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Brief Title: Feasibility Study Using Zone-MPC Controller, HMS and Technosphere® Insulin Inhalation System From MannKind Corp

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CLINICAL PROTOCOL

Revision 4

Artificial Pancreas Device

Feasibility Study using Zone-MPC Controller (Zone-Model Predictive Control) and Health Monitoring System (HMS) and Technosphere® Insulin Inhalation System from MannnKind Corp.

	Name	Function/ Title	Signature	Date
Prepared by	Dr. Howard Zisser, MD	Director of Clinical Research and Diabetes Technology Sansum Diabetes Research Institute		
Approved by	Dr. Eyal Dassau, PhD	Senior Investigator & Diabetes Team Research Manager Department of Chemical Engineering University of California, Santa Barbara		

SPONSOR

Sansum Diabetes Research Institute
Principal Investigator: Howard Zisser, M.D.
Director of Clinical Research and Diabetes Technology
2219 Bath Street
Santa Barbara, CA 93105
Ph: 805-682-7638
Fax: 805-682-3332

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EXECUTIVE SUMMARY

This clinical trial is a feasibility study to assess the performance of an Artificial Pancreas (AP) device using the Artificial Pancreas System (APS©) platform for subjects with type 1 diabetes using rapid acting insulin as well as pre-prandial inhaled insulin (Technosphere® Insulin Inhalation System by MannKind Corporation). This is a follow-up study to the approved feasibility study IDE G110093. The new proposed study and IDE G110093 use the same device and follow the same clinical protocol with the addition of the pre-prandial inhaled insulin in this new proposed feasibility study. The CGM for this proposed study is the next generation of Dexcom CGMs, the G4® System which was recently approved by the FDA. The goal of this proposed study is to explore the feasibility of using multiple insulin delivery routes in order to mimic the physiology of both 1st and 2nd phase insulin secretion. The intent is to exploit the rapid action achieved by inhaled insulin to compensate for part of the meals and utilize the conventional subcutaneous route for management of basal insulin and as second phase meal-related insulin. Preliminary analysis of the results of IDE G110093 have been very encouraging and are supportive of this new proposed study using inhaled insulin to reduce the post-prandial peak. The AP device is a closed-loop between a Dexcom® G4® System (Dexcom® Incorporated, San Diego, CA) continuous glucose monitor (CGM) and a OneTouch® Ping® Glucose Monitoring System (Animas Corp, Westchester, PA) subcutaneous insulin delivery pump (CSII). The AP device is controlled by a zone-Model Predictive Control (zone-MPC) algorithm augmented by a safety algorithm named the Health Monitoring System (HMS). The clinical study will include 12 to 20 adults subjects aged 21 to 65 years old.

The study consists of an evaluation of the Artificial Pancreas device during a 24-hour closed-loop in a clinic environment (Sansum Diabetes Research Institute, Santa Barbara, CA). The 24-hour period includes:

- 2 unannounced meals (evening dinner and breakfast of 50 g CHO each) preceded with a nominal dose of Technosphere® inhaled insulin;
- 1 period of 30 minutes of exercise at 50% of the predicted heart rate reserve (HRR) preceded with a snack and followed by a snack 3 hours later (on Day 2);
- complete night from 12:00 am to 7:00 am;

The subject will arrive at approximately 4:00 pm to the CRC (clinical research center), the closed-loop will be initiated at approximately 4:30 pm that same day and continued until 4:30 pm the next day. A physician will be monitoring the patient with the artificial Pancreas (AP) device at all time.

The proposed study will evaluate the performance of the AP device combined with Technosphere® Insulin Inhalation Powder in predicting the fall and rise of glucose values and in regulating insulin delivery to mitigate extreme blood glucose variations during the following challenges:

- following unannounced meals,
- during a nocturnal period, and
- during a period of active exercise.

The goal is to demonstrate that the AP device is able to maintain the subject blood glucose within a safe range at all times. One of the objectives of the study will be to measure the percent of time spent in the following zones:

- [80-140] mg/dL at all times unless described otherwise
- [80-140] mg/dL during the nocturnal period
- [70-180] mg/dL postprandial, for 5 hours following the unannounced meals
- [70-150] mg/dL during and for 3 hours following exercise

In particular, an analysis will report on 1-hour and 2-hour postprandial glucose level and 6-hour area-under-the-curve (AUC) when compared to G110093 to evaluate the impact of the Technosphere® insulin (only for those subjects who enrolled in both clinical studies).

It is anticipated that following the planned challenges, glucose value might increase temporarily beyond those ranges. These excursions will be reviewed and analyzed (value and duration) and the study will determine how the AP device mitigates those excursions and maintains glucose levels within a safe and acceptable range. The clinical study will also review any event that occurs during the course of the 24-hour closed-loop: hypoglycemic events, hyperglycemic events, outside intervention, other Adverse Event, Serious Adverse Events, Unanticipated Adverse Device Effect, and device complaints for the commercial devices used. A root cause analysis of the event will be performed to determined if it is related to the device or the drug and if the drug, which drug (subcutaneous or Technosphere® Insulin). Safety of the patient will remain the primary goal. The goal of the AP device combined with the Technosphere® Insulin Inhalation Powder (with Gen2C inhaler) is to operate without outside intervention even when challenged by meals or exercise unless the outside intervention is requested by the Health Monitoring System (HMS). The subject will just inhale one 10U dose prior to meals. This is approximately 4U of subcutaneous insulin.

The table below is a synopsis of the proposed clinical protocol.

Title of the protocol	Feasibility Study using Zone-MPC Controller (Zone-Model Predictive Control) and Health Monitoring System (HMS) and Technosphere® Insulin Inhalation System from MannKind Corp.
Sponsor	Sansum Diabetes Research Institute (SDRI)
Investigational Device	Artificial Pancreas (AP) device: Artificial Pancreas System platform (APS©) from the University of California, Santa Barbara and SDRI with: • OneTouch® Ping® Glucose Management System with modified Meter-Remote from Animas® Corp or the OmniPod® Insulin Management System from Insulet Corp. • Dexcom® G4® CGM System (CGM) from Dexcom® Corp • Control algorithm: zone-Model Predictive Control (zone-MPC) with safety Health Monitoring System (HMS)
Drug	Approved rapid acting insulin (subcutaneous): Humalog®, Apidra® or Novolog® Investigational inhaled insulin: Technosphere® Insulin Inhalation System (Gen2C inhaler) by MannKind Corp. IND 61,729
Study Purpose	<u>Primary objective of this feasibility study:</u> To evaluate the performance of the AP device while the subject is under close medical supervision in the Clinical Research Center (CRC) setting. This objective will be assessed by subjecting the AP device (combined with the Technosphere® Insulin Inhalation Powder) and the subject to several challenging situations, such as meals, exercise, and nocturnal period. The study will evaluate the percent of time the glucose level of the subject remains within pre-specified target ranges: • Target range (unless described otherwise): [80-140] mg/dL • Overnight target range: [80-140] mg/dL • Target range 5 hours after meal: [70-180] mg/dL • Target range during exercise: [70-150] mg/dL • Target range 3 hours after exercise: [70-150] mg/dL The study will also evaluate the glucose level at 1- and 2-hour postprandial and the area-under-the-curve (AUC) at 6-hour post-prandial. <u>Secondary objectives:</u> To evaluate the performance of the AP device combined with the Technosphere® Insulin Powder System: • when glucose values are outside of the desirable ranges, • in analyzing the values and duration of the extremes, in particular if <70 mg/dL and <60 mg/dL. • in analyzing adverse events, • in analyzing outside interventions not following the recommendation of the HMS, • if the same subjects were enrolled in this study and the original IDE G110093 study (protocol revision 2.2): comparing the glucose profile between the two clinical studies with and without the Technosphere® Insulin.
Study Design	Non-randomized, uncontrolled, feasibility study conducted in the United-States at one clinical site, with one principal investigator. <u>Overview of the procedures:</u>

	Following the successful screening and informed consent process: During the week prior to the CRC visit, the subject will review glucose control and insulin pump settings with study staff, with goal to aim for optimal glucose control. (Subject's basal rate settings are used for insulin delivery during closed-loop mode when glucose is predicted to be within determined glucose zones, and insulin to carbohydrate ratios are used in study test meal calculations). Two to three days prior to the CRC visit, the subject will attend an outpatient visit for the insertion, by study staff, of two CGM sensors, as well as to receive training and instructions on how to care for the CGM. The CGM will be in blinded mode during the 2-3 days as an outpatient. The Bayer Contour® NEXT EZ blood glucose meter will be used for all CGM calibrations. Two to three days after this sensor insertion visit, the subject will return to the CRC for approximately 25-28 hours, during which the evaluation of the AP device will occur. The CGM will be unblended. On the first day of the CRC visit, the subject will arrive at approximately 4:00 pm. If the subject's blood glucose is greater than 250 mg/dL at arrival to the clinic, the study will be rescheduled. All times are +/- 30 minutes. • Closed-loop will start at approximately 4:30 pm. • A small evening meal (~50g CHO) will be given at approximately 6:30 pm without announcing it to the device, i.e. without providing any information to the device. The meal will be preceded by administering a single dose of Technosphere® Insulin (10U) using the Gen2C inhaler. • Night time will be from approximately 12:00 am to 7:00 am. • Another small meal (~50 g CHO) will be given for breakfast at approximately 7:00 am. The meal will be preceded by administering a single dose of Technosphere® Insulin (10U) using the Gen2C inhaler. • At 11:00 am, the subject will be given a snack (~16 g CHO) and start exercise. • The subject will exercise for 30 minutes at 50% of his/her target heart rate. • At approximately 2:00 pm, the subject will be given another snack (~16 g CHO). • At around 4:30 pm, i.e. 24 hrs after starting, closed-loop will end. During the CRC visit, all diabetes care and use of the AP device will be the responsibility of the investigator. The insulin brand (subcutaneous) used during the CRC session will be the same as the brand used by the subject. Technosphere® Insulin will be delivered using the 10U Gen2C cartridge per the Investigator's Brochure manufacturer's instructions. A detailed plan for diabetes monitoring and for responding to hypoglycemia and hyperglycemia will be in place as described by this protocol. Subject will be monitored closely by trained study staff during the entire CRC visit. A physician will be present at all time. The CGM will be calibrated as required by the manufacturer, as well as approximately 30 minutes before each meal and before bedtime. Additional calibrations may also be performed as required. Blood glucose will be monitored by YSI at least every 30 minutes. More frequent monitoring may be performed as defined in the protocol to ensure the safety of the patient. Each time a YSI measurement will be taken, a finger stick measurement using the CONTOUR® NEXT EZ blood glucose monitoring system will be performed to

