Pilot Study 3 of Outpatient Control-to-Range: Safety and Efficacy with Day-and-Night In-Home Use

Version 4.0

Protocol Chair

Boris Kovatchev, Ph.D.
University of Virginia

Site Principal Investigators

Stacey Anderson, M.D., University of Virginia
Eric Renard, M.D., Ph.D., University of Montpellier, France
Claudio Cobelli, Ph.D., University of Padova, Italy
Bruce A. Buckingham, M.D., Stanford University
Francis J. Doyle III, Ph.D., UC Santa Barbara; William Sansum Diabetes Center
Moshe Phillip, M.D., National Center for Childhood Diabetes, Israel

Coordinating Center

Jaeb Center for Health Research
Roy W. Beck, M.D., Ph.D. (Director)
John Lum, M.S. (Assistant Director)
Tampa, FL

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

1.1. Background and Rationale

Automated closed-loop control (CLC) of blood glucose (BG), known as the "artificial pancreas" (AP), can have tremendous impact on the health and lives of people with type 1 diabetes (T1D). The CLC idea is not new - it can be traced back decades ago when the possibility for external BG regulation had been demonstrated by studies using intravenous (i.v.) BG measurement and i.v. infusion of insulin and glucose [1-5]. Although these systems resulted in excellent BG control, they were cumbersome and unsuitable for long-term or outpatient use [6-10]. With the advent of minimally-invasive subcutaneous (s.c.) continuous glucose monitoring (CGM), increasing academic and industrial effort has been focused on the development of s.c.-s.c. artificial pancreas systems, using CGM coupled with continuous subcutaneous insulin infusion (CSII). In 2006, the JDRF initiated the Artificial Pancreas Project, sponsoring several centers in the U.S. (including the University of Virginia team) and Europe to carry closed-loop control research [11]. In 2008, NIDDK launched an artificial pancreas initiative, and in 2010, the European AP@Home consortium was established. By 2010 the artificial pancreas became a global research topic engaging physicians and engineers in unprecedented collaboration. Key milestones of this development are described in a Perspective in Diabetes [12].

Two of the key technological achievements that led directly to the development of the core technology for this study are described below:

- ***In Silico* Model of the Human Metabolic System:** A paradigm change accelerating the progress of AP development was the introduction of our computer simulator of the human metabolic system, which was based on the most sophisticated to date model of glucose-insulin dynamics [20,21], and included a "population" of N=300 "subjects" in 3 "age groups:" children, adolescents, and adults [22]. Simulation experiments now allow a CGM device, an insulin pump, and any control algorithm to be linked in a CLC system and tested *in silico*, prior to their use in clinical trials. In January 2008 the FDA accepted our simulator as a *substitute to animal trials for the testing of CLC strategies*. This opened the field for rapid and cost-effective *in silico* experiments. Only three months later, in April 2008, the first trials began at the universities of Virginia (UVA), Montpellier (France), and Padova (Italy) using CLC designed *entirely in silico* [23]. The simulator of the human metabolic system is described in Master File 1521 of February 2008.

- **Modular Architecture of CLC:** In 2009 we introduced an engineering blueprint allowing CLC systems to be assembled from independent (but compatible) modules, each performing a specific control function, e.g. prevention of hypoglycemia or postprandial insulin corrections [24,25]. The modular architecture allowed for sequential testing and clinical deployment of CLC components and provided a structured framework of nodes and conduits for building *network closed-loop systems [25]*.

Key milestones of this development that are directly relevant to the proposed project are outlined in Figure 1 and below, and are also described in our recent *Perspectives in Diabetes* [12]:

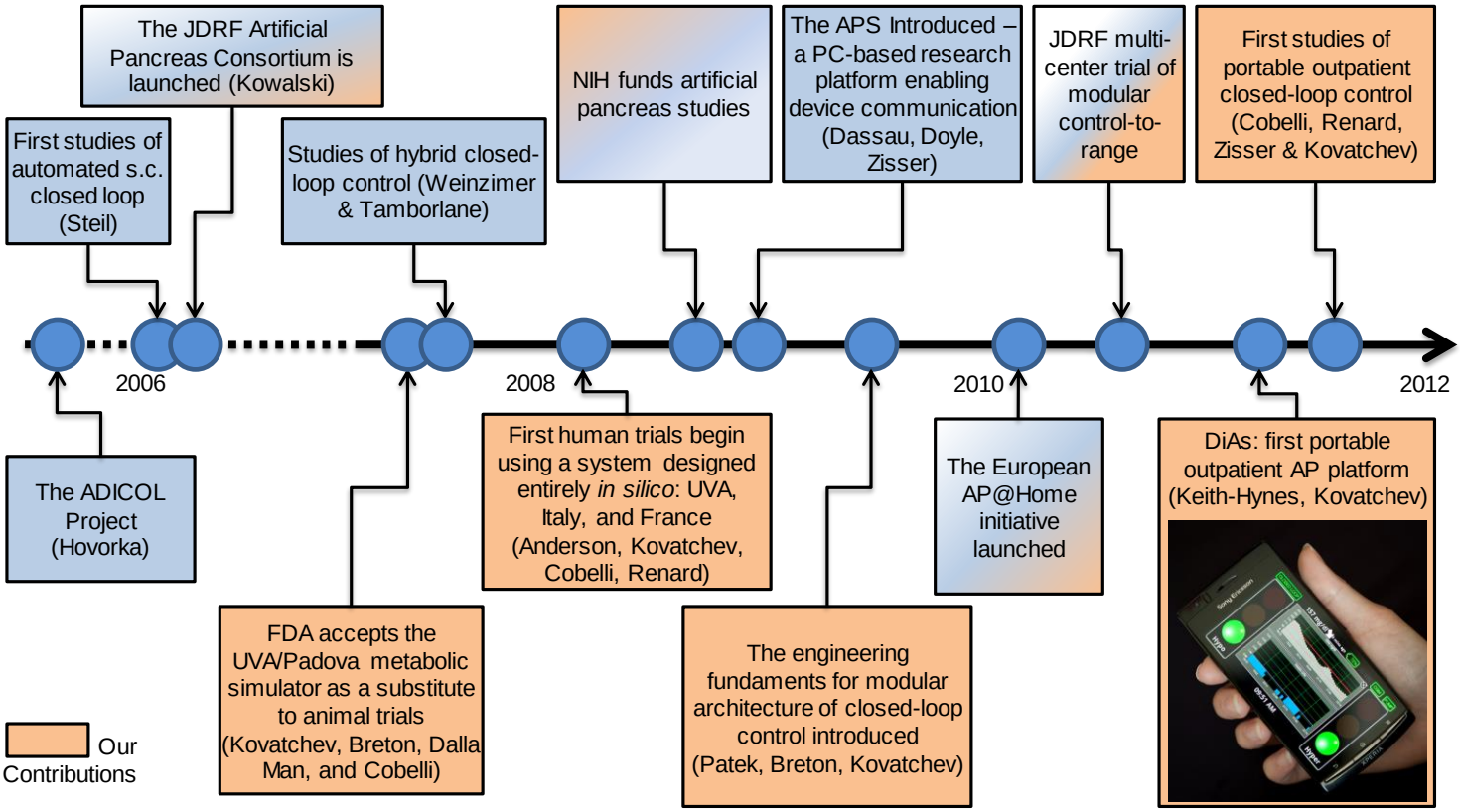


Figure 1: Timeline of the artificial pancreas technology developments in the last decade

1.2. Preliminary Studies

Inpatient Clinical Trials:

Between 2008 and 2011, promising results from inpatient CLC studies were reported by several groups [13-15,16-19,26-28]. Most of these studies pointed out the superiority of CLC over standard CSII therapy in terms of: (i) increased time within target glucose range (typically 70-180 mg/dl); (ii) reduced incidence of hypoglycemia, and (iii) better overnight control. In these early studies, insulin pump commands were entered manually [29]. Automated communication between CGM devices, insulin pumps, and control algorithms was made possible in 2008 when a research platform – the Artificial Pancreas Software (APS) – was introduced [30], enabling fully-integrated closed-loop control, defined as having all of the following three components: (i) automated data transfer from the CGM to the controller: (ii) real-time control action, and (iii) automated command of the insulin pump. In 2012 we published the first randomized cross-over study of fully-integrated CLC. This study enrolled 38 patients with T1D at three centers and tested two different control algorithms achieving noteworthy glycemic control and prevention of hypoglycemia [31].

- **The JDRF Multi-Center Trial of Control-to-Range** began in 2010 and is now completed, with 56 adults and adolescents recruited in 7 centers around the world. While results from this study are forthcoming, two of its elements should be emphasized in the context of this proposal: (i) the CLC algorithm was designed *entirely in silico* and the study received regulatory approval based on *in silico* evaluation using our metabolic simulator [22]; (ii) the control algorithm for this study was *based on our modular architecture* [24,25] and included three interacting control modules: a safety module preventing hypoglycemia [32], a range control module responsible for insulin corrections [24], and an insulin-on-board module safeguarding against insulin stacking [33].

- **The European AP@Home Trial** "Comparison of two artificial pancreas systems for closed loop blood glucose control versus open loop control" used our modular control architecture [24] and safety system

[32] as well. This study was multi-national, recruiting 48 subjects with type 1 diabetes in 6 European countries. Hypoglycemia (% time spent <3.9 mmol/L) was reduced almost threefold during closed loop, both in ITT and PP analyses: 6.4 and 6.3 for OL, vs. 2.05 and 0.45 in CL (overall P=0.001). Percent in euglycemic range stayed constant from 62.7% to 59.2% [34].

These early studies tested prototypes of key algorithmic components that are entering the proposed work, specifically the Safety Supervision Module (SSM) and the Range Control Module (RCM).

STUDIES OF PORTABLE OUTPATIENT ARTIFICIAL PANCREAS:

The CLC transition to ambulatory use began in 2011 with the introduction of the **Diabetes Assistant (DiAs)** – the first portable outpatient artificial pancreas platform. DiAs was developed at the University of Virginia, and its specifications were detailed in two patent applications [35,36]. In October 2011, DiAs was used in two pilot trials of portable outpatient AP done simultaneously in Padova and Montpellier [37]. These 2-day pilot trials enabled a subsequent multi-site feasibility study of ambulatory AP, which was completed recently at UVA, Padova, Montpellier, and at the Sansum Diabetes Research institute (SDRI), Santa Barbara, CA [38]. This study concluded that DiAs is a feasible prototype for a portable outpatient CLC system.

Figure 2: DiAs portability

- **Feasibility of Outpatient CLC** (JDRF-1): Twenty patients with T1D were enrolled at the Universities of Padova, Montpellier, Virginia, and SDRI, Santa Barbara. Each trial continued for 42 hours. The U.S studies were conducted entirely in outpatient setting (e.g. hotel or guest house); studies in Italy and France were hybrid hospital-hotel admissions. A CGM/pump system (Dexcom Seven Plus/Omnipod) was placed on the subject and was connected to DiAs (see Figure 2). The patient operated the system via the DiAs GUI in open-loop mode (first 14h of study), switching to closed-loop for the remaining 28h. Study personnel monitored remotely via 3G or WiFi and were available on site for assistance. The system communications worked properly 97.7% of the time (a total of 807.5h: 274h in open-loop and 533.5h in closed-loop). In open interviews patients indicated overall satisfaction, a professional "look and feel", and user "understandability" of the DiAs GUI. This study demonstrated that a contemporary smart phone is capable of running outpatient CLC and introduced a prototype system (DiAs) for further investigation. The system wearability and convenience of use were confirmed by the study participants [38].
- **Efficacy of Remote Monitoring** (Helmsley-1): In 2012 we performed a study of children with T1D enrolled in a Stanford summer camp, with the objective to test if CGM with remote monitoring using DiAs helps reduce the incidence and duration of severe hypoglycemia (< 50 mg/dL) overnight. Three sessions at two camp sites were performed with N=20 children per session. Children were randomized to a control group wearing CGM

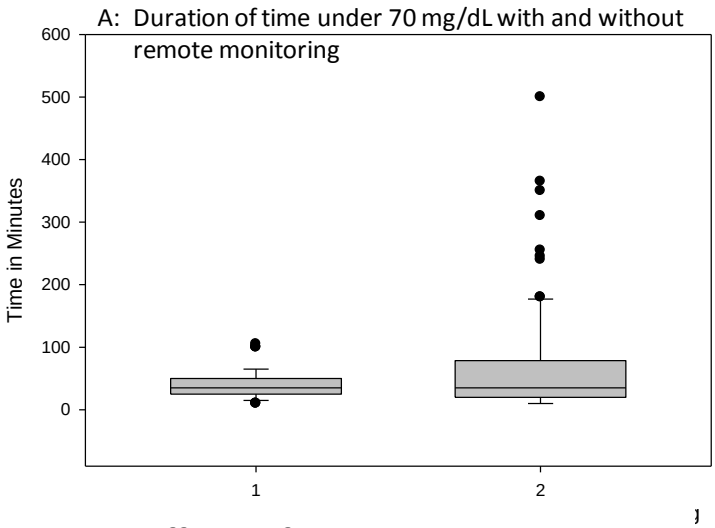


Figure 3: Efficacy of overnight remote monitoring using DiAs as a sensor companion at a summer camp for children with T1D

alone (Dexcom G4), or to G4 connected to DiAs as a "sensor companion" enabling remote monitoring. For the control group, hypoglycemia treatment was based on standard diabetes camp night-time SMBG; for the remote monitoring group, hypoglycemia treatment was initiated at 70 mg/dl observed by staff on the remote monitor. As presented in the figure to the right, remote monitoring reduced significantly the duration of hypoglycemia <70mg/dl and <50mg/dl [39]. Most importantly, the connection between Dexcom G4, DiAs, and the remote monitoring site was very reliable: server logs show that the connection was uninterrupted for 1,314 hours of operation out of 1,360 possible hours, or 97% of the time.

