of type 1 diabetes. Although continuous glucose monitoring-assisted insulin pump therapy and multiple daily injections combined with continuous glucose monitoring have become the standard regimen, these treatments 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, which, in 2017, led 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 meta-analyses^{4,5} suggesting that the artificial pancreas system could increase the proportion of time spent in the optimal glucose range by 10 percentage points, reduce the time spent in hypoglycaemia by half, and improve HbA_{1c} by 0.3 percentage points. However, only five trials^{6–10} lasted longer than 4 weeks, involving 229 patients in total. Additional knowledge is needed regarding the metabolic

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Research in context

Evidence before this study

We searched PubMed from database inception to Nov 5, 2018, for randomised trials published in English 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"). We limited our analysis to studies of 4 week duration or longer of single hormone systems in adult outpatients. We identified five randomised trials that lasted 4, 6, 8, or 12 weeks. Three of the trials were done using successive versions of the same algorithmic system. Three studies featured a day-and-night closed-loop delivery system and two studies investigated evening-and-night or night only automated delivery. Four trials had a crossover design, and one trial had a parallel group design. Three studies included patients with baseline glycated haemoglobin (HbA_{1c}) ranging from 8.1 to 8.5% (65–69 mmol/mol), one study included patients with HbA_{1c} less than 7.5% (<58 mmol/mol), and one study included patients with a mean baseline HbA_{1c} of 7.5% (58 mmol/mol).

Closed-loop insulin delivery was associated with an increased proportion of time spent within the glucose target range (3.9–10.0 mmol/L; 8.6–12.2 percentage point improvement in the overnight studies and 10–11 percentage point improvement in the day-and-night studies), and a reduction in hypoglycaemia. Three studies showed a reduction in HbA_{1c}, ranging from 0.25 to 0.36% (2.73–3.93 mmol/mol). Remote monitoring was implemented in two studies, but its modality and impact were not reported.

Added value of this study

To our knowledge, our study is the first randomised controlled trial of an approved closed-loop system with CE marking. To date, this study is the largest randomised crossover trial of a

closed-loop system in an ambulatory setting, and the second largest trial. To date, no controlled studies have assessed the use of the closed-loop systems for longer than 12 weeks (24 h per day). This is the largest trial, with the longest duration to date, to assess tubeless patch pumps. The Diabeloop Generation 1 (DBLG1) system is an original, comprehensive solution to a clinical need, integrating a patch-pump, a glucose sensor, and a command module hosting a hybrid algorithm with customisation settings, which was combined with real-time remote monitoring in this study. This original closed-loop system was associated with a significant improvement in the proportion of time that glucose concentration was within the target range (3.9–10 mmol/L) compared with sensor-assisted pump therapy, and a significant reduction in the percentage of time glucose concentration was within the hypoglycaemic range. The closed-loop system was associated with improvements across the whole range of baseline HbA_{1c} values: patients at risk of hyperglycaemia spent a longer time within the target glucose range, and patients with low glucose values at baseline spent a reduced proportion of time in the low glucose range (<70 mg/dL [<3.9 mmol/L]). We included adult patients with type 1 diabetes with a broad range of HbA_{1c} concentrations at baseline, which indicates that results could be generalisable to real-life settings.

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, without 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.

and safety outcomes, the definition of optimal indications and responders, and the organisation of health-care delivery associated with the artificial pancreas system. The Diabeloop Generation 1 (DBLG1) system features a hybrid, single hormone closed-loop device, which was reinforced by structured remote monitoring for this study. The primary aim of this study was to assess whether the DBLG1 system provides better glycaemic control than usual sensor-assisted insulin pump therapy over a 12-week period. A video abstract is available online.

See Online for video

Methods

Study design and participants

We did a multicentre, open-label randomised controlled crossover study at 12 university hospitals in France (appendix). Adult patients (aged ≥ 18 years) were eligible if they had type 1 diabetes for 2 years or longer, glycated haemoglobin (HbA_{1c}) of 10% or less (86 mmol/mol), preserved hypoglycaemia awareness (Gold score ≤ 4),¹¹ insulin requirements of 50 U per day or less, and had

See Online for appendix

been treated with external insulin pump therapy for at least 6 months. Eligible patients also had to live in an area covered by a Global System for Mobile communications network. Patients who had severe hypoglycaemia in the previous 12 months were excluded. Full inclusion and exclusion criteria are described in the appendix.

The institutional review board Comité de Protection des Personnes (French Committee for the Protection of Persons participating in biomedical research) approved the study and the trial was authorised by the French National Safety Authority (ANSM). All patients provided signed written informed consent. The study protocol is available in the appendix (p 19).

Randomisation and masking

Eligible participants who still met criteria after the run-in period were randomly assigned (1:1) to receive insulin treatment via the hybrid closed-loop DBLG1 system followed by sensor-assisted pump therapy, or vice versa.