	collect information, but no decision will be made from the results of the finger stick. If the HMS recommends giving CHO to the subject, the investigator will follow the recommendation. Any other outside intervention by the investigator will terminate the study session for that subject. If clinical results from a subject are found to be suboptimal with excessive hyperglycemia or excessive hypoglycemia alarms, the *responsiveness factor* of the control algorithm may be adjusted for the study of the next subject. Once the glucose level of the patient is back to more than 90 mg/dL for more than 1 hour, and the glucose level is less than 180 mg/dL with ketones less than 0.6 mmol/L, the patient will be discharged from the CRC. On the day following the CRC visit, the study staff will be in contact, by telephone or in person with the subject for follow-up.
Subject Population	Adults aged 21-65 years Type 1 diabetes mellitus for at least one year Using an insulin infusion pump with rapid acting insulin for at least six months
Sample Size	12 to 20 subjects
Duration of the subject participation	Total duration by each subject is expected to be approximately one week from time of contact to review glucose control to follow-up after discharge from CRC visit.
Study Center	Sansum Diabetes Research Institute, Santa Barbara, CA
Inclusion Criteria	• Clinical diagnosis of type 1 diabetes for at least one year and using an insulin pump for at least 6 months with commercially available rapid acting insulin • The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed. • Age 21 to 65 years • For females, not currently known to be pregnant or nursing • HbA1c between 5.0% and 10%, as measured with DCA2000 or equivalent device • Forced expiratory volume in 1 second (FEV1) ≥ 70% Third National Health and Nutrition Examination Survey (NHANES III) predicted • Forced vital capacity (FVC) ≥70% NHANES III predicted • Forced expiratory volume in 1 second as a percentage of forced vital capacity(FEVl/FVC)≥NHANES III lower limit of normal (LLN) • Willing to perform the calibration of the study CGMs using a finger stick only and willing to follow instructions for insulin pump and CGM wear. • Willing to use the study CGM and study insulin pump during closed-loop. • Able to and agrees to avoid the following medication starting 24 hours before sensor wear through completion of CRC visit: acetaminophen, and

	pseudoephedrine. • An understanding of and willingness to follow the protocol and sign the informed consent.
Exclusion Criteria	• Pregnancy (as determined by a positive blood pregnancy test performed in females of childbearing capacity during screening visit and urine test at time of admission for in-patient visit) or nursing mother. • Diabetic ketoacidosis in the past 6 months prior to enrollment requiring emergency room visit or hospitalization • Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment • Current treatment for a seizure disorder; o Subjects with a history of seizures may be included in the study if they receive written clearance from their neurologist • Cystic fibrosis • Active infection • A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as cognitive deficit. • Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation, including subjects not able to read or write. • Coronary artery disease or heart failure. o Subjects with a history of coronary artery disease may be included in the study if they receive written clearance from their cardiologist • Presence of a known adrenal disorder • Active coronary artery disease or heart failure • 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 o Adequately treated thyroid disease and celiac disease do not exclude subjects from enrollment • Abuse of alcohol • 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 exercise protocol • Current use of a beta blocker medication

	• Laboratory results:
	  o Hematocrit < 30% or >55%
	  o A1C > 10%
	  o Abnormal liver or renal function (Transaminase >2 times the upper limit of normal, Creatinine> 1.5 mg/dL)
	  o Labs drawn at screening visit or within one month prior to screening (for other purposes) will suffice for enrollment purposes related to hematocrit
	• Subject has skin conditions that, in the determination of the investigator, would preclude wearing the study devices (infusion set and sensor), in the abdomen. Examples include but are not limited to: psoriasis, burns, scaring, eczema, tattoos, and significant hypertrophy at sites of device wear; any known allergy to medical adhesives.
	• Currently on long-term treatment using prednisone.
	• If subject had been on short term treatment of prednisone, defer enrollment until underlying condition and prednisone treatment have resolved.
	• Allergy to study drug, food or other study material
	• History of asthma, COPD (chronic obstructive pulmonary disease), or any other clinically relevant chronic lung disease
	• Respiratory track infection within 4 weeks before screening
	• Clinically significant screening ECG, physical examination, laboratory test, or vital sign abnormality
	• Exposure to any investigational drug within 30 days.
	• History of malignancy within the 5 years before screening (other than basal cell carcinoma)
	• Inability, in the opinion of the investigator, to adequately inhale Technosphere® Inhalation powder
	• Abnormal spirometry
	• Currently smoking or discontinued smoking (including cigarettes, cigars, pipes) over the past 6 months.
	• Highly sensitive to insulin: insulin-to-carbohydrate ratio I:C > 1:12.
	• Current participation in another investigational trial (unless participation to original protocol of IDE G110093) or has previously participated to this study.

1. DESCRIPTION OF THE DEVICES

1.1. Overview and hardware

The subject of this application is an Artificial Pancreas device also referred to as the AP device. The AP device is intended for use in people with type 1 diabetes and is designed to automatically deliver insulin using a commercially available insulin pump and to continuously monitor subcutaneous glucose levels using a commercially available continuous glucose monitor (CGM). The AP device is intended to adjust insulin doses only when glucose concentration is, or is predicted to be, outside the specified zone [80-140] mg/dL. It includes a redundant safety control that will send warnings of impending hypoglycemia and recommend eating carbohydrates immediately to prevent hypoglycemia. The Artificial Pancreas device is a closed-loop system linking a subcutaneous Continuous Glucose Monitor (CGM) and a subcutaneous insulin delivery pump, which is controlled by an algorithm. The device incorporates a Model Predictive Control (MPC) algorithm and a Health Monitoring System (HMS) as an additional safety feature. The AP device is augmented with the use of the Technosphere® Insulin Inhalation System (Gen2) that will deliver a fix amount of ultra-rapid-acting insulin whose absorption and exposure times are similar to that observed in normal physiology. The inhaled insulin will only be used prior to a meal to mimic phase 1 of insulin secretion and reduce the post-prandial peak. The powdered insulin is currently under review (Phase III of IND 61,729)

The AP device is composed of:

- Artificial Pancreas System (APS©) platform from the University of California, Santa Barbara and Sansum Diabetes Research Institute (UCSB/SDRI) (MAF-1625). The APS© is the infrastructure that allows the communication between all the elements of the device, i.e, connection with:
    - OneTouch® Ping® Glucose Management System (Animas Corp, Westchester PA) continuous subcutaneous insulin infusion (CSII) pump (K080639 and MAF-1777 for the modified meter remote to interface with the APS©) or the OmniPod® Insulin Management System (Insulet Corp, Bedford, MA) (CSII) pump (K042792 and MAF-1542 for the modified Insulet Personal Diabetes Manager to interface with the APS©)
    - Dexcom® G4® System (Dexcom® Inc, San Diego, CA) subcutaneous continuous glucose monitor (CGM) monitor

(P120005 with Dexcom G4® Receiver DevKit to interface with APS© platform).

- Zone-MPC control algorithm developed in collaboration between UCSB and SDRI.
- Health Monitoring System (HMS) algorithm developed by UCSB which issues safety notifications to the subject and support personnel to prevent impending hypoglycemia.

The artificial pancreas device augmented with the Technosphere® Insulin Inhalation System is described in Figure 1–1~~Figure 1–1~~.