- **Safety of CLC during Exercise** (NIH-1). In 2011-2012 we continued to validate our CLC approach during challenging disturbances such as physical activity. While demonstration of hypoglycemia protection immediately after exercise had been made in [31], hypoglycemia during exercise was reduced by informing the CLC system of exercise (automatically or manually) and modifying the notion of hypoglycemic risk underlying our safety strategy.

Ten type 1 diabetic subjects (3/7 males/ females, weight 68.9±3.1 kg, age 38±3.3 years, HbA1c 6.9±0.2%) participated in a randomized cross-over clinical trial. The CTR algorithm was implemented in the DiAs portable artificial pancreas.

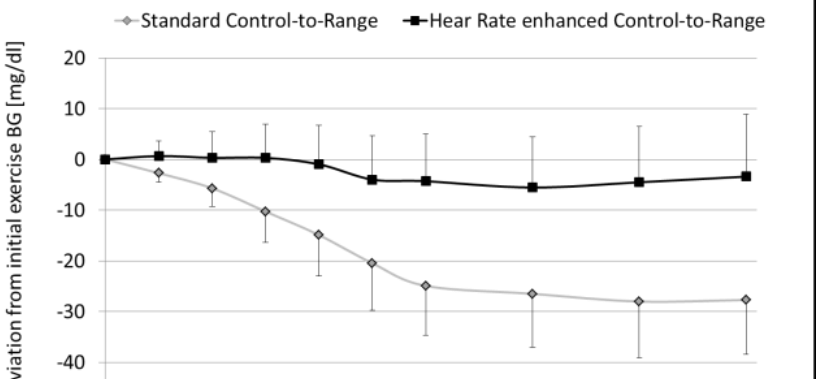


Figure 4: Reduction of exercise induce glycemic drop by EX informed CLC

Informing the CTR algorithm of physical activity reduced significantly the BG decline during exercise (-30mg/dl vs -5mg/dl, p=0.022); indicated marginally lower LBGI (p=0.3) and fewer hypoglycemic events during exercise (0 vs. 2 events, p=0.16), and resulted in overall higher percent time within the target range (81% vs. 75%, p=0.2). LBGI and average BG remained unchanged overall, during recovery, and overnight.

- **Efficacy of Outpatient CLC** (JDRF-2). This was the first randomized cross-over trial of outpatient CLC. This study received FDA approval on November 20, 2012 (IDE #G120210) and was subsequently approved by the regulatory agencies in Italy and France. All clinical trials were initiated shortly thereafter and were completed by the end of May 2013 at the four study sites: UVA, Padova, Montpellier, and UCSB/Sansum.

To achieve its primary objective, this had an unblinded, randomized, cross-over design with each patient participating in two 40-hour outpatient admissions: (a) Experimental involving automated CTR; (b) Control using CGM-augmented insulin pump treatment. Both the Experimental and Control admissions of the study used the DiAs system running in *Closed-Loop* or *Open-Loop* mode, respectively:

- *Closed-Loop Mode:* During the daytime (7:00-23:00) of the Experimental Admission, DiAs ran a CTR algorithm that consisted of the SSM responsible for prevention of hypoglycemia and of the RCM responsible for optimization of glucose control and mitigation of hyperglycemia. In the U.S. trials, during the nighttime (23:00-7:00) of the Experimental Admission, DiAs ran in Safety-Only mode that employed the SSM and turned off active insulin delivery by the RCM. This was required by FDA in order to avoid frequent SMBG overnight and provide the patients with more home-like conditions. In the European studies, the RCM was not turned off overnight.
- *Open-Loop Mode:* During the entire Control Admission, DiAs ran in Open-Loop mode, serving as a CGM receiver and insulin pump PDM but without running any control algorithms.

In both Closed- and Open-loop mode DiAs was controlled by the subject, with assistance from the study personnel as needed. All interactions were handled by the DiAs Graphical User Interface (GUI).

During this study we used the DiAs system for approximately 700 hours in closed-loop control and another 700 hours in open-loop mode. There were no serious adverse events. The results were presented at the 2013 ADA Scientific Sessions (June 23, 2013) [42] and are now in press in *Diabetes Care*. Briefly, intention-to-treat analysis including all available data revealed the following preliminary results:

- Compared to open-loop control, the SSM reduced significantly the frequency of hypoglycemia (BG<70mg/dl) from 2.4 to 1.2 episodes requiring carbohydrate treatment/subject on open- vs. closed loop, p=0.02;
- As originally planned, the effect size of this risk reduction was assessed by the Low BG Index (LBGI) - a risk marker for hypoglycemia. This resulted in effect size of 0.64 (p=0.003). Thus, the primary goal of the study to achieve effect size of 0.4 (see specific aims) has been exceeded.
- The reduction in hypoglycemia was achieved without significant increase in time spent in hyperglycemia and with only a marginal increase of 9 mg/dl in patient's average glucose.

- **Efficacy and safety of overnight closed loop control in adolescent during summer camp.** (Helmsley-2). In 2013, we tested our CLC system to determine the safety and efficacy of an automated, modular control to range system in providing overnight closed-loop (OCL) control in children and adolescents with type 1 diabetes attending diabetes summer camps.

Twenty participants with type 1 diabetes were randomized to either OCL (using DiAs) or sensor-augmented therapy (control conditions) per night over the course of a 5 to 6 day diabetes camp. Subjects completed 54 OCL nights and 52 control nights.

Comparing the groups on an intention to treat basis, the median percent time spent in range, from 70-150 mg/dL, was 62% (29, 87) for OCL nights versus 55% (25, 80) for control, p =0.233. In terms of algorithm performance, on nights during which the system was functional for at least 6 h, the median time spent in range was 73% (51, 90) for OCL versus 55% (26, 79) for control nights, p=0.012. There was less time spent in the hypoglycemic range < 50 mg/dL, < 60 mg/dL and < 70 mg/dL during OCL compared to the control period, p=0.003, p=0.002 and p<0.001, respectively.

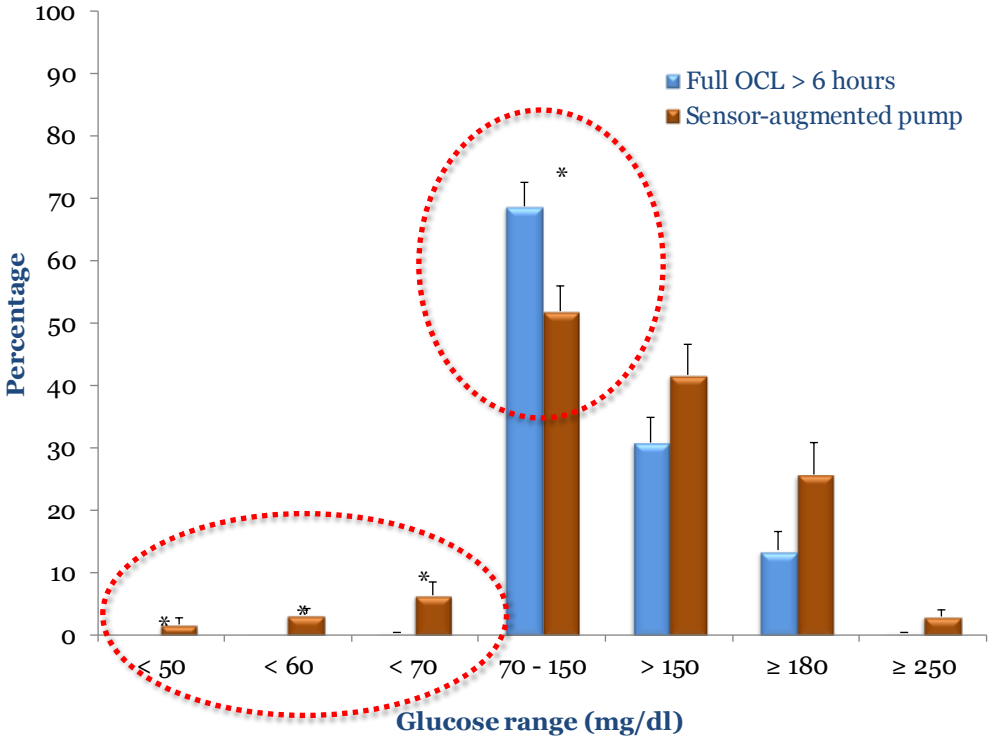


Figure 5: distribution of glycemia during overight closed loop control (blue) vs. sensor augmented pump (red).

This study concluded that the DiAs OCL algorithm (USS Virginia, identical to the algorithm to be used in the proposed work) is effective in improving time spent in range as well as reducing nocturnal hypoglycemia in children and adolescents with T1D in a summer camp setting.

- **Performance of closed loop control following missed meal bolus in adolescents** (UVA-Launchpad)

In 2013 we tested the DiAs system during one of the most common glycemic disturbances (especially in adolescents): missed bolus at meal/snack. We evaluated 16 adolescents 13-18 years old in a randomized cross-over trial of CLC vs. usual care following ingestion of a snack of 30 grams of carbohydrate. No insulin was given following the CHO ingestion. The system showed a clear increase of time spent in safe (and optimal) glycemic range when on CLC, without inducing hypoglycemia (see Figure 6).

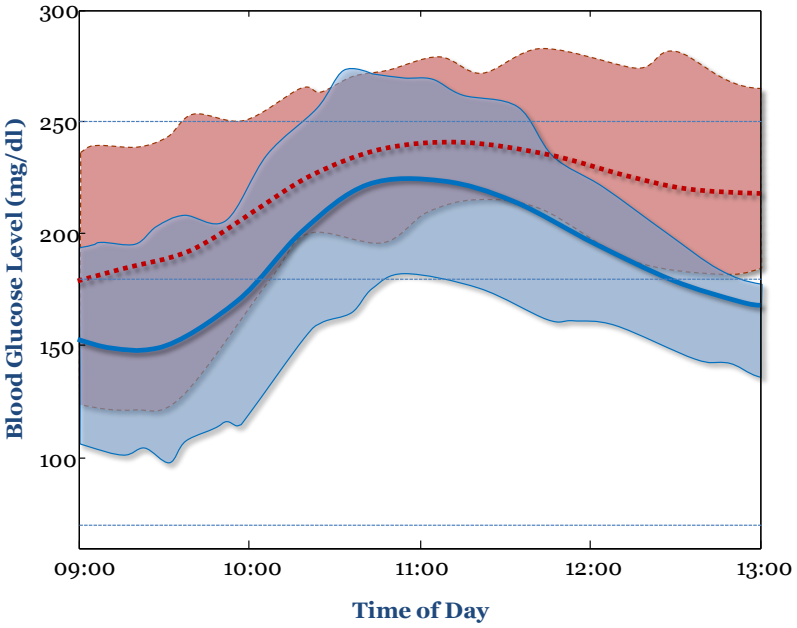


Figure 6: Glycemic excursion (median and quantiles) after uninsulinized 30g CHO intake. CLC is shown in

These results indicate that DiAs equipped with a control algorithm identical to the one in the proposed work, can safely mitigate mismanagement of insulin around meals.

- **Performance of overnight control in adult with T1DM.** (NIH-2)

Continuing to look in the performance of DiAs equipped with our CTR algorithm we ran a study in 10 adults for 5 consecutive days, in hybrid day/night control. The scientific basis for this study was that DiAs equipped with USS Virginia could significantly improve control overnight and "reset" the patients' glycemic control by bringing them in tight control every morning. Participants would then go about their regular day and resume CLC after dinner.

Interim results from the first 10 participants in the study were presented at ATTD 2014 (Vienna, Austria) and showed very significant improvement of the overnight control (~30mg/dl improvement in average glycemia and +25% time spent between 80 and 150mg/dl), and normal glycemia for virtually all patients in the morning (153.8 ± 59.7 mg/dl vs. 118.5 ± 22.6 mg/dl, $p<0.0001$). These improvements in glycemic control were further enhanced by reduction in hypoglycemia - see Figure 7.