After the run-in period, randomisation was done using an automated web-based program (ClinInfo, Lyon, France) with random permuted blocks of two, stratified by site. Investigators and participants were not masked to treatment allocation.

Procedures

After screening and inclusion, patients entered a 2-week run-in period, during which time they were trained to use the interventional insulin pump (Cellnovo Generation 1; Cellnovo, Paris, France) and the continuous glucose monitoring device at home. After this period, compliant patients who satisfied a competency and safety checklist (appendix) were randomly assigned.

Patients then received insulin via either the hybrid DBLG1 system (closed-loop; DBLG1 group) for 12 weeks or the sensor-assisted pump therapy (open-loop; sensor-assisted pump therapy group) for 12 weeks, in the order assigned at randomisation, with an 8-week washout period in between.

Patients assigned to the sensor-assisted pump therapy group returned to their usual treatment with their own pump, combined with a Dexcom G5 Mobile continuous glucose monitoring system (Dexcom, San Diego, CA, USA). Participants were free to activate or shut off sensor alarms and no recommended thresholds were used for high-glucose and low-glucose alarms.

Patients assigned to the DBLG1 group in the first 12 week treatment period used the Cellnovo insulin patch-pump managed by the Diabeloop application (Regulation v2017.04.20; Diabeloop, Paris, France) installed on an android smartphone (Motorola Moto E XT1524, Motorola, Chicago, IL, USA) and connected to the Dexcom G5 continuous glucose monitoring system using Bluetooth Low Energy technology. At the start of the closed-loop period, at the request of the ANSM, patients were admitted to the local hospital research facility for 48 h to receive training on closed-loop insulin delivery, whereby a dedicated nurse taught patients how to use the various components of the system (sensor, pump, smartphone) and how to respond to an alarm. The nurse was then responsible for remote monitoring and phone interaction with the given patient. Remote monitoring was implemented at the request of the ANSM. Customisation of the closed-loop system required it to be tuned through eight settings (appendix), which was done during this initial 48 h stay. The DBLG1 system, which combines an algorithm based on machine-learning within a physiological framework with an expert system and self-learning algorithms, is a hybrid closed-loop device that requires the patient to record carbohydrate intake semi-quantitatively, and intensity and duration of planned physical activities. Details on the algorithm and customisation, remote monitoring, and generation of automatic text messages have been published previously¹² and are described in the appendix. Target glucose concentration was set at 6.05 mmol/L (110 mg/dL). After

48 h, patients were discharged and returned home, and followed-up remotely for a period of 12 weeks. In both the DBLG1 and sensor-assisted pump therapy groups, hospital visits were scheduled at weeks 1, 3, 6, 9, and 12 to download data from the command terminal or Dexcom receiver, to monitor adverse events, and to complete satisfaction questionnaires.

During the washout period, patients returned to their usual pump treatment and stopped using Dexcom G5 continuous glucose monitoring, but were free to use previous continuous glucose monitoring or flash glucose monitoring, if any. All participants used their usual, fast-acting insulin analogue (lispro, aspart, or glulisine); ultra-fast acting aspart was not allowed. During the first 12-week treatment period, three severe hypoglycaemic events were reported and reviewed by the Data Safety and Monitoring Board (appendix). A fault in a safety sensor of the CellNovo pump was identified. In agreement with the regulatory authority (ANSM), the study protocol was amended and patients used the Kaleido insulin patch-pump (ViCentra, Utrecht, Netherlands) in the second 12-week treatment period (appendix), but otherwise remained unchanged. The washout period was extended to 30 weeks to enable implementation of 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 based on continuous glucose monitoring during the 12-week treatment period.¹³ The secondary efficacy outcomes were the percentage of time sensor glucose concentration was within the optimal target range (4.4–7.8 mmol/L [80–140 mg/dL]), time with glucose concentrations in hypoglycaemia (<70 mg/dL) during the 12-week treatment period (measured by continuous glucose monitoring, defined by any threshold crossing <3.9 mmol/L [<70 mg/dL], 3.3 mmol/L [60 mg/dL], and 2.8 mmol/L [50 mg/dL]), and time with glucose concentrations in hyperglycaemia (>10.0 mmol/L [180 mg/dL], >13.9 mmol/L [250 mg/dL], and >16.7 mmol/L [300 mg/dL]), during 24 h and during the night (defined as 00 00 h to 06 00 h), mean sensor glucose concentration during each 12-week period (calculated as mean of each 24 h interval), HbA_{1c} measured at the beginning and end of each treatment period, coefficient of variation of glucose (calculated as mean of each 24 h interval), low and high blood glucose index and blood glucose risk index during each 12-week treatment period, and total insulin intake (units of insulin delivered by pump), and the number and the amount of carbohydrate intakes during the last week of each period. Data regarding insulin intakes, as well as ingested carbohydrates for prevention or treatment of hypoglycaemia will be reported elsewhere.