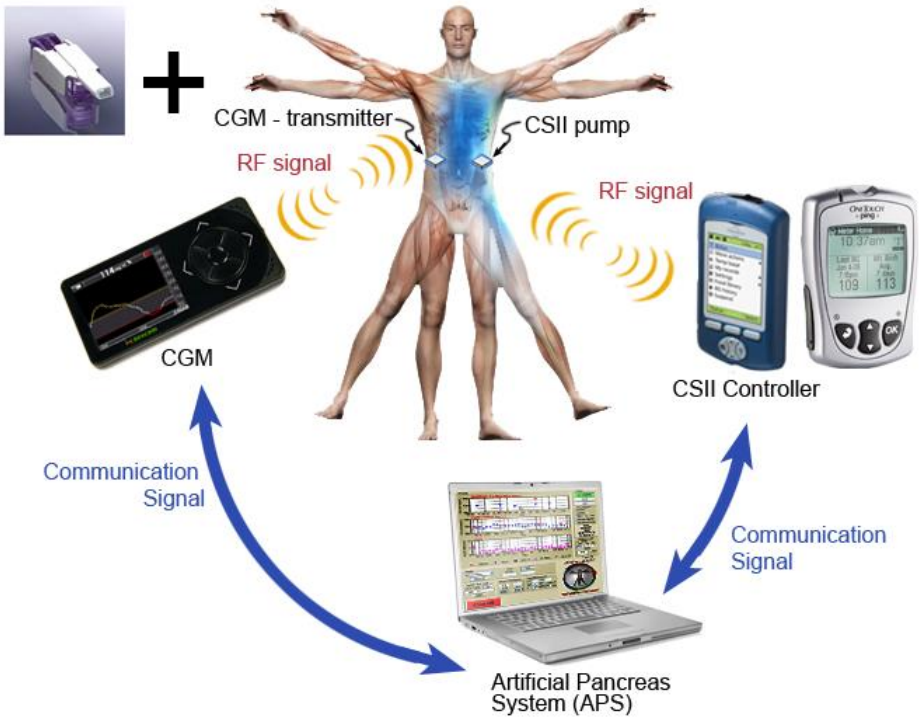

Figure 1–1: Artificial Pancreas Device

The Dexcom G4® CGM System, as shown in Figure 1-2 is composed of:

- Dexcom G4® Receiver
- Dexcom G4® Transmitter
- Dexcom G4® Sensor

Figure 1–2: G4® receiver (left), G4® transmitter (center), G4® sensor (with applicator, pod and sensor probe)

The Gen2 Inhalation System consists of the following, as described in Figure 1–3 and Figure 1-4.

- Is developed and manufactured by MannKind Corporation (Paramus, NJ). The New Drug Application (NDA) file is currently being reviewed by FDA (IND 61,729). Clinical studies are in Phase III. A letter of authorization to access the IND can be found in Appendix 1 of the IDE submission Supplement #3.
- Delivers the Technosphere® Inhalation (TI) Powder to the lung. It is supplied with nominal strength of 10U (blue) and 20U (green) insulin cartridges. The powder consists of 3 units (U) of insulin per milligram.
- The inhaler does not require manual activation and relies on inspiratory flow as the sole source of energy to fluidize and deagglomerate the powder for inhalation.

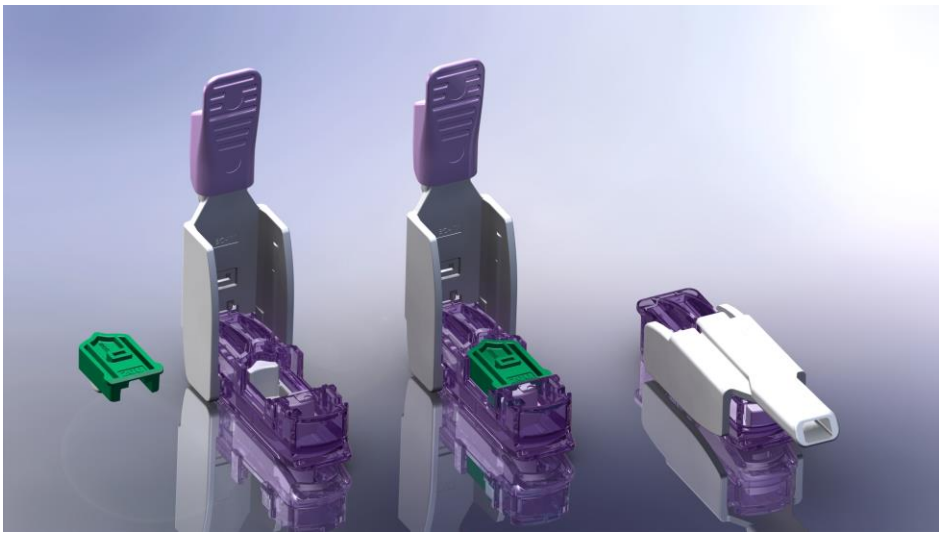

Figure 1–3: Gen2 TI inhaler (MannKind Corp) in open position ready to insert, remove cartridge, open with cartridge and closed

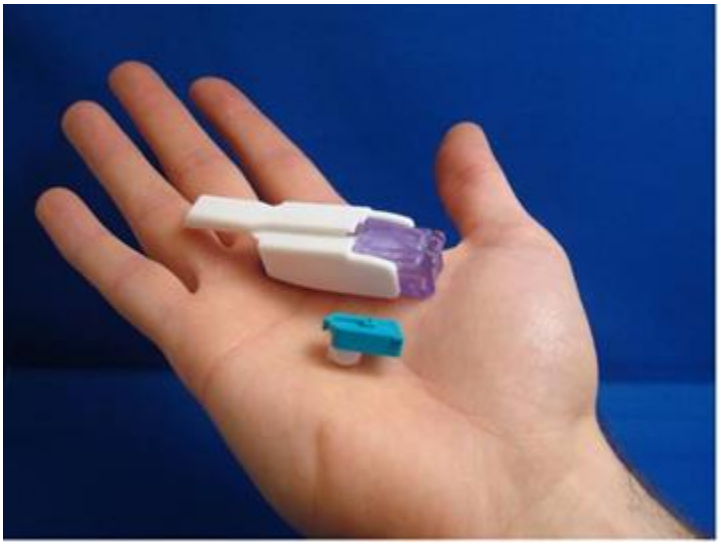

Figure 1–4: Gen2 TI inhaler (MannKind Corp) in closed position with cartridge on the side

In addition to YSI measurements as required periodically, a finger stick measurement will be obtained using the CONTOUR® NEXT EZ blood glucose monitoring system (details provided in Appendix 7 of S005). This information will be collected for information only and no decision will be made on the results of the finger stick.

1.2. Continuous glucose monitor (CGM)

The Dexcom® G4® System Continuous Glucose Monitor (CGM) has been approved by FDA under PMA P050012 (S045 on 8/17/2012) and has not been modified. An additional software, the Dexcom G4® Receiver Tool DevKit software has been installed on the study laptop to interface with the APS© platform.

The CGM unit consists of an interstitial glucose sensor, inserted under the skin of the abdomen into the fatty tissue. An applicator with a removable needle is used to insert the sensor. The process of insertion is similar to the insertion of an insulin infusion set. The sensor is held in place by adhesive tape, and a small transmitter is snapped into place over the sensor. The transmitter communicates every 5 minutes by radiofrequency to a hand-held receiver. During the CRC phase of the study, the receiver is connected to the laptop computer to provide the glucose information to the algorithms: zone MPC and HMS. The CGM will require calibration with a fingerstick blood glucose value as stipulated by the manufacturer's instructions as well as before meals and bedtime. The purpose is to ensure the most accurate sensor value for the study to understand the effectiveness of the control algorithm. In this study the calibration will be performed with the CONTOUR® NEXT EZ blood glucose meter (commercially available, unmodified product k111268). In order to minimize the risk of cancellation of the clinical study due to a sensor problem, the subject will wear two sensors, and at the time of the CRC stay, the investigator will select which sensor to use, and document the rationale, as noted in the procedure section. This will be done before the start of the 24-hour closed-loop. Should the selected CGM fail during the CRC visit, the investigator will be able to switch to the backup CGM and continue the study, and will document the reason and impact of the change.

1.3. Insulin pump

The insulin pump used in this clinical study may be the OneTouch® Ping® insulin pump with modified Meter-Remote or the OmniPod™ Insulin Management System with the modified Insulet Personal Diabetes Manager (PDM). The pump delivers insulin subcutaneously through an infusion set, in this study the Inset® 30 infusion set. The OneTouch® Ping® insulin pump is not modified and has received 510k clearance (K080639). Only the Meter-Remote software has been modified to allow the algorithm to send commands from the APS© platform to the insulin pump by way of the modified Meter-Remote. The Meter-Remote is connected by USB to the laptop and communicates to the One Touch® Ping® insulin pump by radiofrequency. The

Meter-Remote will not be used for blood glucose monitoring or sensor calibration in this study. (A separate unmodified CONTOUR® NEXT EZ meter will be used for CGM calibrations.). The OmniPod™ Insulin Management system had not been modified and has received 510(k) clearance (K042792). Only the Insulet PDM has been modified to communicate with the APS® platform. Both insulin delivery systems, the OneTouch® Ping® and the OmniPod™, have been validated as components working with the APS® infrastructure (MAF-1625).

1.4. Control algorithm

The control algorithm is unique to this application: it combines a zone-Model Predictive Control (MPC) algorithm with the added safety feature of the Health Monitoring System (HMS) which provides warnings and notifications of impending hypoglycemia to request outside intervention, such as absorption of fast acting glucose. The notification is not only available to the subject via the AP device, but also to the physician or another person who could be located remotely in the future (this IDE exclusively takes place in the clinical research setting in presence of a physician). The HMS algorithm uses the same CGM data as the zone-MPC control algorithm but utilizes a separate algorithm for trending and predictions of future glucose values. Using a redundant and independent algorithm is an important safety feature of the overall AP device. The HMS will send a warning to the AP device and a text message to the attending physician (present at all times) whenever it predicts a glucose value below 70 mg/dL within the next 15 minutes. The warning will include a recommendation to give the subject approximately 16 g of carbohydrates. The warning must be acknowledged for the pop-up window to close. The acknowledgement gives the choice to “accept” or “ignore” the warning and recommendation.