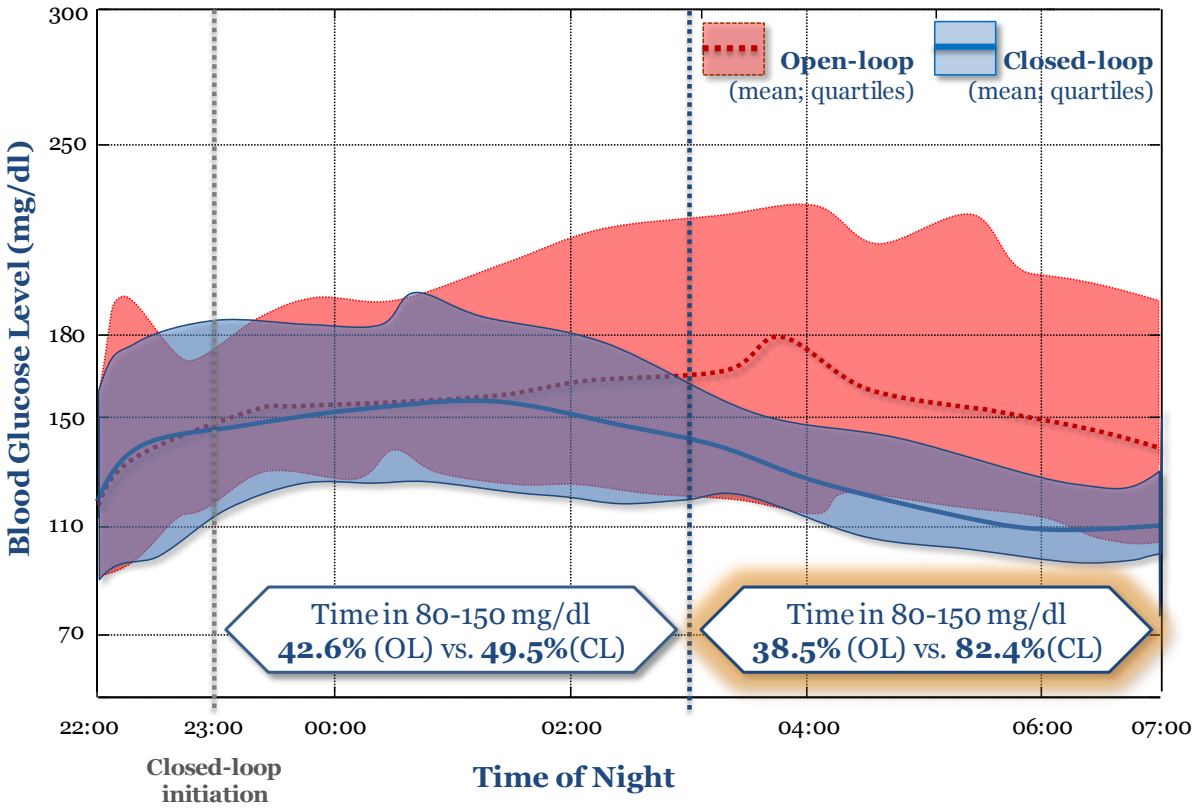


Figure 7: Glycemic excursion (median and quantiles) overnight. CLC is shown in blue, sensor augmented pump in red

The Table below summarizes the main outcomes of this study:

	Sensor-Augmented Pump	Closed-Loop Control	P-value
Average Blood Glucose at 7AM	153.8	118.5	<0.001
Average Blood Glucose (mg/dl)	167.7	139.2	0.004
Percent time within 70-180mg/dl	60.0%	84.5%	0.002
Percent time below 70mg/dl	2.14%	0.61%	0.06

In addition, overnight glucose control correlated with glucose control during the next day, r=0.4, p=0.08. Peak glucose and glucose variability during the day (DiAs inactive) were improved after CLC nights: Peak glucose of 217mg/dl vs. 236mg/dl; Standard deviation of BG of 35.2 vs. 41.6 mg/dl during the days following closed-loop vs. the days following open-loop nights.

These results confirm the glycemic benefits associated with use of DiAs overnight, and indicate potential improvements of control during the day due to improved glycemia during the preceding night. The system used in Study NIH-2 is identical to the system that will be used in the proposed work.

In conclusion, the data collected during over 3,500 hours of outpatient DiAs use in open-loop, closed-loop, and sensor-alone modes in adults and children with type 1 diabetes will be used to fine-tune the control system, to power this planned trial, and to obtain regulatory approval for the transition of the DiAs CTR system to longer-term studies at home.

1.3. Considerations in Protocol Development

The ultimate goal of the JDRF artificial pancreas project is the development of a commercially available artificial pancreas. As part of the development effort, clinical trials are needed to address a number of issues that are of critical importance to achieving JDRF's ultimate goal. Algorithm development, a particularly important aspect of "closing the loop", has proceeded to the point that a system can now be tested. Prior to utilizing a closed-loop system in a large trial in an outpatient setting, it is necessary to evaluate the system in a small pilot outpatient study to demonstrate that patients are not being subjected to an unreasonable risk of illness or injury.

1.4. Study Objective

The purpose of this pilot study is to establish that safe day-and-night use of a control-to-range automated insulin management system using continuous glucose monitoring (CGM) and subcutaneous insulin pump infusion in individuals with type 1 diabetes in the home environment is achievable, and to collect efficacy data to help inform a larger clinical trial.

1.5. Closed-Loop Control System

The devices that will be used in the Closed-Loop Control System (Figure 8) are standardized across all study sites and include the following components:

- DiAs – a smart-phone medical platform;
- Dexcom Share AP Continuous Glucose Monitor connected to DiAs via wireless ANT+ connection; or Dexcom G4 Platinum connected to DiAs via CGM receiver and USB-Bluetooth relay hardware;
- Roche Accu-Chek insulin pump connected to DiAs via wireless Bluetooth;
- Remote Monitoring Server connected to DiAs via 3G or local Wi-Fi network, and
- Modular Closed-Loop Control Algorithm Running on DiAs, which is of Control-to-Range (CTR) class

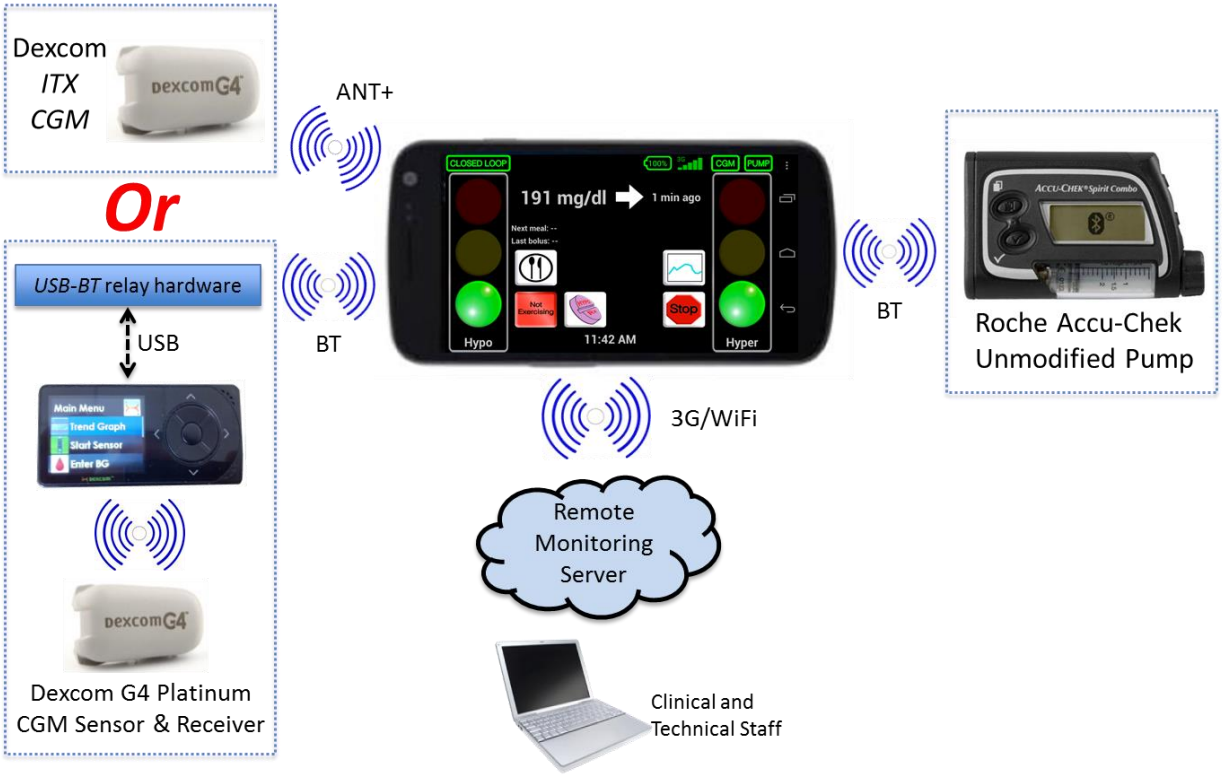


Figure 8: Schematic showing the components of the closed-loop system

Synopsis of Study Protocol

Major Eligibility Criteria

- Clinical diagnosis of type 1 diabetes
- Use of insulin for at least 12 months
- Use of an insulin infusion pump for at least 6 months
- Age ≥18 to <70 years old
- HbA1c <10.0%; if HbA1c <6.0% then total daily insulin must be ≥0.5 U/kg
- No hospital admissions for DKA in last 12 months
- No hypoglycemic seizure or loss of consciousness in last 12 months
- Hypoglycemia awareness as demonstrated by a Clarke Hypoglycemia Awareness score of 2 or lower
- Access to internet and cell phone service at home, and a computer for downloading device data
- Living with a significant other or family member ("companion") committed to participating in all training activities, knowledgeable at all times of the participants location, and being present and available to provide assistance when the system is being used at night
- Commitment to maintaining uninterrupted availability via cell phone and avoiding any overnight travel for the duration of each two-week period using the closed-loop system

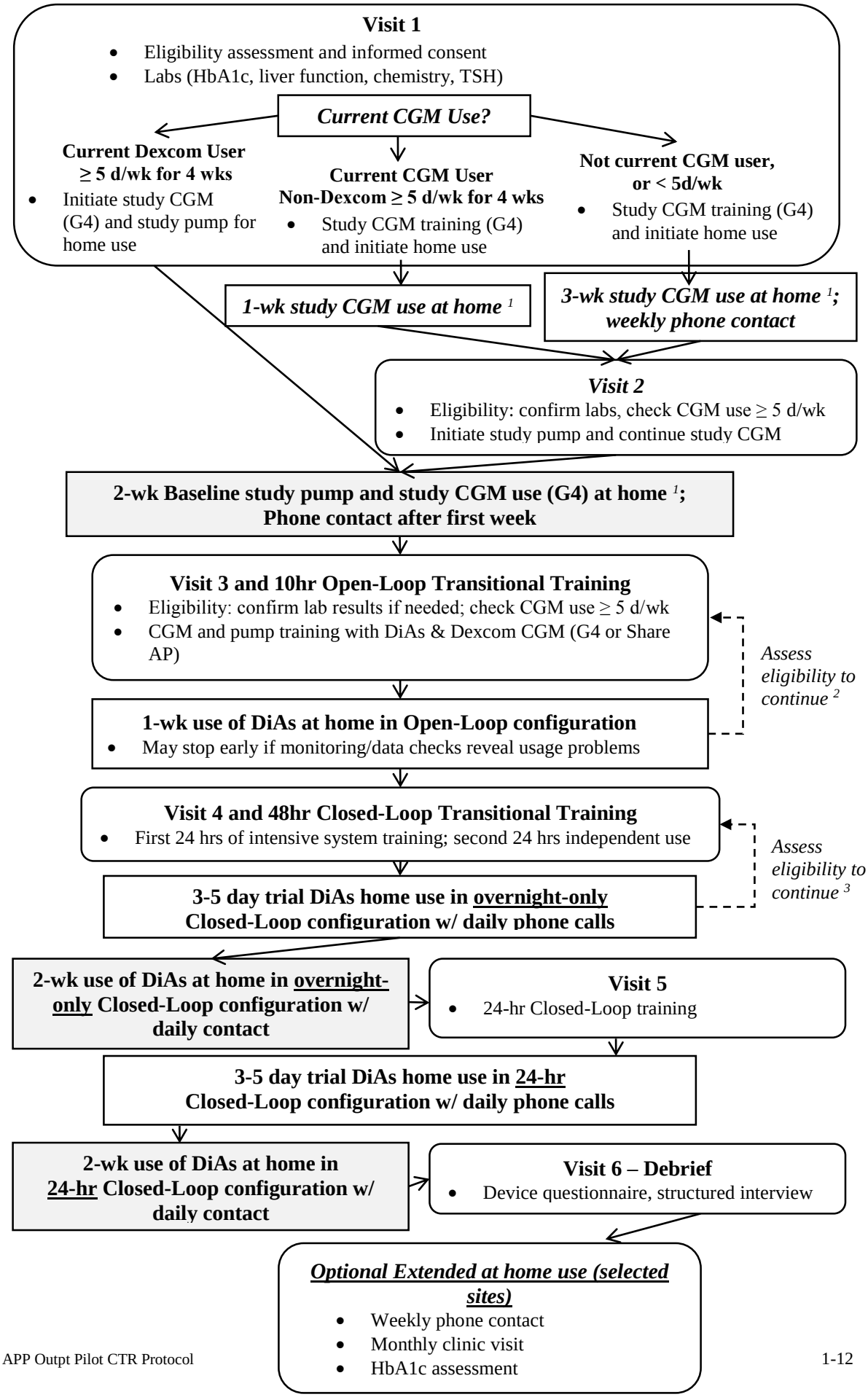
Sample Size

Up to 60 adult subjects age ≥18 to <70 years old so that 30 subjects complete the entire study at six clinical sites in the United States and Europe.