Safety outcomes were the number of severe hypoglycaemic events (>360 mg/dL [20 mmol/L]) or significant

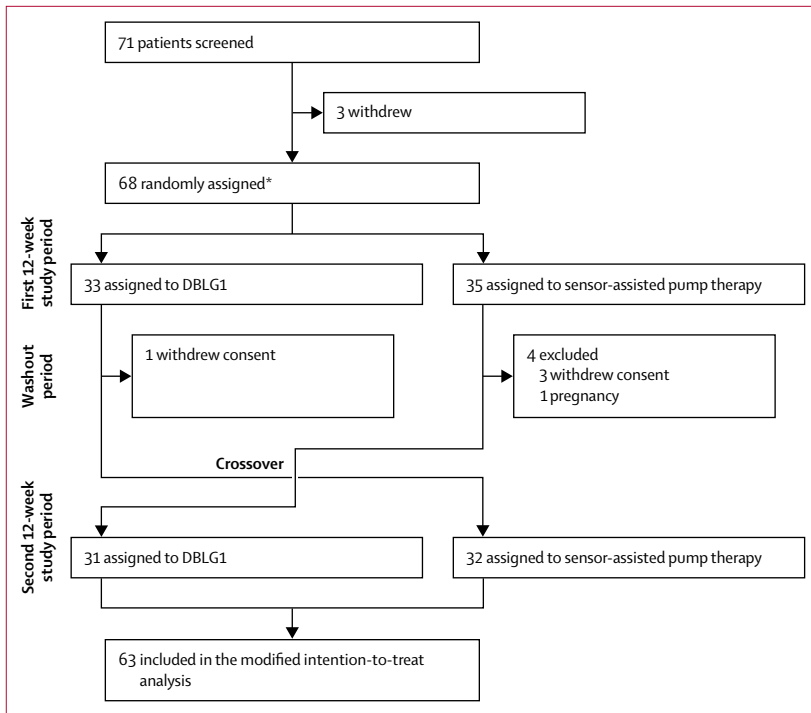


Figure 1: Trial profile
 The median duration of the washout period was 30 weeks (IQR 25.9–31.7) and ranged from 16 to 45 weeks. DBLG1=Diabeloop Generation 1. *Four patients did not participate in the run-in phase because they had previous experience with the DBLG1 system.

	mITT population (n=63)
Sex	
Women	39 (62%)
Men	24 (38%)
Age, years	48.2 (13.4)
Bodyweight, kg	70.8 (11.0)
Body-mass index, kg/m ²	24.8 (3.5)
Duration of diabetes, years	28.0 (13.6)
HbA _{1c} , %	7.6 (0.9)
HbA _{1c} , mmol/mol	59.4 (9.8)
Total daily insulin, U per day	36.3 (8.9)
Data are n (%) or mean (SD). mITT=modified intention-to-treat. HbA _{1c} =glycated haemoglobin.	

Table 1: Baseline characteristics of the mITT population

ketosis [plasma ketone >3 mmol/L]), the number of severe hyperglycaemic episodes (capillary blood glucose ≥20.0 mmol/L [360 mg/dL]) or significant ketoacidosis (plasma ketone >3 mmol/L), number of hypoglycaemic episodes (defined by any crossing of 70 mg/dL [3.9 mmol/L], 60 mg/dL [3.33 mmol/L], or <54 mg/dL [3 mmol/L] glucose thresholds), number of severe hypoglycaemic events requiring intervention of a third party for sugaring, number of severe hypoglycaemic events with loss of consciousness, number of hospital admissions for severe hypoglycaemia or ketoacidosis, the

number of sugarings and amount of carbohydrate intake in the last week of each treatment period, and the number of technical incidents causing interruptions of the closed loop.

Additional outcomes were the percentage of time spent in the closed-loop functional mode and assessed patient satisfaction using the Diabetes Treatment Satisfaction Questionnaire and three visual analogical scales testing satisfaction, ease of use, and pleasantness of the system.

Sensitivity analysis were done to test the robustness of the results. We also did post-hoc analyses investigating the potential impact of remote monitoring, and the relationships between baseline HbA_{1c}, sensor glucose levels, and the primary outcome.

Statistical analysis

The statistical analysis plan was defined before database lock. The analysis was done by a contract research organisation (RCTs, Lyon, France) using SAS software (version 9.4). Efficacy analyses were done in the modified intention-to-treat population, which included all randomly assigned patients who completed both 12-week treatment periods. Safety analyses were done in all randomly assigned patients who were exposed to either of the two treatments at least once during the study. We based our power calculation on previous trials of the DBLG1 system.¹⁴ We calculated that a sample size of 50 patients would provide 94% power at the 5% significance level to detect a difference between the closed-loop treatment period (assumption 77.8%) and the open-loop treatment period (assumption 71.5%). Accounting for dropouts, we increased the target recruitment number to 71 patients.