The zone-MPC control algorithm is at its core a Model Predictive Control (MPC), which incorporates an explicit model of human T1DM glucose-insulin dynamics. The model is used to predict future glucose values and to calculate future controller moves that will bring the glucose profile into the desired range. Software constraints ensure that insulin delivery rates are constrained between minimum and maximum values. The first insulin infusion (out of n steps) is then implemented. At the next time step, k +1, the process is repeated based on the new measured glucose value and the last insulin rate. The algorithm adjusts insulin delivery automatically to achieve and maintain the patient’s glucose level within a predetermined safe range: 80-140 mg/dL. The only variable that may be adjusted between subjects is the *responsiveness factor* which is the ration of *Q/R.* It can be described as the agility of the control algorithm to respond to

changes in glucose concentration. Three levels may be evaluated: *Q/R* with a ratio of 1:12, 1:15 and 1:50 (from most responsive to least responsive). The default setting is considered to be the nominal ratio of *Q/R* of 1:15. The first subject will be evaluated using that setting. Then, following results from each subject, if results showed poor glucose control, as defined by frequent hypoglycemia alerts or excessive hyperglycemia, in the investigator's opinion, the *responsiveness factor* may be adjusted to the most agile setting of 1:12 or most conservative setting of 1:50 for the next subject.

The total number of subjects will remain 12 to 20 total. Each subject will only be evaluated using one *responsiveness factor* setting. Changes to another setting will be based on prior clinical results and decision of the investigator for the next subject. This will be a clinical decision to add to the overall safety of the study. All changes of the *responsiveness factor* between subjects and their justifications will be documented.

2. STUDY OBJECTIVES

2.1. Study's challenges

The purpose of this feasibility study is to evaluate the performance of the AP device while the subject is under close clinical supervision in a Clinical Research Center (CRC) setting. The assessment will take place over a continuous 24-hour closed-loop period with three types of challenges:

- **Unannounced meals**

  The purpose of this challenge is to evaluate the performance of the AP device to safely regulate the glucose level when the subject has an unannounced meal. In other words, it will determine whether the AP device auto-regulates insulin delivery following the meal and keeps the glucose concentration of the subject within the range [70-180] mg/dL for most of the 5 hours following the meal.

- **Overnight glucose control**

  The purpose of this challenge is to evaluate the performance of AP device during the night. It will determine whether the AP device will safety regulate the glucose concentrations of the subject during the night, i.e. if the glucose concentrations will remain within the [80-140] mg/dL range during sleep.

- **Exercise**

  The purpose of this challenge is to evaluate the performance of the AP device when the subject is exercising. The goal is to determine whether the AP device can maintain a safe glucose range or whether there is a need for an

exercise detection signal to improve glucose control during the exercise period. The analysis will determine if glucose level remains within the [70-150] mg/dL range during exercise and for most of the 3 hours following exercise.

2.2. Primary and secondary endpoints

The assessment of the performance of the device will be based principally on two types of metrics:

- Primary endpoints: percentage of time spent within a specific zone, in particular the desired zone [80-140] mg/dL. Other zones will be defined after meal or exercises.
- Secondary endpoints: review of the extremes of the glucose values of the subject, duration of those extremes and the review of any event requiring outside intervention to treat hypoglycemia or hyperglycemia.

The primary endpoint of the clinical study is the amount of time spent within a specified glucose target range. In this study there will be different ranges depending on both time of day and time after meals and exercise:

- Target range (unless described otherwise): [80-140] mg/dL
- Overnight target range: [80-140] mg/dL
- 5 hours postprandial target range: [70-180] mg/dL
- During exercise: [70-150] mg/dL
- 3 hours post-exercise: [70-150] mg/dL

The secondary endpoints of the clinical study include excursions outside the range, the maximum value of the excursion, the duration the subject remains outside of the target ranges and whether or not there is any outside intervention to treat hypo- or hyperglycemia. The extremes are defined as follows:

- For hyperglycemia: any blood glucose value >400 mg/dL (measured by YSI)
- For hypoglycemia: any blood glucose value <60 mg/dL (measured by YSI)

In addition, a secondary end-point will consist in analyzing CGM values that were trending beyond the desirable ranges. The analysis will determine the percent of time spent in the following zones:

- If glucose value per CGM is ≥300 mg/dL for more than 1 hour;
- If glucose value is predicted to be ≤70 mg/dL by CGM ;
- If glucose value per CGM is ≤70 mg/dL;
- If glucose value per CGM is ≤60 mg/dL;

The secondary endpoints will also be assessed by evaluating all safety events. The levels of hypoglycemia and hypoglycemia are described by Table 15–2~~Table 9–2~~.

3. BACKGROUND INFORMATION

3.1. Ethical background

The study will be conducted in accordance with the Declaration of Helsinki (1964), including all amendments, International Conference on Harmonization (ICG), Good Clinical Practice (GCP) guidelines and relevant local laws and regulations.

The final protocol and informed consent form will be reviewed and approved by Cottage Health System (Santa Barbara, CA) Institutional Review Board (IRB) (IRB #10-36) following the approval of this IDE by the FDA and prior to any subject screening being conducted. Any changes to the clinical protocol will be communicated to the FDA and the IRB as required by the regulations. Periodic and final study reports will be communicated to both FDA and IRB. The investigator will report Unanticipated Adverse Device Effect (UADE) and Serious Adverse Event (SAE) to both the FDA and IRB per reporting requirements.

Each subject will be provided with oral and written information describing the nature and duration of the study. Prior to initiation of any study-related procedures, the subject will sign and date a written informed consent to participate in the study and will also sign and date, if separate, the authorization form required under HIPAA, authorizing the use and disclosure of the subject's protected health information. The signed original informed consent form (ICF) and HIPAA authorization form will be retained with the study center's records and each subject will receive a copy of each form he/she has signed. The subject will also sign the California Bill of Rights. The investigator must be satisfied that the subject has understood the information provided before written consent is obtained. The original informed consent documentation must be made available for inspection by the investigator. Documentation of the informed consent form process will be available in the subject's source

documents. Informed Consent form draft can be found in Appendix 8 of the original IDE.

3.2. Summary of known risks and benefits

As this is a feasibility study, there are known risks and benefits. Providing close clinical supervision mitigates the risks as much as possible. Most of the risks are not unique to the study and are typical for patients using CGM and insulin pumps and who are having their blood glucose level checked using standard methods. The known risks are:

- Hyper and hypoglycemia brought on by changing the diet and insulin regimen and exercise during the trial.
- Weight gain or loss may be caused by changes in diet and insulin dosing during the study.
- Using the CGM or insulin pump: risk of bruising, infection, pain and/or bleeding at the site of insertion and skin site reaction to adhesive.
- Blood sampling with finger stick: minor discomfort and risk of infection at site of finger stick.
- Blood sampling with a needle: risk of infection at site of venipuncture, fainting, bruising, formation of a blood clot, pain and/or bleeding at the site of venipuncture.
- 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.
- On rare occasions, heart or lung problem identified during the exercise test.

However, the benefits of the study are multiple. Results will support moving one step closer toward a future portable autonomous artificial pancreas for type 1 diabetic patients. This feasibility will evaluate the performance of a zone-MPC and HMS algorithms as well as the concept of an overall Artificial Pancreas using a subcutaneous glucose monitor and insulin pump with unannounced meals, night and exercise.

3.3. Summary of past findings

3.3.1. Overview

Similar studies have been performed in the past using the APS© platform and other types of algorithms. Using a subcutaneous glucose sensor and a subcutaneous insulin delivery method presents the advantage of using currently available and proven technology, while expanding the intended

use of those devices. The challenge associated with those devices is the delay of data from the sensors and the delay of the action of the insulin delivered. Results to date have been very promising. All closed-loop evaluations have been limited to in-clinical settings of 12 to 48 hours cycles. They have shown that, with currently approved CGMs and insulin delivery pumps, it is possible to automatically regulate glucose level within an acceptable range. In particular artificial pancreas devices reduced and most frequently avoided hyperglycemia during the day and nocturnal hypoglycemia.

3.3.2. Necessary future development

Future studies need to be designed to address larger challenges of unannounced food intakes as well as situations when the patient is under stress or exercising. Generally, additional studies are necessary to identify and optimize control algorithms. Those algorithms, tailored to be optimal for each patient will need to include multiple layers of safety mechanisms to prevent hyperglycemia and hypoglycemia. Eventually, it is also desirable to expand the testing to offer a choice of CGMs and insulin delivery pumps to give flexibility to the patient.

3.3.3. Overview of recent results: IDE G090129

IDE G090129 sponsored by UCSB and Sansum Diabetes Research Institute (SDRI) was approved by FDA on April 2010. The study of 10 subjects evaluated the performance of a closed-loop artificial pancreas using the APS© platform with the Dexcom® SEVEN® PLUS (Dexcom®, San Diego, CA) CGM, the OmniPod™ (Insulet Corp, Bedford, MA) insulin delivery pump and the mpMPC control algorithm and IOB (insulin-on-board) constraints. The control algorithm of that study was a control-to-target Model Predictive Control algorithm, i.e. the target was 110 ± 30 mg/dL. The algorithm was also referred to as mpMPC with IOB constraints. The algorithm was customized for each patient based on data collected during 3 outpatient days prior to the in-clinic day. The insulin delivery of the subjects was entirely controlled by the artificial pancreas during the closed-loop in the CRC setting. The closed-loop lasted for approximately 10 hours for each subject and included one unannounced meal. The subject was closely monitored in the CRC setting. The clinical trial took place at the Sansum Diabetes Research Institute (Santa Barbara, CA). The first subject underwent closed loop in August 2010. To-date, 10 subjects have been enrolled and completed the trial.