Protocol Summary

Subject participation will last roughly 11-14 weeks depending on the subject's current CGM use as detailed in Figure 9 below: 0-3 weeks of home use of the study CGM, 2 weeks of baseline home use of the study pump and study CGM together; a 1-day admission for open-loop transitional training of study subject and companion with the full system, 1 week of open-loop home use of the system, a 2-day admission for closed-loop transitional training of study subject and companion, 3-5 days plus 2 weeks of home use of the system in nocturnal-only closed-loop configuration, and finally 3-5 days plus 2 weeks of home use of the system in 24-hour closed-loop configuration. Subjects at selected centers meeting the criteria listed in Section 3.13 will have the option to continue home use of the system in 24-hour closed-loop configuration for up to 6 months. The purpose of the extended wear is to collect safety data related to prolonged use of the system. During this time, clinic visits will be monthly and phone contacts will occur each week that there is not a clinic visit.

Figure 9: Study flow diagram


Visit 1
Eligibility assessment and informed consent
Labs (HbA1c, liver function, chemistry, TSH)
Current CGM Use?
Current Dexcom User ≥ 5 d/wk for 4 wks
Initiate study CGM (G4) and study pump for home use
Current CGM User Non-Dexcom ≥ 5 d/wk for 4 wks
Study CGM training (G4) and initiate home use
Not current CGM user, or < 5d/wk
Study CGM training (G4) and initiate home use
1-wk study CGM use at home [1]
3-wk study CGM use at home [1]; weekly phone contact
Visit 2
Eligibility: confirm labs, check CGM use ≥ 5 d/wk
Initiate study pump and continue study CGM
2-wk Baseline study pump and study CGM use (G4) at home [1]; Phone contact after first week
Visit 3 and 10hr Open-Loop Transitional Training
Eligibility: confirm lab results if needed; check CGM use ≥ 5 d/wk
CGM and pump training with DiAs & Dexcom CGM (G4 or Share AP)
Assess eligibility to continue [2]
1-wk use of DiAs at home in Open-Loop configuration
May stop early if monitoring/data checks reveal usage problems
Visit 4 and 48hr Closed-Loop Transitional Training
First 24 hrs of intensive system training; second 24 hrs independent use
Assess eligibility to continue [3]
3-5 day trial DiAs home use in overnight-only Closed-Loop configuration w/ daily phone calls
2-wk use of DiAs at home in overnight-only Closed-Loop configuration w/ daily contact
Visit 5
24-hr Closed-Loop training
3-5 day trial DiAs home use in 24-hr Closed-Loop configuration w/ daily phone calls
2-wk use of DiAs at home in 24-hr Closed-Loop configuration w/ daily contact
Visit 6 – Debrief
Device questionnaire, structured interview
Optional Extended at home use (selected sites)
Weekly phone contact
Monthly clinic visit
HbA1c assessment

[1] Subjects who failed to use the study CGM for at least 5 days/week during their home use period but are otherwise eligible to continue in the study may perform one additional 1-week home use run-in at investigator discretion.
[2] ≥80% open-loop system use and deemed adequately trained by staff; if needed, may repeat Visit 2 and home use period one time
[3] Deemed adequately trained by staff; may repeat portions of Visit 3 with clinicians one time, if needed

1.6. General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

Data will be directly collected in electronic case report forms, which will be considered the source data.

There is no restriction on the number of subjects to be enrolled by each site towards the overall recruitment goal.

A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

The protocol is considered a significant risk device study, due to the fact that the closed loop system is experimental. Therefore, an IDE from the FDA is required to conduct the study.

CHAPTER 2: SUBJECT ENROLLMENT AND STUDY INITIATION

2.1. Study Population

Enrollment will proceed with the goal of 30 total subjects ≥18 to <70 years old completing the Main Study protocol. A maximum of 60 subjects may be enrolled in the study in order to achieve the goal of Main Study protocol completion by 30 subjects. A recruitment goal will be to enroll 8 or more subjects who are 18-25 years old.

2.2. Eligibility and Exclusion Criteria

2.2.1. Eligibility

To be eligible for the study, a subject must meet the following criteria:

1) Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year and an insulin pump for at least 6 months
2) Age ≥18 to <70 years
3) HbA1c <10.0%; if HbA1c <6.0% then total daily insulin must be ≥0.5 U/kg
4) For females, not currently known to be pregnant
   If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative urine pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study.
5) Demonstration of proper mental status and cognition for the study
6) Currently using insulin-to-carbohydrate ratio to calculate meal bolus sizes
7) Hypoglycemia awareness as demonstrated by a Clarke Hypoglycemia Awareness score of 2 or lower
8) Access to internet and cell phone service at home, and a computer for downloading device data
9) Living with significant other or family member committed to participating in all training activities, knowledgeable at all times of the participant's location, and being present and available to provide assistance when system is being used at night
10) Commitment to maintaining uninterrupted availability via cell phone and avoiding any overnight travel for the duration of each two-week period using the closed-loop system
11) An understanding of and willingness to follow the protocol and sign the informed consent

2.2.2. Exclusion

The presence of any of the following is an exclusion for the study:

1) Admission for diabetic ketoacidosis in the 12 months prior to enrollment
2) Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment
3) History of a seizure disorder (except hypoglycemic seizure), unless written clearance is received from a neurologist
4) Coronary artery disease or heart failure, unless written clearance is received from a cardiologist
5) History of cardiac arrhythmia (except for benign premature atrial contractions and benign premature ventricular contractions which are permitted)
6) Cystic fibrosis
7) A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
   - Inpatient psychiatric treatment in the past 6 months for either the subject or the subject's primary care giver (i.e., parent or guardian)

- Presence of a known adrenal disorder
- Abnormal liver function test results (Transaminase >2 times the upper limit of normal); testing required for subjects taking medications known to affect liver function or with diseases known to affect liver function
- Abnormal renal function test results (calculated GFR <60 mL/min/1.73m2); testing required for subjects with diabetes duration of greater than 5 years post onset of puberty
- Active gastroparesis
- If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, lack of stability on the medication for the past 2 months prior to enrollment in the study
- Uncontrolled thyroid disease (TSH undetectable or >10 mlU/L); testing required within three months prior to admission for subjects with a goiter, positive antibodies, or who are on thyroid hormone replacement, and within one year otherwise
- Abuse of alcohol or recreational drugs
- Infectious process not anticipated to resolve prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis)

8) A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication or disease in the judgment of the investigator will affect the completion of the protocol

9) Current use of the following drugs and supplements:
   - Acetaminophen
   - Any medication being taken to lower blood glucose, such as Pramlintide, Metformin, GLP-1 Analogs such as Liraglutide, and nutraceuticals intended to lower blood glucose
   - Beta blockers
   - Oral or injectable glucocorticoids
   - Any other medication that the investigator believes is a contraindication to the subject's participation

2.3. Eligibility Assessment and Baseline Data Collection

Potential subjects will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel and local laboratory testing if needed to screen for exclusionary medical conditions. Subject exclusion will be at the discretion of the investigator based on study inclusion/exclusion criteria and lab results.

2.3.1. Historical Information and Physical Exam

A history will be elicited from the subject and extracted from available medical records with regard to the subject's diabetes history, current diabetes management, other past and current medical problems, past and current medications, and drug allergies. A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant).

For eligible subjects, the study will be discussed with the subject. The subject will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. If the subject agrees to participate, the Informed Consent Form will be signed. A copy of the consent form will be provided to the subject and another copy will be added to the subject's clinic chart.

Written informed consent must be obtained from the subject prior to performing any study-specific procedures that are not part of the subject's routine care.

2.3.2. HbA1c

HbA1c level will be measured at baseline using the method utilized by the clinic as part of patient care: DCA2000 or equivalent NGSP-certified point-of-care method or local laboratory. HbA1c measurements performed as part of usual clinical care within 2 weeks prior to obtaining informed consent for participation in the trial may be used.

2.4. Authorization Procedures

As part of the informed consent process, each subject will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review what study specific information will be collected and to whom that information will be disclosed. After speaking with the subject, questions will be answered about the details regarding authorization.

CHAPTER 3: STUDY PROTOCOL

3.1. Visit 1 – Screening and Study CGM/Pump Training Visit

At the Screening Visit the following procedures will be performed / criteria will be checked and documented:

- Signed and dated informed consent
- HbA1c assessment via fingerstick and DCA2000 or equivalent NGSP-certified point-of-care method (value within 2 weeks prior to enrollment acceptable)
- Inclusion and exclusion criteria
- Demographics (date of birth, gender, race and ethnicity)
- Diabetic history
- Medical history
- Substance use history (drinking, smoking, and drug habits)
- Concomitant medications
- Physical examination
- Weight, height
- Vital signs including oral temperature and orthostatic measurement of blood pressure and pulse
- Urine pregnancy test for all premenopausal women who are not surgically sterile
- Blood draw for:
    - Chemistry panel for subjects with diabetes duration of greater than 5 years post onset of puberty (values within 3 months prior to enrollment acceptable).
    - Liver function tests in subjects taking medications known to affect liver function or diseases known to affect liver function (values within 3 months prior to enrollment acceptable).
    - TSH within 3 months for subject with a goiter, positive antibodies, or who are on thyroid hormone replacement. A normal TSH within the past year is otherwise acceptable.
    - C-peptide level (non-fasting is acceptable)
- Clarke Hypoglycemia Awareness questionnaire
- Subjects will be provided with a study blood glucose meter, test strips, and standard control solution to perform quality control (QC) testing at home per manufacturer guidelines. All study blood glucose meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The subject will be instructed to perform quality control testing of the BG meter at home at least once every seven days, and to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails the testing. Subjects will be required to perform SMBG measurements at minimum 7 times daily (before meals, about 2 hours after meals and at bedtime) throughout the study. Subjects will be reminded to use the same study glucometer for all finger sticks and calibrations and to only use SMBG values (not CGM values) to guide treatment decisions.
- In addition to the BG meter, subjects will receive a Study Emergency Kit for the treatment of low or high blood glucose. Subjects will also be provided with a study blood ketone meter, test strips, and standard control solution to perform quality control (QC) testing at home per

manufacturer guidelines. All study blood ketone meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The subject will be instructed to perform quality control testing of the ketone meter at home at least once every seven days, and to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails the testing. Subjects will be instructed to perform blood ketone testing as described in Section 4.4.4.

- Current CGM use will be evaluated, with data download of any CGM currently in use. Eligible subjects will receive study CGM (Dexcom G4) training and take one of three paths forward in the study:
    - Dexcom CGM users with ≥5 days/week use over past 4 weeks
      These subjects will not require any further CGM run-in and will move directly to Visit 2 (below) concurrent with Visit 1.
    - Non-Dexcom CGM users with ≥5 days/week use over past 4 weeks
      These subjects will be given study CGM (G4) supplies and move into a 1-week home use period with the study CGM to confirm the ability to use the CGM successfully.
    - CGM non-users or current CGM users with <5 days/week use over past 4 weeks
      These subjects will be given study CGM (G4) supplies and move into a 3-week home use period with the study CGM to confirm the ability to use the CGM successfully and to help establish baseline glycemic control during frequent CGM use. Subjects will be contacted weekly by study staff to review CGM data and diabetes management.

The total amount of blood to be withdrawn during this screening visit is ~6 cc. The visit will last approximately 2-4 hours.

3.2. Visit 2 – Study Pump Training and Initiation

Subjects with ≥5 days/week Dexcom CGM use during 4 weeks prior to Enrollment

Visit 2 will be completed concurrently with Visit 1.

Subjects without ≥5 days/week Dexcom CGM use during 4 weeks prior to Enrollment

Visit 2 will occur following the 1- or 3-week CGM home run-in period described above. A urine pregnancy test will be repeated for all premenopausal women who are not surgically sterile. The study CGM will be downloaded to determine whether the subject wore the CGM for at least 5 days/week during the home use period.