Comparisons of continuous outcomes between the closed-loop and open-loop periods were done using a mixed model for repeated measures. The model included the treatment group (closed-loop vs open-loop) and the treatment period as fixed effects and the patient as a random effect. The model was adjusted for HbA_{1c} level at the beginning of each treatment period and site.

Since distributions of percentage of time spent in the different glucose target ranges were close enough to the parametric assumptions, the mixed model was used for the primary analyses. We did not adjust for multiple comparisons within the secondary endpoints.

To evaluate the robustness of the results, sensitivity analyses were done using the same model with log-transformed data on the percentage of time spent in hypoglycaemia, hyperglycaemia, and within the different target ranges. We also did a sensitivity analysis of the change of device, required for safety reasons, by adding the treatment-by-period interaction in the primary model of the primary endpoint. We did a prespecified per-protocol analysis to examine the primary and secondary outcomes when algorithm regulation was active.

This trial is registered with ClinicalTrials.gov, number NCT02987556.

	DBLG1 (n=63)	SAP (n=63)	Paired difference* (95% CI)	p value
Time spent at glucose concentration				
3.9–10.0 mmol/L†	68.5% (9.4)	59.4% (10.2)	9.2% (6.4 to 11.9)	<0.0001
4.4–7.8 mmol/L	39.3% (7.9)	33.5% (7.9)	5.8% (3.7 to 7.9)	<0.0001
>10.0 mmol/L	29.5% (10.2)	36.3% (10.2)	-6.8% (-9.7 to -3.9)	<0.0001
>13.9 mmol/L	7.4% (6.3)	11.7% (6.3)	-4.3% (-6.2 to -2.4)	<0.0001
>16.7 mmol/L	2.4% (3.1)	4.3% (3.1)	-2.0% (-3.0 to -1.0)	0.0002
<3.9 mmol/L	2.0% (2.4)	4.3% (2.4)	-2.4% (-3.0 to -1.7)	<0.0001
<3.3 mmol/L	0.8% (0.8)	2.0% (1.6)	-1.3% (-1.6 to -0.9)	<0.0001
<2.8 mmol/L	0.2% (0.8)	0.7% (0.8)	-0.5% (-0.7 to -0.3)	<0.0001
HbA _{1c} change from baseline‡	-0.29% (0.6)	-0.14% (0.6)	-0.15 (-0.33 to 0.03)	0.098
HbA _{1c} change from baseline‡ (mmol/mol)	-3.20 (5.7)	-1.57 (5.6)	-1.63 (-3.57 to 0.31)	0.098
Glucose concentration (mmol/L)	8.7 (0.8)	9.1 (0.8)	-0.4 (-0.6 to -0.1)	0.012
Coefficient of variation of sensor glucose (%)	31.0 (3.9)	33.3 (3.9)	-2.3 (-3.1 to -1.5)	<0.0001
LBGI	0.6 (0.8)	1.1 (0.8)	-0.5 (-0.6 to -0.4)	<0.0001
HBGI	6.7 (2.4)	8.4 (2.4)	-1.7 (-2.6 to -0.9)	0.0001
BGRI	7.3 (2.4)	9.5 (2.4)	-2.2 (-3.0 to -1.4)	<0.0001

Data are mean (SD) or mean difference (95% CI). No significant period effect was observed. DBLG1=Diabeloop Generation 1. SAP=sensor-assisted pump. HbA_{1c}=glycated haemoglobin. LBGI=low blood-glucose index. HBGI=high blood-glucose index. BGRI=blood-glucose risk index. *Adjusted for baseline HbA_{1c} and site. Mean difference of closed-loop period minus open-loop period. †Primary endpoint. ‡Baseline defined as the start of each treatment sequence.

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

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. 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

Between March 3, 2017, and June 19, 2017, 71 patients were screened for eligibility, three of whom withdrew before entering the run-in period. Four participants had previous experience with the DBLG1 system and thus did not participate in the run-in period. Overall, 68 patients were randomly assigned (33 to the DBLG1 and 35 to sensor-assisted pump). Six patients were randomly assigned at each of the 12 treatment centres, with the exception of two centres where five and three patients were recruited, respectively. Of the 68 patients who were randomly assigned, five dropped out during the washout period, one because of pregnancy and four who withdrew consent. The remaining 63 patients completed both 12-week treatment periods and were included in the modified intention-to-treat (mITT) analysis set (figure 1). The last patient visit was completed on Aug 28, 2018. The median duration of the washout period was 30 weeks (IQR 25.9–31.7; range 16–45 weeks). Because of safety concerns around the device used in the first 12-week period of DBLG1, an alternate device was used after the crossover in the second 12-week period. A sensitivity analysis of the primary endpoint revealed no carryover effect ($p=0.96$) or period effect ($p=0.28$; appendix), which indicated that results from sensitivity analyses were similar and confirmed the robustness of the primary outcome results.