Early analysis of the preliminary results of IDE G090129 are presented in Figure 3–1~~Figure 3–1~~. As can be seen the closed-loop results are all in the

A + B zones of the Control Variability Grid Analysis (CVGA) which are desirable zone. Four of the ten subjects were in the A-zone and six in the B-zone, trending mostly towards the high end. This picture analysis shows that the controlling algorithm was able to maintain the subject within a safe zone automatically even when following an announced meal. There was no adverse event reported during the study.

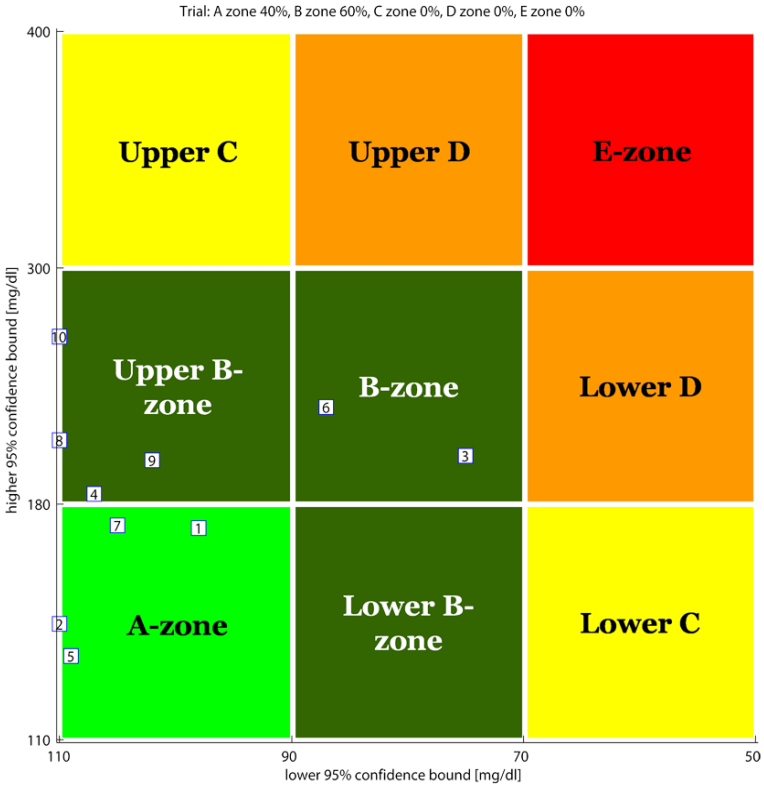

Figure 3–1: CVGA of preliminary results of closed-loop under IDE G090129

Another feasibility study using the same control algorithm (mpMPC with IOB constraints), the APS© platform, same CGM (Dexcom® SEVEN® PLUS) and same CSII (OmniPod™) has been completed in Israel (Schneider Children's Medical Center). Glucose control of twelve subjects was automated using the closed-loop system for a period of approximately 6 hours. During that time, the system was challenged with an unannounced meal of 30 to 40 g of carbohydrate after a starting point of low to mild hyperglycemia (180-250 mg/dL). Results showed that glucose level was maintained with the safe range of [80-180] mg/dL 70% of the times and the low and high blood glucose indices were 0.12 and 6.9 respectively. No hypoglycemia episodes were reported. Severe hyperglycemia was reported in only 3 trials with postprandial peaks of 275, 288 and 276 mg/dL.

3.3.4. Overview of most recent results: IDE G110093 with same AP device as in this proposed protocol

The clinical protocol of this IDE study using the same Artificial Pancreas device was originally approved in August 2011 and preliminary results are presented below. Up to this point, thirteen subjects have been enrolled and twelve have completed their clinical trial. The results of the twelve study-days are presented in Appendix 9 of the submission (refer to S003 submission). Figure 3–2 and Figure 3–3 are examples of snapshots of glucose, CGM and YSI profiles of two subjects during the 24-hour closed-loop. These are typical of the various profiles, they include post-prandial peaks and HMS alerts which effectively prevented hypoglycemia. The ingestion of carbohydrate following the HMS alert is indicated on the snapshots.

Of the 12 enrolled subjects, the first enrolled subject did not complete her first study-day as explained hereafter and had to return: before arriving at the CRC for the start of the closed-loop session, took 3.35 units of insulin to correct for her hyperglycemia (correction factor of 1 to 70) for an elevated capillary glucose value of 270 mg/dL at 2:09 pm, approximately 2 hours before her visit to the CRC. Upon being connected to the Artificial Pancreas during initialization the HMS predictive alarm was triggered due to her glucose rate of fall due to the recent outpatient correction bolus. All procedures for glucose rescue were followed. The HMS was triggered an additional 3 times over the next 2 hours. YSI nadir was 44 mg/dL with mild symptoms of hypoglycemia. The admission was stopped at this time. Additional oral glucose was given. The subject was discharged home once her glucose concentration was stabilized at a safe level and was rescheduled for a different study day.

Overall, the results from the 12 subjects showed that there were no safety events. The HMS safety alert effectively predicted imminent hypoglycemia and issued a recommendation, which was followed each time to ingest carbohydrate, hence preventing hypoglycemia. There was no CGM or YSI measurements below 60 mg/dL. The time spent between 60 and 70 mg/dL was minimal (only 1% of the overall time, on average was spent below 70 mg/dL).

The primary end-points as described by the approved clinical protocol were to measure the percent of time the glucose level of the subject remains within the following pre-specified target range:

- Target (unless described otherwise): [80-140] mg/dL
- Target overnight: [80-140] mg/dL
- Target 5 hours after meal: [70-180] mg/dL
- Target during exercise: [70-150] mg/dL
- Target 3 hours after exercise: [70-150] mg/dL

Table 3–1 is a summary of the average time spent in each zone as measured by YSI. The same table for results measured by CGM can be found in Appendix 9 of the IDE submission.