Eligibility will be reassessed incorporating any screening lab results available from Visit 1 in addition to CGM use. Subjects who failed to use the study CGM for at least 5 days/week during their home use period but are otherwise eligible to continue in the study may perform one additional 1-week home use run-in at investigator discretion and then repeat Visit 2.

All Eligible Subjects

Eligible subjects will receive study pump training, and will begin a 2-week baseline home use period with the study pump and the study CGM (G4). Subjects will be contacted after the first week at home to review and discuss diabetes management.

Pump training will include:

- The subject and the care partner will be fully instructed on the study insulin pump. A qualified staff member will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board and correction boluses. Additional topics not be limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, changing batteries, navigation through menus, bolus procedures including stopping a bolus, pairing procedures with the meter remote, etc.
- The study team will assist the subject in study pump infusion site initiation and will start the subject on the study pump. The study pump will be programmed with the subject's usual basal rates and pump parameters. The subject's personal pump will be removed.
- The subject will be supervised with the study pump during at least one meal or snack bolus to ensure subject understanding of the pump features.
- The subject may eat meals and bolus for the meals using the study pump per the home routine.
- The subject and diabetes care partner will be encouraged to review the literature provided with the pump, infusion sets, and meter remote after the training is completed.

3.3. Home Use with Study Pump and Study CGM

Eligible subjects will complete a 2-week home use period with the study pump and study CGM (G4) to establish baseline glycemic control with CGM-augmented pump therapy and to familiarize the subjects with the study pump. Subjects who fail to use the study CGM for at least 5 days/week during this period will be ineligible to continue in the study. At investigator discretion, this phase can be repeated once.

3.4. Visit 3 – 10-hour Open-Loop Transitional Training Visit

Visit 3 will consist of a ~10 hour training session in a transitional setting at a hotel or clinic during which the subject and companion will be trained to use the DiAs to control the study pump, including meal announcement, meal bolusing, exercise, and switching back and forth between Pump (open-loop) mode and Stopped mode. A urine pregnancy test will be collected for all premenopausal women who are not surgically sterile.

Prior to initial use, the DiAs system will be initialized by a study team member with each subject's individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern.

Study team members will train the subject and companion in performing specific tasks including the following:

- The study team will confirm the pump parameters entered in the system with the study physician.
- How to switch the system between Pump mode (open-loop, preprogrammed basal insulin delivery) and Stopped mode depending on circumstances.
- How to calibrate the CGM unit during the study.

- How to access the CGM trace from the primary sensor via a CGM button on the DiAs user interface.
- How to activate the meal screen of the DiAs system any time insulin will be given with a meal or any time additional correction insulin is desired.
- How to inform the system of hypoglycemia treatment via a hypoglycemia treatment button on the DiAs user interface after each ~16 grams of glucose is consumed.
- What to do when exercising while using the system (subject will participate in light exercise). The exertion level will not exceed what the subject is accustomed to during daily living.
- How to perform blood ketone testing and perform rescue therapy actions with the glucagon kit
- The subject and companion will be assessed for understanding of the system interface and how to react to safety/alert messages.
- The subject and companion will be given a printed User Guide as a reference.

The subject must be able to complete system-related tasks independently to be eligible to continue in the study. Eligible subjects will receive sufficient device supplies to use the DiAs at home for one week.

3.5. Home Use with DiAs System in Open-Loop Configuration

Eligible subjects will complete a 1-week home use period with the full DiAs system in open-loop configuration. During this home use period, closed-loop operation will be disabled so that the subject cannot inadvertently switch into closed-loop mode. Remote monitoring will be available during this period for the purposes of data collection and ad hoc assessment of system performance by study clinicians or engineers. However, automated safety monitoring will be inactive.

Subjects who fail to use the system for more than 80% of the time during this phase will be ineligible to continue in the study. At investigator discretion, this phase can be repeated once.

Subjects eligible to continue in the study will be instructed to insert a CGM sensor 1-5 days prior to the Closed-Loop Transitional Training visit so that the system can be tested with sensors in various stages of use.

3.6. Visit 4 – Closed-Loop Transitional Training Visit

Visit 4 will consist of a ~48 hour Training and System Assessment session in a transitional setting at a hotel or clinic during which the subject and companion will be trained to run the study system and all of its components and modes, including closed-loop operation.

A urine pregnancy test will be collected for all premenopausal women who are not surgically sterile.

Each of the two 24-hour periods will include a similar series of system challenges using the different operational modes of the study system. The subject will be encouraged to maintain his or her usual sleep schedule during these overnight admissions. During the first half of the admission, study staff will be immediately present for training and to respond to system issues. During the last half of the admission, study staff will be nearby and available, but will not immediately assist the subject in completing the described training tasks or responding to system issues (unless the study is stopped due to a problem that is unable to be resolved by the subject).

Prior to closed-loop use, the DiAs system will be initialized by a study team member with each subject's individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern.

Study team members will train the subject and significant other or family member ("companion") in performing specific tasks including the following:

- The study team will confirm with the subject the pump parameters entered in the system with the study physician.
- The subject and companion will be instructed how to switch between Closed-Loop mode, Pump mode (open-loop, preprogrammed basal insulin delivery), Safety mode, and Stopped mode depending on circumstances.
- The study team, the subject, and the companion will review the training for all tasks learned during the Open-Loop Transitional Training visit regarding use of the DiAs during exercise, to monitor the CGM, to record calibrations, deliver boluses, record hypoglycemia treatments, and respond to messages and alarms.
- The subject and companion will be re-educated as needed throughout the first 24-hour period and will be given a printed User Guide as a reference.

At the end of the visit, eligible subjects will receive sufficient device supplies to use the DiAs at home for three weeks.

3.7. Overnight-Only Closed-Loop Home Use Trial Period

After successful 48-hour Transitional Training, the subject will initiate a 3-5 day trial period of home use of the system in overnight-only closed-loop configuration during which remote monitoring will be in place. The subject will be instructed to activate closed-loop operation each evening any time between just before eating dinner and prior to bedtime, with the expectation that the subject will remain at home after initiating closed-loop operation. The subject will be instructed to switch back to open-loop mode upon waking up in the morning.

While using the closed-loop system, the subject will be instructed to avoid deviating from his/her regular daily routine in regards to diet and exercise and to maintain his or her usual sleep schedule during the course of the study. The subject will specifically be asked to avoid consuming more than 3 alcoholic drinks in any one day. The subject will be instructed to perform a fingerstick BG at least 7 times daily (before meals, about 2 hours after meals and at bedtime). The subject will also be instructed to avoid use of closed-loop mode during periods of illness with an elevated temperature >101.5 degrees Fahrenheit, periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reactions or asthma attack in addition to use of oral or injectable glucocorticoids.

After each night of closed-loop use, clinical staff will assess the subject's system use via a review of the subject's data from the previous day and a telephone interview. The study team will determine whether the subject used the system in the appropriate mode at least 80% of the time during the day and night and will assess a variety of other criteria that characterize successful operation of the system.

Subjects who meet the success criteria on three days in a period of up to five days are eligible, at the discretion of the investigator, to continue to the next phase of the study.

Subjects who do not meet the success criteria on three nights in a period of up to five days may, at the discretion of the investigator, repeat part or all of the Visit 3 closed-loop transitional training and then repeat the 3-5 day overnight-only closed-loop home use trial period one time.

3.8. Two-Week Overnight-Only Closed-Loop Home Use Period

Eligible subjects will use the DiAs system at home in overnight-only closed-loop configuration every day for two weeks with daily contact with clinical staff. Remote monitoring will be in place. If a subject is unable to use the system on one or more days due to illness or other factors, the use period may be extended at investigator discretion to obtain 14 total days of system use.

3.9. Visit 5 – Debrief Following Overnight-Only Closed-Loop Home Use

After completion of two weeks of overnight-only closed-loop home use, subjects will return to the clinic for Visit 5.

A urine pregnancy test will be collected for all premenopausal women who are not surgically sterile. Eligible subjects will receive sufficient device supplies to use the DiAs at home for an additional three weeks.

3.10. Day-and-Night Closed-Loop Home Use Trial Period

The subject will initiate a 3-5 day trial period of home use of the system in 24-hour closed-loop configuration during which remote monitoring will be in place. The subject will be instructed to use the system in a closed-loop mode except when no calibrated CGM sensor is available. The subject will be instructed to perform a fingerstick and switch the system to Safety Mode prior to exercising or engaging in potentially dangerous activities such as operating a motor vehicle or operating heavy machinery. When exercising, the subject will be instructed to limit activity to no more than one hour at no more than a moderate level of intensity.

The subject will be reminded about the closed-loop use guidelines in section 3.7 above relating to diet, sleep, exercise, alcohol use, fingerstick testing, epinephrine use, glucocorticoid use, and illness.

After each day of system use, clinical staff will assess the subject's system use via a review of the subject's data from the previous day and a telephone interview. The criteria in section 3.7 will be used to characterize successful operation of the system.

Subjects who meet each of the success criteria on three days in a period of up to five days are eligible, at the discretion of the investigator, to continue to the next phase of the study.

3.11. Two-Week Day-and-Night Closed-Loop Home Use Period

Eligible subjects will use the DiAs system at home in 24-hour closed-loop configuration every day for two weeks with daily contact with study staff. Remote monitoring will be in place. If a subject is unable to use the system on one or more days due to illness or other factors, the use period may be extended at investigator discretion to obtain 14 total days of system use.

3.12. Visit 6 – Debrief Following Day-and-Night Closed-Loop Home Use

After completion of two weeks of day-and-night closed-loop home use, subjects will return to the clinic for Visit 6. Subjects will participate in a structured interview including a DiAs-specific usability questionnaire to share their experience with the DiAs system and give their recommendations for system improvement and complete the Clarke Hypoglycemia Awareness questionnaire. All study supplies will be returned to the study team.

3.13. Optional – Extended Day-and-Night Closed-Loop Home Use

At selected sites (based on subject eligibility and availability), approximately 10-20 subjects who exhibit safe and competent use of the system at home based on the criteria below will be given the option to continue home use of the system in Day-and-Night Closed-Loop mode for up to 5 months:

- Did not experience severe hypoglycemia or hyperglycemia/DKA (not associated with infusion set failure) as defined in Section 5.1
- Did not develop >1.0 mmol/L ketones on 3 or more study days in the one-month period between clinic visits due to prolonged periods of inadequate insulin delivery
- Study staff were able to contact the subject or the care partner without difficulty and in a timely manner when the DiAs was in use
- The subject used the system appropriately including the following:
  - Responded to system alarms and treated hypo- and hyperglycemia appropriately
  - Avoided deviating from his/her regular daily routine in regard to diet and exercise and maintained his or her usual sleep schedule
  - Avoided consuming more than 3 alcoholic drinks in any one day
  - Performed a fingerstick BG at least 7 times daily (before meals, about 2 hours after meals and at bedtime) and/or appropriate fingerstick BG testing by investigator discretion
  - Avoided use of closed-loop mode during periods of illness with an elevated temperature >101.5 degrees Fahrenheit, periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reaction or asthma attack in addition to use of oral or injectable glucocorticoids
- If female and sexually active, subject agrees to continue to use a birth control method to prevent pregnancy while a participant in the study and understands that the use of a "highly effective" birth control method[1] is the best way to avoid accidental pregnancy during the extended 5-month participation period.

[1] *Highly effective birth control methods are those that can achieve a failure rate less than 1% per year when used consistently and correctly and include:*

- *Combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
- *Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*
- *Intrauterine device (IUD)*
- *Intrauterine hormone-releasing system (IUS)*
- *Bilateral tubal occlusion*
- *Vasectomised partner*
- *Sexual abstinence*

- Study staff confirms that subject continues to meet additional eligibility criteria that were assessed when subject was initially enrolled in the study.

During the first 2-week period of the extension, subjects and care partners will be contacted twice weekly and then once weekly during weeks without a clinic visit. Weekly educational reminders regarding proper use of the study system will be incorporated. Subjects will return monthly for a follow-up clinic visit and subject's data and system use will be assessed. Continued participation will be dependent on the subject's continuing to fulfill the criteria above. The same remote monitoring plan described in protocol Section 4.4.8 will apply.

If the participant or care partner needs to travel during the 5 month home use period or deviate from restrictions imposed during closed-loop use (e.g. fasting required for religious reasons, holiday meal anticipated to exceed normal eating habits, weekend hiking trip anticipated to exceed 1 hour of exercise, etc.), the subject will switch to usual home care (open loop therapy) during that time and resume closed-loop therapy upon return.

After completion of the 5-month home use period, subjects will return to the clinic for a final visit. An HbA1c sample will be collected (value within 2 weeks prior to the final visit is acceptable). Subjects will also be asked to complete DiAs-specific usability questionnaire to share their experience with the DiAs system and give their recommendations for system improvement and complete the Clarke Hypoglycemia Awareness questionnaire. All study supplies will be returned to the study team.