Baseline characteristics of patients are summarised in table 1. Baseline HbA_{1c} was 7.6% (SD 0.9; 59.4 mmol/mol [SD 9.8]; range 5.7–9.6% [39–81 mmol/mol]; distribution shown in the appendix). Of the 63 patients, none had macroangiopathy, 20 (32%) had retinopathy, and six (9.5%) had permanent positive microalbuminuria (incipiens nephropathy). 58 (92%) of 63 patients had experience in flexible insulin therapy and carbohydrate counting.

Primary and secondary outcomes are summarised in table 2. 24 h sensor glucose profiles for the whole 12-week period in each group are shown in figure 2. The proportion of time spent with glucose within the target range of 3.9–10.0 mmol/L was higher in the DBLG1 group (68.5% [SD 9.4]) than the sensor-assisted pump therapy group (59.4% [10.2]) with a mean difference of 9.2% (95% CI 6.4–11.9; $p<0.0001$). 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. For patients in the DBLG1 group, time spent in hypoglycaemia was significantly lower than the sensor-assisted pump group (2.0% [SD 2.4] vs 4.3% [2.4]; mean difference -2.4% [95% CI -3.0 to -1.7]; $p<0.0001$ for time spent below 3.9 mmol/L; table 2). Mean HbA_{1c} was reduced by 0.29% (3.2 mmol/mol; SD 0.6) in the DBLG1 group and 0.14% (1.57 mmol/mol; 0.6) in the sensor-assisted pump therapy group with a mean difference of -0.15% (-0.33 to 0.03; $p=0.098$). Patients with higher HbA_{1c} concentrations at baseline had greater improvements in the proportion of time glucose concentration was within the target range than did patients with lower baseline HbA_{1c} concentrations (appendix). A post-hoc analysis showed that patients

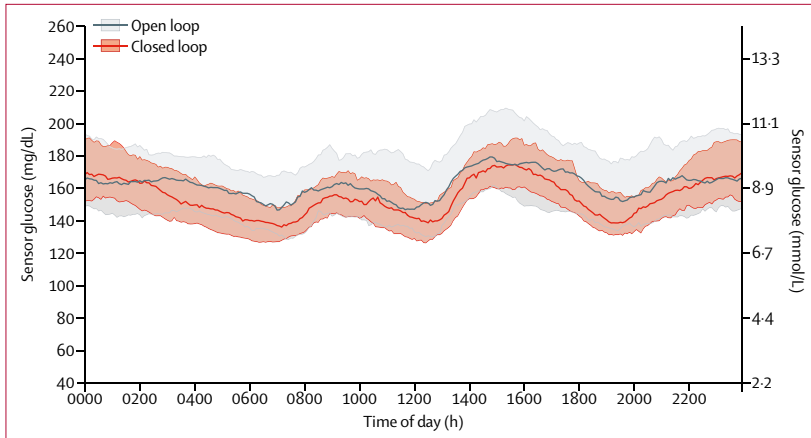


Figure 2: Median (IQR) sensor glucose concentrations during closed-loop and control periods for the 24 h duration over the study period
 The solid red line and red shaded areas represent the closed-loop period. The solid dark grey line and grey shaded areas represent the control period.

	Closed-loop period (n=68)	Control period (n=68)
Diabetic ketoacidosis	0	0
Severe hyperglycaemia	9*	0
Severe hypoglycaemia	5†	3‡

Data are number of events. Severe hyperglycaemia was defined as capillary blood glucose >20 mmol/L. Severe hypoglycaemia was defined as intervention of a third party for correction of hypoglycaemia. *Five severe hyperglycaemic events occurred in one patient, and four severe hyperglycaemic events occurred in three patients. †Three severe hypoglycaemia events (one event in three patients) occurred during the first 12 week treatment period due to hardware dysfunction and two events (one event in two patients) occurred during the second 12 week treatment period due to human error. ‡Two severe hypoglycaemia events (one event in two patients) occurred during the first 12 week treatment period and one severe event occurred in one patient during the second 12 week treatment period.

Table 3: Serious adverse events in the safety analysis set

with the highest continuous glucose concentrations during the 12-week sensor-assisted pump therapy sequence had the largest improvements in the time glucose concentration was within the target range during the 12-week DBLG1 period (appendix). Patients who spent the highest proportion of time within the low glucose range (<70 mg/dL) during the sensor-assisted pump therapy sequence had the greatest reduction in time spent in hypoglycaemia during the DBLG1 period (appendix).