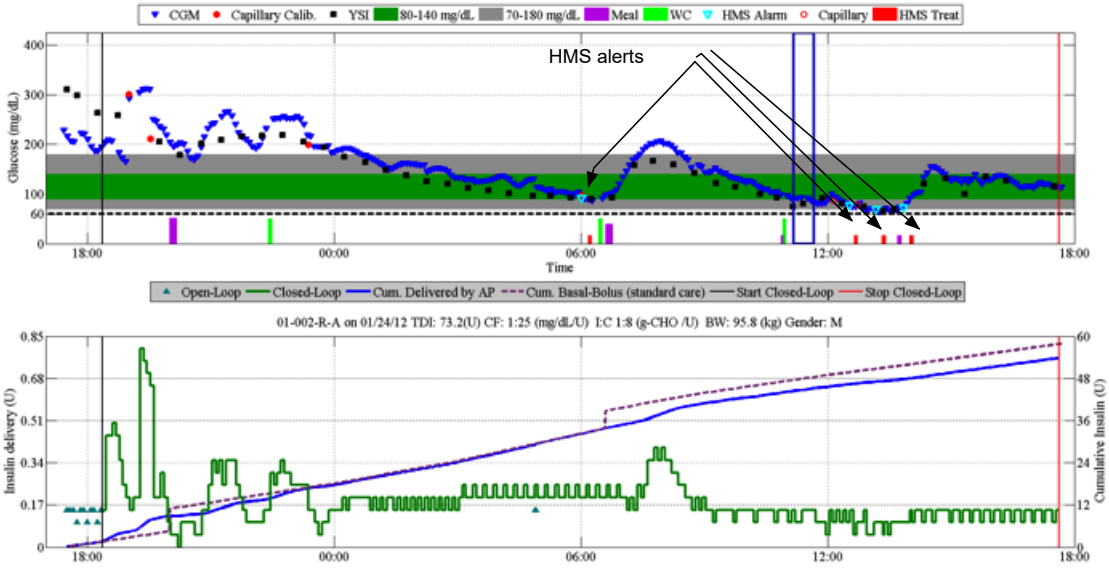

Figure 3–2: Snapshot of glucose, CGM and YSI profile or subject 01-002

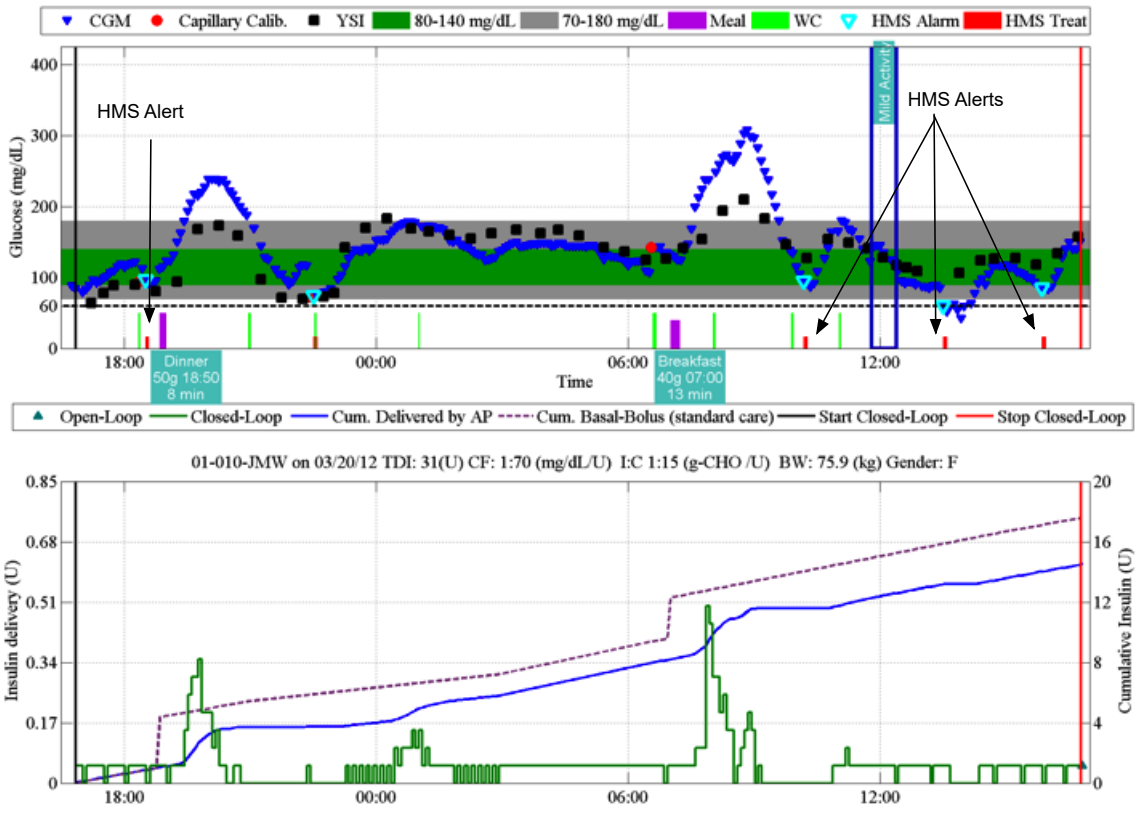

Figure 3–3: Snapshot of glucose, CGM and YSI profile or subject 01-010

Table 3–1: Overall time in range by YSI for 12 subjects

	Entire CL	CL excl meals & exercise	Midnight to 7am	Dinner Meal	Breakfast Meal	30 minute exercise	Exercise +3 hrs	3 hrs post exercise
<70	1%	1%	0%	0%	2%	0%	3%	4%
70-180	**4.** 81%	**5.** 92%	**6.** 92%	72%	63%	92%	89%	89%
>180	18%	7%	8%	28%	35%	8%	7%	7%
<70	1%	1%	0%	0%	2%	0%	3%	4%
70-150	63%	83%	79%	39%	45%	54%	67%	68%
>150	36%	16%	21%	61%	53%	46%	30%	28%
<80	5%	4%	1%	4%	7%	0%	7%	13%
80-140	**7.** 52%	**8.** 73%	**9.** 70%	30%	30%	38%	56%	87%
>140	43%	23%	29%	66%	63%	62%	36%	0%

Note: CL = closed-loop

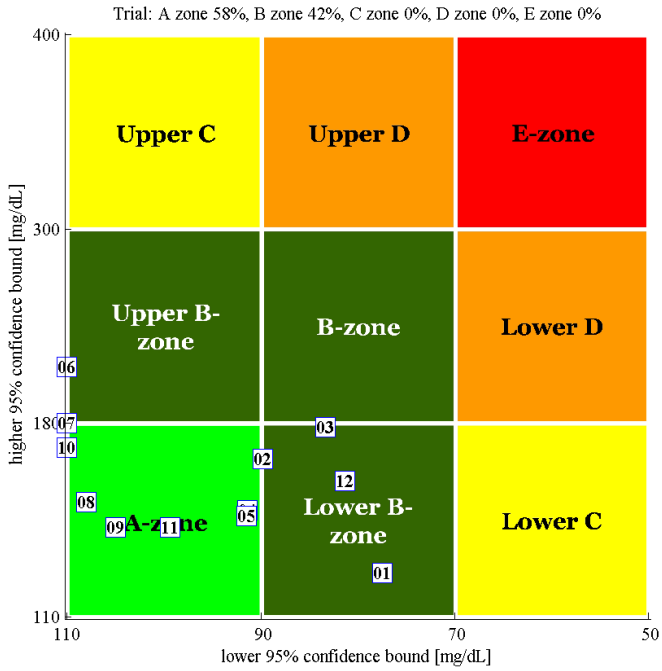

Figure 3–4: CVGA during overnight period (midnight to 7:00 am)

Over the 24-hour closed-loop period when the AP device monitored glucose level and automatically delivered insulin, for 81% of the time by YSI, the glucose level was within [70-180] mg/dL range: this included a nocturnal period, 2 meals and an exercise period.

When excluding the periods following the meals and exercise segment, the total time spent within the [70-180] mg/dL zone increased to 92% when measured by YSI. Most frequently, when following a meal, the glucose level increased. During the 5-hours following each meal, the subjects spent on average 63-72% in the zone [70-180] mg/dL while they spent 89% in that same zone during the 3-hours following the 30-minutes exercise segment at moderate intensity. The control of the AP device during the nocturnal period was particularly effective as, on average, the subjects spent 92% of their time within the zone [70-180] mg/dl, 70% of the time within the narrower zone [80-140] mg/dL and 0% below 70 g/mL. A summary of the nocturnal results is illustrated by CVGA (Figure 3–4) where all data points are within the A and B zones.

The actual profile from each subject will vary due to multiple factors including the initial glucose level and initial slope (trend) of each subject. However, in summary, the data showed that when measured by YSI or CGM, the glucose level of the subject was in control the majority of the

times with some peaks following meals and valleys following exercise, but never reaching values that could affect the safety of the patient. The peaks and valleys are explained by the fact that insulin delivery is automatically controlled with no input from the user indicating the start of a meal, the size of the meal, or the start of exercise. Therefore, the algorithm must detect the beginning effect of the meal (increased of glucose level) or beginning of the exercise (decrease of glucose level) to start reacting and anticipating further glucose increase and decrease and to adjust insulin delivery above or below basal levels accordingly. The redundant safety alert system (HMS) effectively requested ingestion of CHO when predicting hypoglycemia. Those recommendations were followed and hypoglycemia was avoided.

With those early results, the AP device showed that, for the evening and breakfast meals, it was able to detect the meal and prevent excessive post-prandial peaks and maintained the glucose level within a safe range.

The glucose level during and after the exercise period has a different profile for each subject because of the difference in the trend preceding the exercise session. There was no hypoglycemic event or HMS alert during the exercise period

In conclusions, this preliminary analysis of the results showed that the AP device is able to detect meals and react appropriately to prevent excessive post-prandial peaks. It also works effectively in anticipating risks of hypoglycemia and alerting the physician / subject to ingest carbohydrate. The redundant safety mechanism functioned as anticipated.

Because of the post-prandial peak, the new clinical study is proposing to use a dose of Technosphere® Insulin Inhalation Powder at the beginning of each meal. TI is a very fast acting insulin. It is anticipated that the TI will mimic the early phase of prandial insulin hence, will reduce the post-prandial peak. This will allow the AP device to operate more effectively as a regulator of glucose level using subcutaneous delivery of insulin. Besides the added TI dose at the beginning of each meal, the clinical design will remain exactly the same (only the meal size of the breakfast will be increased to 50 g of CHO to be the same as the evening meal).

9.1. Description of population studied

Although there is no restriction in recruitment of subjects as to race or ethnicity, it is expected that the subjects will primarily be non-minority white. The population of Santa Barbara is primarily non-minority Whites and Latinos of

predominantly Mexican descent, with African Americans, Asians and America Indians comprising less than ten percent of the population. Because type 1 diabetes disproportionately afflicts the Northern European population and is rare among Latinos of Mexican descent, it is not expected that minorities or non-English speaking subjects will be enrolled. Subjects will be recruited using the Sansum Diabetes Research Institute database of patients.

It is expected that the ratio of men to women will be close to 1:1.

The population studies in this clinical trial eligible is adults aged 21-65 years of age with type 1 diabetes mellitus for at least one year. For more details, refer to Sections 11.15~~.1~~ and11.25~~.2~~.

The in-clinic portion of the trial will take place at the Sansum Diabetes Research Institute (SDRI). Informed consent will be obtained before the study procedures are conducted.

9.2. Literature data references

The current treatment method for insulin-dependent diabetic patients requires either multiple daily subcutaneous insulin injections or continuous subcutaneous insulin injection via a pump. Both treatment modes necessitate frequent blood glucose measurements in order to determine the daily insulin requirements for maintaining euglycemia. Because such frequent monitoring involves patient discomfort and is very time consuming, few patients are able to maintain their levels of glucose consistently within a safe range. Mounting evidence suggests that euglycemia is necessary to prevent the complications of diabetes. As a result, being able to develop an automated glucose monitoring and insulin delivery system has been considered a key priority for improving the life of patients with type 1 diabetes.