CHAPTER 4: CLOSED-LOOP CONTROL SYSTEM OPERATION AND SAFETY

4.1. Algorithm Details

The control system consists of several modules (**Figure 10**) with different functions adapted to different activities during the day and night:

- Module 1 –Safety Supervision (SSM) responsible for prevention of hypoglycemia. This is a passive safety module that can only attenuate insulin delivery. This module is active at all times;
- Module 2 – IOB Constraint responsible for prevention of insulin overdose. This is a passive safety module that only tracks insulin on board and provides the information to the safety system. This module is active at all times;
- Module 3 -- Basal Rate (BRM) responsible for augmentation of basal rate up to a total of 3X basal, to compensate for changes in insulin sensitivity (e.g. dawn phenomenon). This module is active at all times;
- Module 4 – Range Control (RCM) is responsible for postprandial correction insulin administered as needed. This module is active during the day when the controller is configured for 24-hour closed-loop operation and is inactive at all times when the controller is configured for overnight-only closed-loop operation.

In addition, the system includes a sophisticated meal bolus calculator that takes into account the current glucose state of the subject and available insulin to make a recommendation for a pre-meal bolus. The recommendation must be confirmed before delivery; if not confirmed, pre-meal insulin is not delivered automatically. The bolus calculator is activated on demand by the user, prior to meals.

By default, the transitions between daytime and nighttime control will be scheduled for 23:00 and 7:00 when the system is configured for 24-hour closed-loop operation. However, these time points are selectable during system setup and can be changed by the user to adapt to their individual regimen.

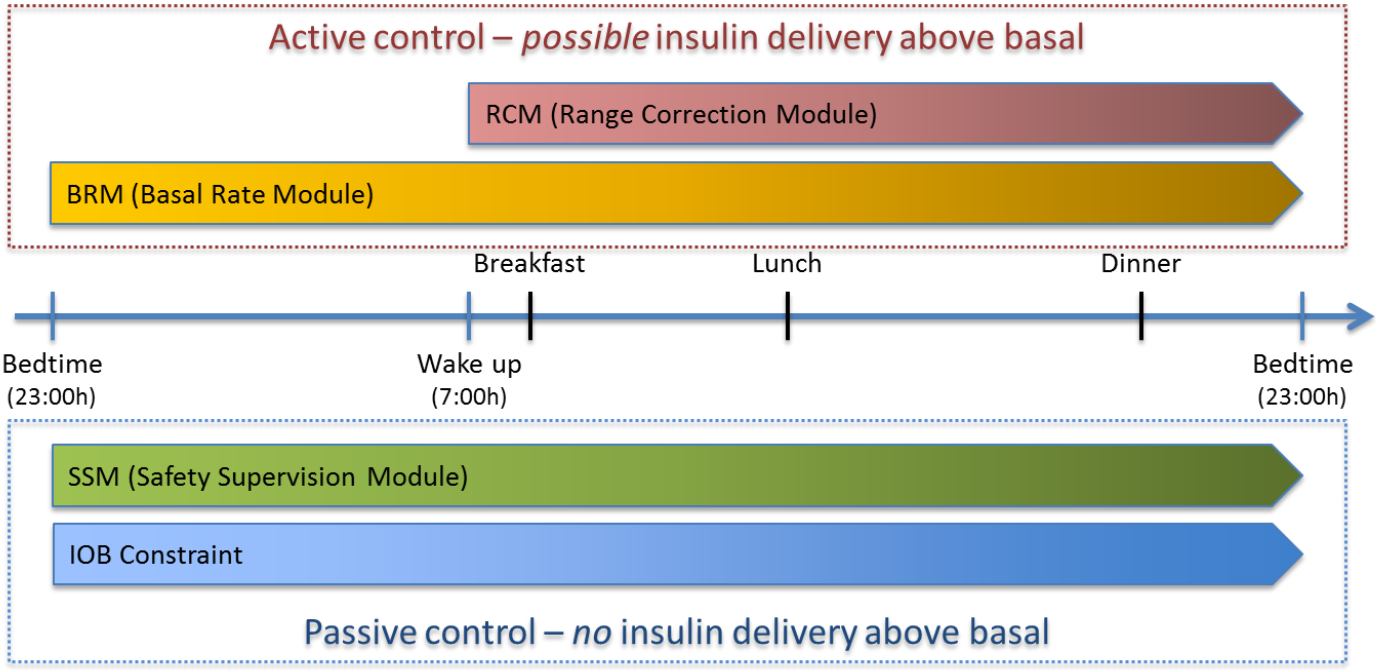


Figure 10: Algorithm Architecture

4.2. System Details

The study system will function in different operational modes in the proposed study: Stopped, Sensor, Pump, Closed-Loop, and Safety. In Pump, Closed-Loop, and Safety mode, the system delivers basal insulin via the insulin pump in a series of small boluses at 5-minute intervals based upon the preprogrammed basal profile of the study subject. In Pump mode, the resulting basal delivery will always match the subject's preprogrammed open-loop basal pattern. In Closed-Loop mode, basal delivery can be attenuated or increased by the control algorithm's SSM, BRM, and RCM modules as described in section 3 above. In Safety mode, basal delivery cannot be increased above open-loop, but can be attenuated by the control algorithm's SSM module as described in section 3 above. Safety mode is intended for use during Closed-Loop study phases when the subject is participating in activities (such as operating a motor vehicle) during which a hypoglycemic event could be particularly hazardous.

If the system malfunctions but the DiAs can still communicate with the pump, the system will fail safe to Pump mode so that the user will continue to receive basal insulin under the direction of the DiAs. If there is a system malfunction in which the DiAs cannot communicate with the pump, the system will fail safe to Stopped mode and the user will begin receiving basal insulin from the pump without any direction from the DiAs within a short period of time.

The table below summarizes the system modes and some of the functionality available in each mode:

Table 1: Basic functionality of system in each operational mode

Mode	Overview	CGM data?	Basal Insulin delivered via DiAs?	Bolus Insulin delivered via DiAs?	Hypo-/Hyper Glycemia Traffic Lights?	Data Transfer to Remote Server to allow monitoring?
"Stopped"	System comes online in Stopped mode and awaits user action. User may switch the system into Stopped mode at any time.	No	No	No	No	No
"Sensor"	Exists primarily for situations where no pump is being used	Yes, if available	No	No	Yes	Yes
"Pump"	Emulates traditional insulin pump behavior of open-loop basal insulin delivery according to preprogrammed pattern; used instead of Closed-Loop mode when replacing CGM sensor	Yes, if available	Yes, identical to preprogrammed pattern	Yes, but only user-requested manual boluses; no automated boluses	Yes	Yes
"Closed Loop"	Control algorithm determines appropriate automated insulin delivery. Can only activate if CGM data is available.	Yes	Yes, according to algorithm based on preprogrammed pattern attenuated or increased when needed	Yes, automated boluses if RCM is active, and user-requested manual boluses at any time	Yes	Yes

"Safety"	Can only switch in if CGM data available	Yes	Yes, according to algorithm based on preprogrammed pattern attenuated when needed	Yes, but only user-requested manual boluses; no automated boluses	Yes	Yes

4.3. Setup and Operation of the Closed-loop Control System

Prior to closed-loop use, the DiAs system is initialized with each subject's individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern. The first initialization of the system will occur during Visit 3 Open-Loop Transitional Training Visit.

During the Open-Loop Transitional Training visit and the subsequent Open-Loop Home Use period, the DiAs system will be configured to prevent the user from switching into Closed-Loop or Safety mode.

During the two-week period of home use in overnight-only Closed-Loop configuration, the control algorithm will be configured to disable the RCM module that is capable of delivering automated correction boluses; control will be achieved through basal rate modulation only.

During the two-week period of home use in 24-hour Closed-Loop configuration, the DiAs system will be reconfigured to enable the RCM module that is capable of delivering automated correction boluses during the daytime.

4.4. Safety Measures

4.4.1. Safety Measures of Insulin Dosing

In Closed-Loop or Safety mode, all dosing is supervised by a dedicated safety supervision system module and insulin correction for meal boluses must be manually confirmed. In Pump, Closed-Loop, and Safety mode:

- Bolus size is checked by the algorithm to ensure it is smaller than the maximum bolus that the pump can handle;
- Switching to "Stopped" mode includes a 'cancel all' delivery message to the pump so that any active but incomplete bolus is cancelled
- All insulin requests are made in the form of boluses or temporary basal rate changes; this ensures that in case of a system crash or pump disconnection, no request has permanence;
- Users will be able to monitor delivered insulin in the plots menu on the phone which is available from the main screen in any operating mode. The remote monitoring displays the delivered insulin and total insulin delivered during the past 4 hours via the web interface;
- It is important to note that IOB constraint is an internal safety feature of the closed-loop system. It is not read from the pump or any other external source. The IOB in the system is computed by the system using a model of the transport and clearance of insulin from the subcutaneous infusion site to the circulation, and is intended to prevent insulin overdose.

4.4.2. Hypoglycemia Safety Protocol

If the subject receives a hypoglycemia red light from the study system, the subject will be instructed to perform a fingerstick test with the study blood glucose meter. The hypoglycemia traffic lights will be active in Pump, Closed-loop and Safety modes as above in section 4.2. If the subject's BG result is ≤80 mg/dL, the subject will be instructed to treat with ~16 grams of oral glucose and indicate treatment was given on the DiAs system by activating the hypoglycemia treatment button. Further details will be included in a Subject User Guide regarding retesting, retreatment, and criteria for glucagon treatment, stopping the system, contacting the study physician, and contacting emergency responders.

Subjects will be required to set the CGM hypoglycemia threshold alarm to a value no less than 60 mg/dl.

4.4.3. CGM Calibration

Throughout the study, the subject will be instructed to calibrate the CGM before meals, before bedtime, and any time there is a calibration request from the CGM itself, provided that the fingerstick glucose is between 40-400 mg/dL and the CGM arrow is flat (horizontal), indicating that the sensor glucose value is not changing rapidly.

4.4.4. Hyperglycemia Safety Protocol

If the subject receives a hyperglycemia red light from the study system, the subject will be instructed to perform a fingerstick test with the study blood glucose meter. The hyperglycemia traffic lights will be active in Pump, Closed-loop and Safety modes as above in section 4.2. If the subject's BG result is ≥300 mg/dL for over 1 hour, or over ≥400 mg/dL at any point, the subject will be instructed to perform a blood ketone measurement with the study ketone meter. Further details will be included in a Subject User Guide regarding criteria for stopping the system, administering correction boluses, retesting, retreatment, infusion set replacement, contacting the study physician, and contacting emergency responders.

Subjects will be required to set the CGM hyperglycemia threshold alarm to a value no greater than 300 mg/dl.

4.4.5. CGM Sensor Failure

If the CGM signal becomes unavailable for an extended period of time during Closed-Loop or Safety mode, the system will revert to Pump mode. The alerts of the Remote Monitoring mitigate the risk for hyperglycemia and potential ketosis: the state or mode of the system is clearly labeled in the remote monitoring module as is the value and time of the last CGM measurement.

4.4.6. Pump Failure

If the insulin pump stops communicating for > 20 minutes, the system will sound an audible alarm and will eventually switch to Stopped mode if the communication problem persists. If loss of pump communication persists for >30 minutes, the pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the controller. If pump alarm conditions persist for an extended period of time, an automated safety alert message will also be transmitted to the designated study team member to monitor the situation and assist the subject if needed to restore pump communication.

4.4.7. Study System Failure

If the study system stops working for more than 30 minutes, the pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the controller. An automated alert will be also be sent to a designated study team member after an extended period of loss of data transmission from the closed-loop system to the remote monitoring system.

4.4.8. Remote Monitoring

The DiAs Web Monitoring and Automated Notification system is an additional safety component that allows any study system to be monitored remotely, providing information for the patient and the system state. Data is transmitted from the phone to the remote server. No system control or configuration commands are accepted by the system from any remote device. The study software directs the data stream to a particular patient within the web server. The subject information screen will make use of subject study identification numbers so that no identifiable data are transmitted. The web server provides a graphical interface that enables clinical and technical personnel to view the logged data and status information in real time. The system offers the possibility to track many patients at the same time, with automated alarms and alerts (Figure 11). In addition, the study staff will get automated messages alerting for critical events. At any time, staff can monitor a specific patient/device in more details by selecting the desired patient in the overview.