17 serious adverse events occurred during both 12-week treatment periods (table 3). None of the 17 events were associated with inappropriate algorithmic recommendation. No patients had ketoacidosis, but nine severe hyperglycaemic events were reported (all in the DBLG1 group) and eight severe hypoglycaemic events were reported (five in the DBLG1 group and three in the sensor-assisted pump therapy group). No patients were admitted to hospital during the two treatment periods. The nine severe hyperglycaemic events occurred in four different patients (five events in one patient) during the

second treatment sequence and were all associated with hardware (tubing, cannula, or pump). Analysis of the five severe hypoglycaemic events in the DBLG1 group showed incorrect bolus dosing as a result of a patient overriding the system (n=1), an error in pairing the pump with the handset at initiation of the closed-loop period between two patients sharing the same room (n=1), and a pump malfunction (n=3). The two severe hypoglycaemic events due to human error occurred during the second 12-week treatment period with the Kaleido device and the three severe hypoglycaemic events due to pump malfunctions occurred during the first 12-week treatment period with the Cellnovo pump. All severe metabolic events that occurred outside of hospital settings were detected by remote monitoring and addressed by the generation of automatic text messages followed by phone contact between the nurse and patient or family. Investigators were then informed by nurses.

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 treatment period. In a prespecified per-protocol analysis of the primary endpoint including all 63 patients, similar results to those of the mITT analysis were observed (DBLG1 69.9% [SD 9.4] vs sensor-assisted pump therapy 59.3% [9.4], mean difference 10.6% [95% CI 7.9–13.3]; p<0.0001; appendix).

Overall, the DBLG1 closed-loop system was non-functional for 16.2% of the 12-week treatment period due to technical malfunction of a single component (pump, sensor, or handset; 39.65% of cases), as a result of the user’s decision (10.2% of cases), or due to both technical dysfunction and the user’s decision (50.2% of cases).

To analyse the potential impact of remote monitoring (post-hoc analysis), we separated the 12-week period into three 4-week periods. We also separated the modifications in settings of the algorithm directly available in the patient user interface of the DBLG1 system into three categories according to their frequency of use. The number of modifications in the eight settings of the algorithm per patient (mean 10.6 adjustments per patient during the entire 12-week period [SD 0.8]) gradually decreased between weeks 1–4 and weeks 9–12 and the number of text messages leading to a phone call to the patient also decreased (mean 4.2 text messages per patient received by nurses during the entire 12-week period [SE 3.5]; appendix). However, the proportion of time spent with glucose concentration within a given range did not differ across the three time periods. No clinically significant differences were identified in metabolic outcomes associated with the frequency of modifications in algorithm settings (appendix).

The mean target glucose concentration, set by default at 6.05 mmol/L, and adjusted manually by the user or automatically by the algorithm throughout the 12 week treatment period, was 6.36 mmol/L (SD 1.0; range per patient 5.6–6.9 mmol/L).

4 h of training was sufficient to teach patients how to use the system and no early side-effects were observed. All investigators and patients agreed that the 48 h inpatient initiation stay was unnecessary.

No significant differences were identified between the DBLG1 group and the sensor-assisted pump group with regard to Diabetes Treatment Satisfaction Questionnaire outcomes or the three visual analogue scales (appendix).

Discussion

This multicentre, open-label, randomised crossover trial showed that the DBLG1 system can improve the proportion of time spent within the recommended glucose target range over a period of 12 weeks compared with sensor-assisted pump therapy. The improvement observed (9.2% increase) is similar to that reported by previous randomised outpatient trials of the same duration^{8,10} and a non-randomised trial of another approved closed-loop device,^{2,3} which all used a single hormone approach.

This trial also showed a significant reduction in time spent in hypoglycaemia. Although the crossover design might have led to inappropriate estimation of the risk of hypoglycaemia,¹⁵ this bias was reduced by the long washout period of our trial. The absence of recommended thresholds for low-glucose alarms in the sensor-assisted pump group might have unfavourably influenced the number of hypoglycaemic events in this group. Previous research has shown the use of a dual hormone approach with results suggesting a reduced incidence of hypoglycaemia,^{16,17} but long-term data are still needed. Further improvements might affect the proportion of time spent in the functional closed-loop mode, (83.8% in our trial vs 71–88% in previous outpatient studies^{3,8–10}). To increase the time spent in the functional closed-loop mode, improvements in the reliability and integration of the technical components of the system, including the pump and sensor, will be required. Diabeloop is the integrator of the system, which comprises the handset manufactured by Diabeloop, the pump, and continuous glucose monitoring. Thus, future modifications of the system could possibly integrate other pumps or continuous glucose monitoring.

Our metabolic results were obtained using a system that combined a closed-loop device with remote monitoring, as requested by French regulatory authorities. Previous trials of closed-loop systems^{3,6,7,18} have included remote monitoring. In the 6-week overnight trial of the MD-Logic artificial pancreas system,⁶ remote monitoring led to 86 phone calls to the patients, mostly associated with safety issues. The DIAs system¹⁸ allows remote monitoring that was assessed in a trial of intense outdoor exercise. To the best of our knowledge, this monitoring was a safety measure and was not associated with modifications in algorithm settings. In a 2018 trial¹⁰ of closed-loop insulin delivery, although automated monitoring was not implemented, contact (visit, phone,

mail) with investigators was four times more frequent in the experimental group than in the control group. In a previous trial of the MiniMed 670G system,¹⁹ remote monitoring enabled some settings of the algorithm to be tuned, mostly during the first weeks and months of the trial, which could have affected whether the closed loop was active or not.

On the basis of our trial design, it is possible that remote monitoring partly contributed to the improved outcome. Telemonitoring of adult patients with type 1 diabetes was shown to be associated with reduced HbA_{1c}.²⁰ Our remote monitoring was centralised and focused on 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 4 weeks of our trial. Although improvement in metabolic outcomes was observed at the early stages following initiation of treatment via the closed-loop system, we hypothesise that system setting adjustments could have contributed to the outcomes observed. However, the proportion of time glucose concentration was within the target range did not improve with time, or in patients with more frequent adjustments.

Modifications of command settings, which are part of the design of the system, contribute to its originality and adaptability to various metabolic phenotypes. Whether adjustments are made through remote monitoring or during face-to-face visits is dependent on health care organisation. In the near future, some settings of the algorithm might be tuned automatically, with the aid of deep-learning long-term algorithms. An uncontrolled trial²¹ showed that automated, cloud-based algorithmic adaptation of basal rate (every week) and carbohydrate ratios (every month) was safe and feasible. Human factors should be taken into account. A paediatric study²² reported that continuous glucose monitoring with remote monitoring could reduce fear of hypoglycaemia and improve other psychosocial metrics including quality of life in parents of children with type 1 diabetes, whereas these qualitative outcomes were not improved in previous continuous glucose monitoring studies without remote monitoring.²³ Remote monitoring raises ethical issues associated with confidentiality that should not be neglected.²⁴

Our trial was among the largest multicentre studies to date, involving 12 centres across France, in which the majority of investigators did not have experience in closed-loop therapy. Thus, 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 associated with human error or malfunctioning hardware. In our study, five of nine adverse events associated with pump malfunction

or hardware occurred in a single patient. Cannula and tubing-related issues represent major limitations of pump therapy and might expose future patients naive to pump treatment to some initial metabolic hazards, without appropriate support and education. Fault detection algorithms might be able to efficiently detect insulin infusion set failures²⁵ and these will be implemented in the future DBLG1 system.

Overall, these reports and our data suggest that professional and human support is needed by some patients in the early phase of closed-loop initiation, which can be provided by transient remote monitoring. Furthermore, tuning of the algorithm might become automatic through autolearning technologies in the near future. Additional studies are needed to confirm whether remote monitoring is useful for the implementation of closed-loop therapy and, if so, to define its optimum modalities (ie, short vs long duration, local vs centralised, all vs selected patients).

The next challenge is to obtain medical insurance coverage, first in Europe then the USA, and to propose practical settings for the implementation of closed-loop therapy. For this purpose, economic data will be needed. Implications of our findings are important in this perspective. Improvements in the time spent within the target glucose range were recently validated using the Diabetes Control Complications Trial dataset and was shown to be strongly associated with the risk of microvascular complications.^{26,27} The hazard rate for the development of retinopathy and microalbuminuria was increased by 64% and 40%, respectively, for each 10 percentage points lower than the mean time in range (41%). Additionally, satisfaction outcomes still need to be addressed. No differences in satisfaction were identified between the groups in our study; however, it might be meaningful to develop specific clinical metrics to assess satisfaction.²⁸

Improvement in HbA_{1c} was not statistically significant in our study. Four previous 12-week home trials^{3,8,10,21} showed a reduction in HbA_{1c} ranging from 0.30 to 0.50%. Our results might be associated with mean baseline HbA_{1c}, which was lower than in two previous controlled trials (7.6% vs 8.3 to 8.5%),^{8,10} although another two previous uncontrolled trials^{3,21} only included patients with a mean baseline HbA_{1c} of 7.0%. In our study, 69.9% of patients had a baseline HbA_{1c} below 8% (<64 mmol/mol). A previous trial of closed-loop insulin therapy¹⁰ showed that reduction in HbA_{1c} was higher in patients with higher baseline HbA_{1c} values than patients with lower baseline HbA_{1c} values. Our data also showed a positive correlation between improvement in outcome and baseline HbA_{1c}. Improvements were observed across the whole range of baseline HbA_{1c} values: patients with hyperglycaemic concern spent a longer time in the target glucose range, and patients with lower glucose values at baseline spent a reduced proportion of time in the low glucose range.

Although the sensitivity analysis showed our results were robust, and both models of pump, when functioning nominally, had good delivery precision, the main effect of switching models between the two sequences was a reduced risk for sudden hypoglycaemic events.

Overall, the main limitations of our study were the absence of an appropriate control for a proper assessment of the effect of remote monitoring, no evaluation of psychosocial and human factors, and the fact that we did not use a parallel group design, which would have provided more information with regard to the effect on HbA_{1c}. Further studies will also address the effect of carbohydrate, protein, and fat intake, and physical activity, with their respective algorithmic management.