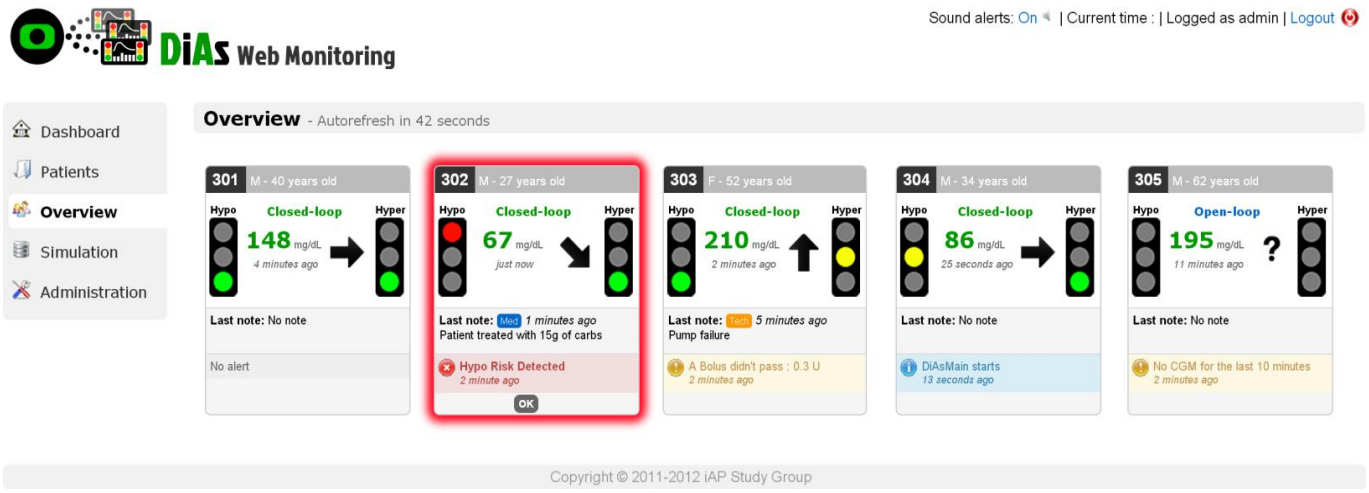


Figure 11: Remote Monitoring Interface

During the Closed-Loop Transitional Training visit, the subject will be intensively supervised using the monitoring and notification system in order to verify that the system cell phone, data link and server are all functioning properly. The subject will be shown how to verify that the data link to the server is working and what to do if the system indicates link failure. The subject will also have a chance to ask questions and discuss with study staff where they may travel during the extended home-use phase of the trial such that continuous monitoring of the system is possible.

During the closed-loop home use period, automated supervision by the remote monitoring and supervision system will continuously analyze subject and system data to screen for medical or technical events which may require manual review by study staff. If the system determines that such an event has occurred, it will notify appropriate medical or technical staff. A full list of

events which will trigger notifications, as well as escalation rules, is available in the regulatory documentation and study procedures documentation.

CHAPTER 5: ADVERSE EVENT REPORTING AND PROTOCOL MONITORING

5.1. Definition

A reportable adverse event is any untoward medical occurrence or any unexpected medical occurrence in a study subject.

Hypoglycemic events are recorded as Adverse Events if the event required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat him or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as Adverse Events if evaluation or treatment was obtained from a health care provider or if the event involved diabetic ketoacidosis (DKA), as defined by the Diabetes Control and Complications Trial (DCCT), and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

5.2. Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the subject at each visit and complete all adverse event forms online. Each adverse event form is reviewed by the Coordinating Center to verify the coding and the reporting that is required.

The investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device or study procedures.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

Adverse events will be coded using the MedDRA dictionary.

Definitions of relationship and intensity are listed on the website data entry form.

5.3. Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity
- Is a congenital anomaly/birth defect

An *Unanticipated Adverse Device Event* is defined as an adverse event caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

Serious or unexpected adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form. The protocol safety monitor responsible for reviewing serious or unexpected adverse events is:

Roy W. Beck, M.D., Ph.D.
Jaeb Center for Health Research
15310 Amberly Drive, Suite 350
Tampa, FL 33647
Phone: (813) 975-8690
Fax: 888-795-2859
Email: rbeck@jaeb.org

The Coordinating Center will notify all participating investigators and the FDA of any adverse event that is both serious and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

5.4. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. Details regarding review will be documented in standalone DSMB procedural documentation. The DSMB will review the final safety data from the first 5 subjects to complete the study and make recommendation regarding continuing the study.

5.5. Potential Risks and Side Effects

Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hyperglycemia and ketone formation are always a risk in subjects with type 1 diabetes and subjects will be closely monitored for this. When wearing sensors and insulin infusion sets there is always a risk of skin rashes, allergic reactions to the tape, or infections at the insertion site.

There is always a risk for a small piece of a sensor remaining under the skin or a sensor or infusion set breaking off under the skin.

5.5.1. Venipuncture Risks

A hollow needle/plastic tube will be placed in the arm for taking blood samples. Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

5.5.2. Fingerstick Risks

About 1 drop of blood will be removed by finger stick for measuring blood sugars and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as finger pokes are part of the usual care for people with diabetes.

5.5.3. Subcutaneous Catheter Risks (Continuous Glucose Sensor)

Subjects using the continuous glucose sensor will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a catheter is left under the skin for more than 24 hours it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causing a bruise (1 in 10 risk).

Study staff should verbally alert the subject that on rare occasions, the continuous glucose sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site. The subject should be further instructed to notify the study coordinator immediately if this occurs.

5.5.4. Risk of Hypoglycemia

As with any person having insulin-dependent diabetes, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days you may not be as aware of symptoms of low blood sugar.

5.5.5. Risk of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A sensor which was functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery.

5.5.6. Risk of Device Reuse

The Dexcom Gen 4 is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver will be reused after cleaning as described below. The transmitter is attached to the sensor but does not enter the skin and the receiver is a hand held device. The transmitter and receiver will be cleaned adhering to hospital protocol as described below. Subjects will be informed that the FDA has approved these devices

for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The Accu-Chek Combo System is labeled for single-patient use. The Accu-Chek Combo system is comprised of the Accu-Chek Spirit Insulin Pump and the Aviva Combo Device. The Aviva Combo device when used as a glucometer will be single patient use at all times. The Accu-Chek Spirit Insulin Pump itself is handheld and is not a glucometer. The subject interactions are primarily with the DiAs interface and the Aviva Combo device, not with the Accu-Chek Spirit Insulin Pump menu interface itself. The Accu-Chek Spirit Insulin Pump handheld device will be reused after cleaning adhering to hospital protocol as described below. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.)

Cleaning Procedure: Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%), quaternary ammonium germicidal detergent (i.e. CaviCide) or household bleach. The contact time on the surface depends on the method used to clean the equipment. CaviCide requires three minutes on the surface. Clorox Germicidal Bleach Wipes require two minutes on the equipment. The surface should remain wet (i.e. slightly damp) with the disinfectant to be considered effective though not wet enough to leave drops of liquid. Equipment will be stored in a clean zipped bag.

5.5.7. Other Risks

Some subjects may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the CSII. If these reactions occur, different adhesives or "under-taping" (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Whenever the skin is broken there is the possibility of an infection. The CGM and pump infusion sites are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is supposed to be used. Therefore participants will be carefully instructed about proper use of the sensor.

Data downloaded from the CGM, pump, and the home glucose and ketone meter will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

5.6. Study Stopping Criteria

5.6.1. Criteria for Individual Subjects

Rules for stopping the study for an individual subject are as follows:

1. System or controller malfunctions that impose on the safety of the subject, unless the problem can be clearly identified and the system definitively repaired
2. Severe hypoglycemia or hyperglycemia/DKA (not associated with infusion set failure) as defined in section 5.1
3. Developing >1.0 mmol/L ketones on 3 or more study days due to prolonged periods of inadequate insulin delivery recommendation (not associated with infusion set failure).

4. The subject requests the study be stopped
5. Subject pregnancy
6. Use of oral or injectable glucocorticoids during closed-loop system operation
7. Study staff are persistently unable to contact the subject or the care partner in a timely manner during the course of the study
8. Persistent subject nonadherence to safety-related procedures such as frequency of fingersticks or hypoglycemia, hyperglycemia and ketone treatment instructions

5.6.2. Criteria for Suspending/Stopping Overall Study

In case of a recurring system malfunction or subject safety issue observed with multiple subjects, the overall study will be suspended while the problem is diagnosed. The study may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

An instance of severe hypoglycemia or hyperglycemia as defined in section 5.1 will result in temporarily stopping additional enrollment of subjects until DSMB review of the data to determine whether the event was triggered by the system or not and whether it is safe to proceed. The currently-enrolled subjects will continue use of the system during this time unless the DSMB determines it is unsafe for them to do so.

5.6.3. Risk Assessment

5. Based on the fact that (1) people with diabetes experience mild hypo- and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention periodic temporary suspension of insulin delivery as well as insulin dosing overnight that may affect overnight or morning blood glucose, (3) safety mitigations are in place that will help to the subject's exposure to hypo- and hyperglycemia should it occur, and (4) rapid reversal of and hyperglycemia can be achieved, it is the assessment of the investigators that this protocol under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of investigators that this study also presents prospect of direct benefit to the subjects and general benefit to others with diabetes as described in Section **Benefits**

CHAPTER 6: MISCELLANEOUS CONSIDERATIONS

6.1. Benefits

One purpose of this research is to reduce hypoglycemia events and severe hypoglycemic reactions. Hypoglycemia is the number one fear of families with someone who has type 1 diabetes and this fear often prevents optimal glycemic control.

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control the glucose level. This research is one step on the path towards development of a fully closed-loop system. The individual participant may not benefit from study participation.

6.2. Subject Compensation

Subjects will be compensated $100 for the 10-hour Open-Loop Transitional Training visit, $250 for the 48-hour Closed-Loop Transitional Training visit, and $25 for each shorter study-related clinic visit during the study. Companions will be compensated $50 for the 10-hour Open-Loop Transitional visit and $125 for the 48-hour Closed-Loop Transitional Training visit.

6.3. Subject Withdrawal

Participation in the study is voluntary, and a subject may withdraw at any time. The investigator may withdraw a subject who is not complying with the protocol. Withdrawal of a subject will be considered for the reasons listed in section 5.6. For subjects who withdraw, their data will be used up until the time of withdrawal.

6.4. Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified subject information may also be provided to research sites involved in the study.

CHAPTER 7: STATISTICAL CONSIDERATIONS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

7.1.Sample Size

N=30 subjects are to be enrolled as a convenience sample in this pilot study. Power was computed for a comparison of the 2 weeks of day+night CTR closed-loop system study period with the baseline sensor-augmented pump period. From data collected in the JDRF CGM RCT, the frequency of glucose values ≤70 mg/dl has been estimated to be 6.0%. For a 33% reduction in this frequency using the closed-loop system, statistical power has been computed to be 84% with N=30 subjects, a two-tailed analysis, and a type 1 error rate of 5%.

7.2. Analysis Plan

For the primary analyses of the main study, all available data from all subjects who completed all or part of the protocol will be included and analyzed.

7.2.1. Primary Outcome Measures

a. The primary efficacy outcome is percentage of time spent in hypoglycemia (<70 mg/dl, 3.9 mmol/L) in the 2 weeks of DiAs at home in day+night closed-loop configuration when compared with the 2-weeks baseline sensor-augmented pump period.
b. A second key efficacy outcome is percentage of time spent in hypoglycemia (<70 mg/dl, 3.9 mmol/L) in the 2 weeks of DiAs at home in overnight-only closed-loop configuration when compared with the nights of the 2-weeks baseline sensor-augmented pump period.

The main safety outcomes are clinical events of severe hypoglycemia and diabetic ketoacidosis as defined in Section 5.1.

7.2.2. Secondary CGM-measured Outcomes

Overall Control

- Mean glucose
- Percentage of sensor glucose values 70 to 180 mg/dL (3.9 to 10.0 mmol/L)
- Glucose variability measured with the coefficient of variation

Hypoglycemia

- Percentage of CGM measured glucose values <60 mg/dL (3.3 mmol/L)
- Percentage of CGM measured glucose values <50 mg/dL (2.8 mmol/L)
- AUC under 70 mg/dL (3.9 mmol/L), 60 mg/dL (3.3 mmol/L), and 50 mg/dL (2.8 mmol/L)
- Low blood glucose index

Hyperglycemia

- Percentage of glucose values > 300 mg/dL (16.7 mmol/L)
- Percentage of glucose values > 250 mg/dL (13.9 mmol/L)
- Percentage of glucose values >180 mg/dl (10.0 mmol/L)
- AUC glucose >180 mg/dL (10.0 mmol/L)

- High blood glucose index

Other Outcomes

Listing of instances with blood ketone levels >0.6 mmol/L

7.2.3. Extension Phase Outcome Measures

The following outcome measures will be summarized for the extension phase:

- Change in HbA1c
- Mean glucose
- Percentage of time spent <50 mg/dL (2.8 mmol/L), <60 mg/dL (3.3 mmol/L), and <70 mg/dL (3.9 mmol/L)
- Percentage of time spent 70-180 mg/dL (3.9-10.0 mmol/L)
- Percentage of time spent > 180 mg/dL (10.0 mmol/L), > 250 mg/dL (13.9 mmol/L), and >300 mg/dL (16.7 mmol/L)
- Glucose coefficient of variation (CV)
- Episodes of DKA events
- Episodes of severe hypoglycemia events
- Instances with blood ketone levels >0.6 mmol/L and >1.0 mmol/L
- Any other reported adverse events

7.3.Statistical Analysis

All primary and secondary outcomes will be analyzed by comparing the metrics calculated from the 2 weeks of day+night and 2 weeks of night-only closed-loop with the metrics from the 2-weeks sensor-augmented pump period (baseline).