In conclusion, we observed that the use of the DBLG1 system, comprising 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 type 1 diabetes with variable HbA_{1c} concentrations at baseline. These clinically relevant findings support the use of closed-loop technology combined with appropriate health care organisation in adults with type 1 diabetes.

Contributors

P-YB, SF, YR, CT, PS, ER, BG, LC, NJ, HH, SB, IX, BD, DR, AP, and GC designed the study. IX and GC wrote the protocol and liaised with regulatory authorities. P-YB, SF, YR, CT, PS, ER, BG, LC, CL-C, NJ, HH, SB, VM, LM, BD, MG, LS-L, AF, DR, SL, MJ, AP, and GC were involved with patient enrolment and follow-up. P-YB, SF, YR, CT, PS, ER, BG, LC, NJ, HH, SB, AP, and GC interpreted data. IX monitored data. P-YB wrote the manuscript. SF, YR, CT, PS, ER, BG, LC, NJ, HH, SB, SL, MJ, AP, and GC edited the manuscript. MD and PJ engineered the algorithm.

Declaration of interests

P-YB has received speaker honoraria from Abbott, Roche, Eli Lilly, Novo Nordisk, and Sanofi and served on advisory board panels for Abbott, Roche, Medtronic, Dexcom, Insulet, Eli Lilly, Novo Nordisk, and Sanofi. SF declares congress invitations from Sanofi, Eli Lilly, MSD, Novo Nordisk, Roche, Abbott, and Boehringer; has received speaker honoraria from Lilly and Novo Nordisk; has served on advisory board panels for Novo Nordisk, Roche, and Sanofi; and owns shares in Diabeloop SA. YR declares congress invitations, honoraria, and consultancy fees from Medtronic, Insulet, Novo Nordisk, Sanofi, and Eli Lilly. CT has received speaker honoraria from Abbott, Eli Lilly, and Sanofi and has served on advisory board panels for Abbott, Roche, and Medtronic. PS declares congress invitations, honoraria, and consultancy fees from Roche. ER has received grants from Abbott, Dexcom, Insulet, Roche, and Tandem; and received consultancy fees from Menarini Diagnostics, Abbott, Air Liquide, Becton-Dickinson, Cellnovo, Dexcom, Eli Lilly, Insulet, Johnson & Johnson, Medtronic, Novo-Nordisk, Roche, and Sanofi-Aventis. BG reports congress invitations, honoraria, and consultancy fees from Abbott, Medtronic, Eli Lilly, Dexcom, and Roche. LC reports congress invitations, honoraria, and consultancy fees from Abbott, Medtronic, Eli Lilly, Novo Nordisk, and Sanofi. CL-C declares congress invitations, honoraria, and consultancy fees from Abbott, Insulet, Eli Lilly, Medtronic, NovoNordisk, and Vitalaire. NJ discloses congress invitations, speaker honoraria, and consultancy fees from Lilly, Sandoz, and Roche and advisory board fees from Sanofi. HH has received congress invitations, honoraria, and consultancy fees from Abbott, Johnson & Johnson, Medtronic, and Roche. SB has received congress invitations, honoraria, and consultancy fees from Abbott, Johnson & Johnson, Medtronic, and Roche. VM received speaker honoraria from Abbott, and Novo-Nordisk. LM has received congress invitations, honoraria, and consultancy fees from Novo Nordisk, Abbott, MSD, and Eli Lilly. BD has received congress invitations from Novo Nordisk, Sanofi, Eli Lilly, Novartis, and board fees or speaker honoraria from Sanofi, Eli Lilly, Novo Nordisk, and Abbott. MG has

received congress invitations from Eli Lilly, Novo Nordisk, LVL Medical, and Sanofi. LS-L has received congress invitations from Sanofi, Novo Nordisk, Eli Lilly, Abbott, and Servier; has received speaker honoraria from Eli Lilly; and is a co-investigator on clinical trials for Roche and Sanofi. AF has received congress invitations from Novo Nordisk. DR has received congress invitations, honoraria, and consultancy fees from AstraZeneca, Janssen, Lilly, Novartis, NovoNordisk, and Sanofi. SL has received speaker honoraria from Abbott, Novo Nordisk, Sanofi, Eli Lilly, and Insulet and has served on advisory board panels for Medtronic. MJ received expenses for congress accommodations, honoraria, and consultancy fees from Abbott, Medtronic, Sanofi, Lilly, Novo Nordisk, AstraZeneca, MSD, Bristol-Myers Squibb, Boehringer-Ingelheim, Amgen, Air Liquide, and Lifescan. AP has received congress invitations, speaker honoraria, and consultancy fees from Abbott, Eli Lilly, Lifescan, Medtronic, Novo Nordisk, Sanofi, and has 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. MD, PJ, and IX declare no competing interests.

Data sharing

The Diabeloop Trial Investigators agree to share de-identified individual participant data, the study protocol, and the statistical analysis plan with academic researchers 3 months after publication. Proposals should be directed to kerbonac@free.fr.

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