The day+night period is defined as any time the system is operational. In calculating any CGM metrics, all 24 hours of day and night will be given equal weight.

Nighttime is defined as the time the algorithm is configured for nighttime operation for a given subject as defined in section 4.1. The metrics for the 2 weeks of night-only closed-loop period will be compared with the corresponding metrics from the 2-weeks baseline period.

Since all primary and secondary outcomes are continuous, the statistical analyses will be similar. Mean ± SD or median (quartiles) will be tabulated separately by baseline vs. closed loop as appropriate for the distribution. A repeated measures regression model will be fit for all the primary and secondary outcomes to compare baseline vs. closed loop. A log (x+0.005) transformation will be applied to the percentage of CGM values ≤70 mg/dl (primary outcome). If this transformation does not give an approximate normal distribution, a ranked normal transformation will be used instead. Similar transformations will be applied to any other outcome measures that have a skewed distribution. All p-values will be two-sided.

Subgroup Analyses

Subgroup analyses will explore differences in outcomes according to HbA1c level, age, T1D duration, C peptide level, and time spent in hypoglycemia (≤70 mg/dl, 3.9 mmol/L) at baseline.

Adverse Events

Episodes of DKA and of severe hypoglycemia at any time along with any other adverse events will be tabulated by treatment group. Details of the event will be also provided.

Device Questionnaire

The results of the questionnaire following the closed-loop at home use period will be summarized.

Other Tabulations

Additional tabulations will include:

- Demographics and clinical characteristics at baseline
- Number of subjects who did not complete the study and reasons for discontinuation
- Distribution of number of hours the CTR closed-loop system was active
- Basic system performance metrics describing technical performance of system (up-time, reliability, etc.)

CHAPTER 8: REFERENCES

1. Albisser AM, Leibel BS, Ewart TG, Davidovac Z, Botz CK, Zingg W. An artificial endocrine pancreas. *Diabetes*, 23:389-396, 1974
2. Pfeiffer et al, EF, Thum C, Clemens AH. The artificial beta cell—A continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system). *Horm Metab Res*, 6: 339–342, 1974.
3. Mirouze J, Selam JL, Pham TC, Cavadore D. Evaluation of exogenous insulin homeostasis by the artificial pancreas in insulin-dependent diabetes. *Diabetologia*, 13 :273-278, 1977.
4. Kraegen EW, Campbell LV, Chia YO, Meler H, Lazarus L: Control of blood glucose in diabetics using an artificial pancreas. *Aust N Z J Med*, 7:280-286, 1977
5. Shichiri M, Kawamori R, Yamasaki Y, Inoue M, Shigeta Y, Abe H: Computer algorithm for the artificial pancreatic beta cell. *Artif Organs*, 2(Suppl):247-250, 1978
6. Clemens AH, Chang PH, Myers RW. The development of Biostator, a glucose-controlled insulin infusion system (GCIIS). *Horm Metab Res Supplement*: 23–33, 1977.
7. Marliss EB, Murray FT, Stokes EF, Zinman B, Nakhooda AF, Denoga A, Leibel BS, and Albisser AM: Normalization of glycemia in diabetics during meals with insulin and glucagon delivery by the artificial pancreas. *Diabetes* 26: 663-672, 1977.
8. Santiago JV, Clemens AH, Clarke WL, Kipnis DM. Closed-loop and open-loop devices for blood glucose control in normal and diabetic subjects. *Diabetes*, 28: 71-84, 1979.
9. EW, Campbell LV, Chia YO, Meler H, and Lazarus L: Control of blood glucose in diabetics using an artificial pancreas. *Aust N Z J Med* 7: 280-286, 1977.
10. Fischer U, Jutzi E, Freyse E-J, and Salzsieder E: Derivation and experimental proof of a new algorithm for the artificial beta-cell based on the individual analysis of the physiological insulin- glucose relationship. *Endokrinologie* 71:65-75, 1978.
11. The JDRF e-Newsletter: Emerging Technologies in Diabetes Research, September, 2006.
12. Cobelli C, Renard E, and Kovatchev BP. Perspectives in Diabetes: Artificial Pancreas: Past, Present, Future, *Diabetes*, 60: 2672-2682, 2011.
13. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV: Fully automated closed-loop insulin delivery versus semi-automated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care*, 31:934-939, 2008.
14. Clarke WL, Anderson SM, Breton MD, Patek SD, Kashmer L, and Kovatchev BP. Closed-Loop Artificial Pancreas Using Subcutaneous Glucose Sensing and Insulin Delivery and a Model Predictive Control Algorithm: The Virginia Experience. *J Diabetes Sci Technol*, 3: 1031-1038, 2009.
15. Bruttomesso D, Farret A, Costa S, Marescotti MC, Vettore M, Avogaro A, Tiengo A, C. et al: Closed-Loop Artificial Pancreas Using Subcutaneous Glucose Sensing & Insulin Delivery, and a Model Predictive Control Algorithm: Preliminary Studies in Padova and Montpellier. *J Diabetes Sci Technol*, 3: 1014-1021, 2009.
16. Hovorka R, Allen JM, Elleri D, et al., Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *The Lancet*, 375: 743-751, 2010.
17. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A Bihormonal Closed-Loop Artificial Pancreas for Type 1 Diabetes. *Science Transl Med*, 2: 27ra27, 2010.
18. Dassau E, Zisser H, Percival MW, Grosman B, Jovanovič L, Doyle III FJ. "Clinical Results of Automated Artificial Pancreatic β-Cell System with Unannounced Meal Using Multi-Parametric MPC and Insulin-on-Board", Diabetes 59 (Supl 1): A94. Proc 70th ADA Scientific Sessions, Orlando, FL., 2010
19. Atlas E, Nimri R, Miller S, Grunberg EA, Phillip M. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. *Diabetes Care*; 33(5):1072-6, 2010
20. Dalla Man C, Rizza RA, and Cobelli C. Meal simulation model of the glucose-insulin system. *IEEE Trans Biomed Eng*, 54:1740-1749, 2007.

21. Dalla Man C, Raimondo DM, Rizza RA, and Cobelli C. GIM, Simulation Software of Meal Glucose-Insulin Model. *J Diabetes Science and Technology*, 1: 323-330, 2007.
22. Kovatchev BP, Breton MD, Dalla Man C, Cobelli C. In Silico Preclinical Trials: A Proof of Concept in Closed-Loop Control of Type 1 Diabetes. *J Diabetes Sci Technol* 3: 44-55, 2009.
23. Kovatchev BP, Cobelli C, Renard E, et al. Multi-National Study of Subcutaneous Model-Predictive Closed-Loop Control in Type 1 Diabetes: Summary of the Results. *J Diabetes Sci Technol*, 4: 1374-1381, 2010.
24. Kovatchev BP, Patek SD, Dassau E, Doyle FJ III, Magni L, De Nicolao G, and Cobelli C. Control-to-range for diabetes: functionality and modular architecture, *J Diabetes Sci Technol*, 3: 1058-1065, 2009.
25. Patek SD, Magni L, Dassau E, Karvetski CH, Toffanin C, DeNicolao G, DelFaverokS, Breton M, Dalla Man C, Renard E, Zisser H, Doyle FJ III, Cobelli C, Kovatchev BP. Modular Closed-Loop Control of Diabetes, *Transactions on Biomedical Engineering*, 29: 2986-3000, 2012.
26. Renard EM, Farret A, Place J, Cobelli C, Kovatchev BP, Breton MD. Closed-loop insulin delivery using subcutaneous infusion and glucose sensing, and equipped with a dedicated safety supervision algorithm, improves safety of glucose control in type 1 diabetes. *Diabetologia* 53: S25, 2010.
27. Hovorka R, Kumareswaran K, Harris J, Allen JM, Elleri D, Xing D, et al. Overnight closed loop insulin delivery in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ*, 342:d1855, 2011.
28. Zisser H, Dassau E, Bevier W, Harvey R, Percival MW, Grosman B, Seborg D, Jovanovič L, Doyle III FJ. Initial Evaluation of a Fully Automated Artificial Pancreas, Diabetes 60 (Supl 1): A41. Proc 71st ADA Scientific Sessions, San Diego, CA., 2011
29. Kovatchev BP. Closed Loop Control for Type 1 Diabetes, Editorial. *BMJ*, 342:d1911, 2011.
30. Dassau E, Zisser H, Palerm CC, Buckingham BA, Jovanovič L, Doye III FJ. Modular Artificial β-Cell System: A Prototype for Clinical Research J *Diabetes Sci Technol*. 2:863-872, 2008.
31. Breton MD, Farret A, Bruttomesso D, Anderson SM, Magni L, Patek S, Dalla Man C, Place J, Demartini S, Del Favero S, Toffanin C, Karvetski CH, Dassau E, Zisser H, Doyle FJ III, De Nicolao G, Avogaro A, Cobelli C, Renard E, Kovatchev BP on behalf of The International Artificial Pancreas (iAP) Study Group. Fully-integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near-normoglycemia. *Diabetes*, doi:10.2337/db11-1445, 2012.
32. Hughes CS, Patek SD, Breton MD, and Kovatchev BP. Hypoglycemia Prevention via Pump Attenuation and Red-Yellow-Green "Traffic" Lights Using Continuous Glucose Monitoring and Insulin Pump Data. *Diabetes Sci Technol*, 4: 1146-1155, 2010.
33. Ellingsen C, Dassau E, Zisser H, Grosman B, Percival MW, Jovanovič L, and FJ Doyle III. Safety constraints in an artificial b-cell: an implementation of Model Predictive Control (MPC) with Insulin-on-Board (IOB). *Diabetes. Sci. Technol.* 3: 536-544, 2009.
34. Heineman L, deVries H, Reduced time in hypoglycaemia when insulin infusion is driven by two closed-loop algorithms in patients with Type 1 diabetes;
a randomized clinical trial, CAT trial study release, http://www.apathome.eu/news/study-resease-cat-trial
35. Kovatchev BP, Breton MD, Keith-Hynes PT, Patek SD. The Diabetes Assistant (DiAs) – unified platform for monitoring and control of blood glucose levels in diabetic patients; PCT/US12/43910, 2012.
36. Kovatchev BP, Breton MD, Keith-Hynes PT, Patek SD. Methods and apparatus for modular power management and protection of critical services in ambulatory medical devices. PCT/US12/43883, 2012.
37. Cobelli C, Renard E, Kovatchev BP, Keith-Hynes P, Ben Brahim N, Place J, Del Favero S, Breton MD, Farret A, Bruttomesso D, Dassau E, Zisser H, Doyle FJ III, Patek S, Avogaro A. Pilot Studies of Wearable Artificial Pancreas in Type 1 Diabetes. *Diabetes Care*, DOI:10.2337/dc12-0660, 2012.
38. Kovatchev BP, Renard E, Cobelli C, Zisser H, Keith-Hynes P, Anderson SM, Brown SA, Chernavvsky DR, Breton MD, Farret A, Pelletier M, Place J, Bruttomesso D, Del Favero S, Visentin R, Filippi A, Scotton R, Avogaro A, Doyle F III (2013). Feasibility of Outpatient Fully Integrated Closed-Loop Control: First Studies of Wearable Artificial Pancreas. Diabetes Care, 36: 1851-1858.doi: 10.2337/dc12-1965

39. DeSalvo D, Keith-Hynes P, Peyser T, Place J, Caswell K, Wilson D, Harris B, Clinton P, Kovatchev BP, Buckingham B. Remote Glucose Monitoring in Camp Setting Reduces the Risk of Prolonged Nocturnal Hypoglycemia. Diabetes Technol Ther, 16, DOI:10.1089/dia.2013.0139, 2014
40. Keith-Hynes P, Guerlain S, Mize LB, Hughes-Karvetski C, Khan M, McElwee-Malloy M, Kovatchev BP. DiAs User Interface: A Patient-Centric Interface for Mobile Artificial Pancreas Systems. J Diabetes Sci Technol, 7: 1416–1426, 2013
41. Place J, Robert A, Ben Brahim N, Keith-Hynes P, Farret A, Pelletier MJ, Buckingham B, Breton M, Kovatchev BP, Renard E. DiAs Web Monitoring: A Real-Time Remote Monitoring System Designed for Artificial Pancreas Outpatient Trials. J Diabetes Sci Technol, 7: 1427–1435, 2013
42. Kovatchev BP, Cobelli C, Renard E, Zisser H et al. Efficacy of Outpatient Closed-Loop Control (CLC). American Diabetes Association 73rd Scientific Sessions: 993-P, Chicago, Il, 2013