In the last two years, at least eight teams have reported results of closed-loop feasibility studies:

- El-Khatib et al.: “A bihormonal closed-loop artificial pancreas for type 1 diabetes” (2010)
- Hovorka et al.: “Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial” (2010)
- Renard et al.: “Closed-loop insulin delivery using a subcutaneous glucose sensor and intraperitoneal insulin delivery: feasibility study testing a new model for the artificial pancreas” (2010)

- Atlas et al.: "MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes" (2010)
- Bruttomesso et al.: "Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: preliminary studies in Padova and Montpellier" (2009)
- Clarke et al.: "Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience" (2009)
- Dassau et al.: "Real-time hypoglycemia prediction suite using continuous glucose monitoring: a safety net for the artificial pancreas" (2010)
- Buckingham et al.: "Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension" (2010)

The detailed review of those studies can be found in the IDE submission related to this clinical protocol.

Some of the studies used insulin only or insulin combined with glucagon. Insulin was most often delivered subcutaneously, but also intra-peritoneally, many types of control algorithms were used (proportional-integral-derivative, fuzzy logic, model predictive control, hypoglycemic prediction, modified linear prediction, Kalman filtering, adaptive hybrid infinite impulse response filter, statistical prediction and numerical logical) and studies were performed on children or adults.

Overall, each automated closed-loop system managed to maintain safer levels of glucose levels than a non-automated system. The variety of types of algorithms being evaluated indicates how active this field of research is. It also indicates that the algorithm that will be most effective and safe for the physiology of a wide range of patients has not been identified yet. The answer will likely consist in using a combination of algorithms. So far, all controlling algorithms showed that they were able to bring glucose level to a safe range and prevent or at least reduce the number of hyper and hypoglycemic events.

10. TRIAL DESIGN

10.1. Overview of clinical study

The study design is a non-randomized, uncontrolled, feasibility study enrolling 12 to 20 adult subjects at one site only. The Sponsor anticipates that the study duration will last up to a year, or until enrollment and testing are completed.

The individual subject participation is anticipated to be approximately of one week's duration (or possibly longer if any visits are rescheduled). The overview of the study design for each subject is described by Figure 10–1~~Figure 4–1~~.

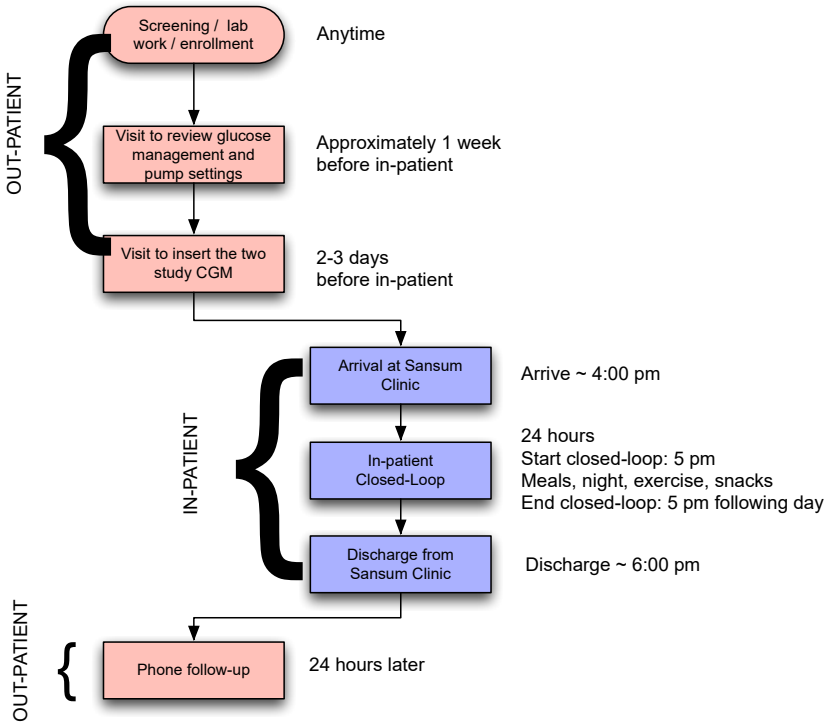

Figure 10–1: Overview of the clinical trial

- Upon successful screening and informed consent process, during the week prior to the CRC visit, the subject will review overall glucose control and insulin pump settings with study staff to aim for optimal glucose control.
- Two to three days prior to the CRC visit, the subject will attend an outpatient visit for the insertion, by study staff, of two CGM sensors, as well as to receiving training and study instructions on how to care for them. The two CGMs will be set to their blinded mode. The Blinded Mode Dexcom® CGM documentation is provided in Appendix 14 of the original IDE submission. The subject will be trained on how to calibrate and care for the study CGMs for the 2-3 days as an outpatient. The subject will be instructed to manage his/her own glucose levels per the method he/she is accustomed to. The subject will not be able to see glucose readings on the blinded receiver of the CGM prior to the CRC visit, however other non-glucose related alarms will be functioning.

- The CRC visit will last approximately 25-28 hours including approximately 24 hours, in closed-loop to evaluate the AP device. During all that period, blood samples will be analyzed using a YSI 2300Stat every 30 minutes or more frequently if requested by the study physician. Each time a YSI measurement is taken, a finger stick measurement with the CONTOUR® EZ blood glucose monitoring system will be used for information purpose only.
    - If the subject's blood glucose is > 250 mg/dL at arrival at the clinical, the clinical study will be rescheduled for that subject.
    - The subject will check in at Sansum Diabetes Research Institute at approximately 4:00 pm and have the insulin pump of the study inserted by the physician. Both CGM receivers will be unblinded during the CRC visit. The subject's own insulin pump will be disconnected. An intravenous catheter will be inserted for blood samples and for IV administration of glucose, if necessary.
    - The closed-loop will start at approximately 4:30 pm.
    - Approximately 2 hours later, the subject will be given a small unannounced meal consisting of 50 g of CHO.
    - The subject will sleep overnight at the center, while connected to the AP device.
    - At 7:00 am, another unannounced meal (breakfast) consisting of 50 g of CHO will be given.
    - At 11:00 am, a small snack of approximately 16 g CHO if YSI value is <120 mg/dL and the subject will start exercising for approximately 30 min at 50% of the his/her predicted heart rate reserve.
    - Approximately 3 hours after end of exercise, a small snack of 16 g CHO will be given.
    - Closed-loop will be stopped at approximately 4:30 pm, 24 hours after starting.
    - The subject will return to using his/her own insulin pump and CGM (open loop), once stable, the subject will be discharged from the CRC. Blood ketones will be measured. The subject will be discharged only if:
        - Blood glucose is greater than 90 mg/dL for 1 hour

- Blood glucose is less than 180 mg/dL with ketones less than 0.6 mmol/L.

- The study personnel will contact the subject in person on site or by phone approximately 24 hours after the discharge as a follow-up.

The *responsiveness factor* used in the control algorithm is decided for each patient based on the results from the previous subject. The default nominal setting of the *responsiveness factor* will be *Q/R* ratio of 1:15. Changes of the *responsiveness factor* will be decided upon clinical results from each subject in evaluating the frequency and severity of hypoglycemia and the hyperglycemia. A subject will only be studied for 1 setting of the *responsiveness factor*. The decision of changing the *responsiveness factor* setting will be made by the investigator to ensure the overall safety of the study.

Figure 10–2~~Figure 4–2~~is a graphical representation of the study design and the expected glucose level profile during the 24-hour closed loop.

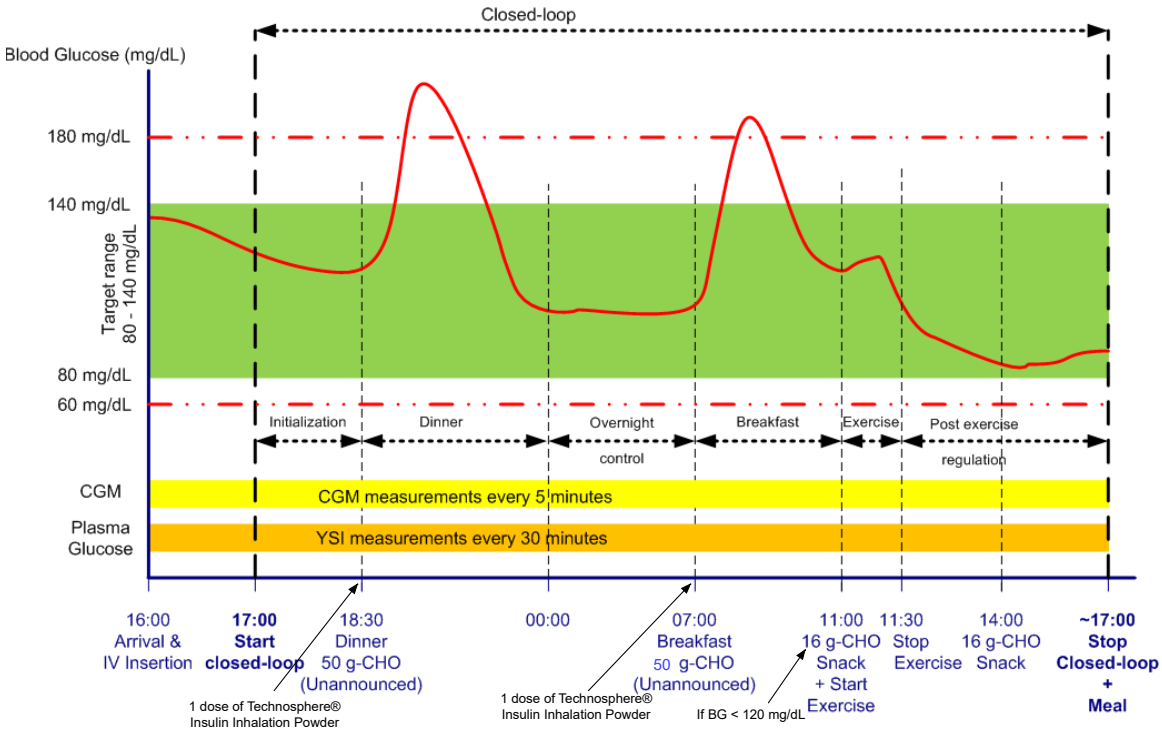

Figure 10–2: Clinical Study Design

10.2. Screening visit: physical exam

Each possible subject must go through a screening visit up to 1 month prior to their participation to the study to determine if he/she meets the eligibility criteria for the study. The patient will be asked questions about his/her health and medication history as well as authorization to access and review his/her medical record. The subject will be given opportunity to ask questions. The screening visit will also include:

- A physical examination
- If the subject is female and of childbearing potential, perform a pregnancy blood test. On admission day at the CRC, a urine pregnancy test will be repeated.
- Vital sign recording: height, weight, temperature, blood pressure, heart rate
- Blood test for routine laboratory evaluation: hemoglobin A1c, thyroid function, kidney function, and liver function
- Description of the clinical trial and food and insulin regimen to follow during in-clinic days.
- Recording of the following:
    - Download of subject's pump settings including basal profile, correction factors and insulin to carbohydrate ratios.
    - Average total daily insulin (TDI)
    - Duration of diabetes
    - Hemoglobin A1c
- Review and approval of the Informed Consent form (IC).

All laboratory testing will be performed by an accredited laboratory. The screening evaluation form can be found in Attachment 9 of the IDE. The Informed Consent form can be found in Appendix 8 of the IDE submission.

10.3. Subject preparation to initiate trial: outpatient

A day or two prior to the initiation of the outpatient phase of the trial, two DexCom G4® glucose sensors will be inserted beneath the skin of the patient according to the manufacturer's recommendations. The patient will be instructed on how to care for the receiver when in the shower or when sleeping

and how to enter the blood glucose readings for calibration. The Dexcom® G4® measures the patient's interstitial glucose level every 5 minutes. The CGM will be in blinded mode and the subject will not be able to see glucose readings on the CGM receiver.

Calibration of the CGM will be performed using CONTOUR® NEXT EZ Blood Glucose meter and strips. Study personnel will perform the Quality Control (QC) procedure to check that the glucose meter is working properly. The QC procedure will use the two Control Solutions (low and high). The results from each control solution must be within the acceptable range indicated by the Control Solution. This meter and strips will be given to the subject to perform all required calibrations of the CGM.

CGM calibration will be performed according to manufacturer's instructions and before meals and bedtime. In addition to the Dexcom® G4® Blinded Mode User Guide, the subject will be given an instruction sheet called "Subject Blinded CGM Instruction Sheet" on how to perform calibration of the CGM during the outpatient phase. During the outpatient phase of the trial, the subject will use his/her own CGM if using one, and his/her own insulin delivery pump. The subject will rely on finger stick blood values for insulin delivery settings and bolus amounts. The subject will be instructed to perform finger-sticks at least four times per day for both routine care and for device calibration. Glucose values for calibration should be taken when glucose values are not changing rapidly, e.g. before meals.

During the outpatient phase of the study, the patient will be encouraged to contact Sansum Diabetes Research Institute to address any question or concern he/she may have. Should there be any event of hyperglycemia or hypoglycemia, the subject would contact the study physician who will determine the safest course of action for the subject. This may include delaying or excluding the patient from the closed-loop phase of the trial.

Subject will be instructed to bring to CRC visit all diabetes care and insulin pump supplies, although subject will use study-provided rapid acting insulin (of same brand used by subject) during CRC visit. Subject will be instructed to charge the CGM units overnight on the night prior to the CRC visit.

If the subject is using CGM at time of enrollment, the subject will not use their own CGM device from the time of study CGM insertion until the time of discharge from the CRC visit.

In case of illness or cancellation, the visits may be rescheduled at the discretion of the investigator.

10.4. In-patient: at the CRC (2-days)

Figure 10–3~~Figure 4–3~~summarizes the key elements of the clinical trial for each patient's CRC visit.

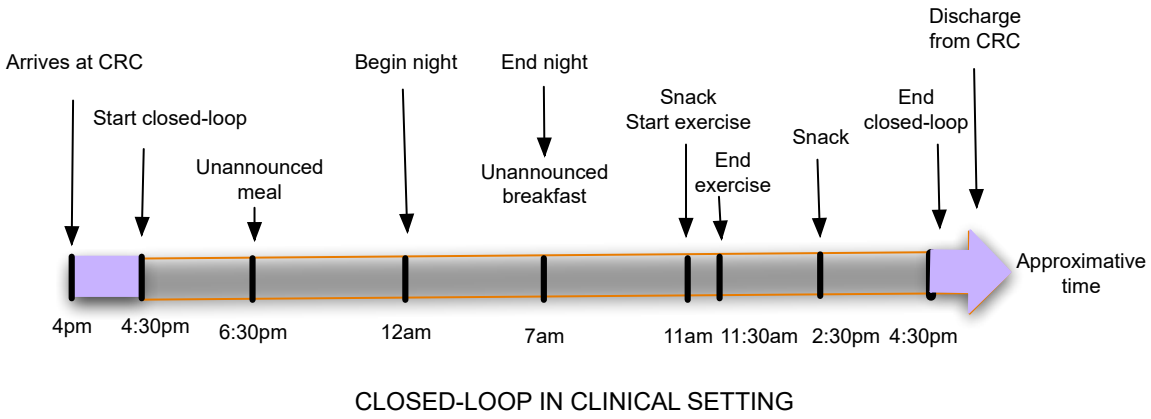

Figure 10–3: Clinical Study Timeline during Closed-Loop

10.4.1. Arrival

The subject will arrive to the CRC center at approximately 4 pm with all diabetes care supplies and using own insulin pump upon arrival. If the subject's blood glucose is greater than 250 mg/dL when they arrive at the CRC, then, the clinical study will be rescheduled. If the subject is female of child bearing potential, a urine pregnancy test will be performed on arrival to the CRC to verify that she is not pregnant. The investigator will also check for any changes in health since the screening visit and the insertion of the CGM. The investigator will determine if any reported health changes may have an impact on the enrollment status of the subject. The subject will already be wearing two CGMs for the study set to blinded mode. Upon arrival, the study staff will unblind both CGMs. The study staff will also perform the Quality Control process on the glucose meter (OneTouch® Ultra®) using two control solutions. The day of the trial, the infusion set of the OneTouch® Ping® Glucose Management System with modified meter remote CSII will be inserted subcutaneously. They will be inserted into the abdomen using a non-hypertrophied area, as clinically determine by the investigator. The pump and its modified meter remote will have been paired and verified by the manufacturer, i.e. Animas® Corporation. The insulin used for the trial is the same as the insulin used

by the subject. A full new cartridge of insulin will be used for the closed-loop phase (same brand as the one normally used by the subject).

An indwelling catheter will be put in place for frequent blood glucose monitoring and for the rapid administration of intravenous glucose if necessary. No heparin and / or heparin lock will be used during the study.

The investigator determines which one of the two CGM devices will be used in the trial and documents the rationale for the decision. For example, the most accurate CGM may be used, and may be determined by the closest sensor glucose value to a meter glucose value performed at the time. The second CGM is considered a mitigation factor, a back-up in case the first CGM ceases to function properly during the trial. During the study, the physician may switch to using the alternate CGM if there was a problem with the radiofrequency communication or any other abnormalities affecting the output of the CGM. The rationale for selecting either one of the CGMs to start the trial will be documented on the CRF. If a CGM has to be switched, the change will be documented and explained. If both CGMs were performing equally, either one of them may be selected. If both CGMs were to cease to function, the clinical trial for the subject would be terminated and the investigator will determine whether it will be rescheduled.

Blood finger stick is performed using the CONTOUR® NEXT EZ Blood Glucose meter and strips.

Once all connections have been verified, the subject will be disconnected from his/her insulin pump and will be connected to the AP device. The AP device is connected as a closed-loop per the AP User Manual, but the control algorithm will not be turned on until approximately 4:30 pm. In effect, the device will operate as an open-loop until the controlling algorithm is turned on, thus closing the loop.

While at the CRC, the subject will calibrate the CGM following the manufacturer's recommendations (~ every 12 hours) and using the CONTOUR® NEXT EZ device. In addition to the recommended calibration, the subject will calibrate the CGM approximately 30 minutes before each meal and before going to bed.

10.4.2. Monitoring

10.4.2.1. On-going monitoring

During the closed-loop phase of the study, the following personnel will be present:

- Study coordinator
- Study engineer
- Study physician

Blood glucose level will be measured using a YSI 2300 Stat at a minimum of every 30 minutes (±10 min) and as described by Table 10–1~~Table 4–1~~. The study physician may request more frequent measurements for safety. If the subject reports symptoms of hypoglycemia, the blood glucose level will be measured with YSI and hypoglycemia guidelines will be followed. The YSI will be used according to manufacturer's instructions and operated by trained study staff. The YSI will be checked a minimum of every 2 hours with the 180 mg/dL standard and recalibrated if YSI glucose standard reads outside the range of 177-183 mg/dL or as needed. All plasma glucose samples will be read on 2 membranes and discrepancies in values that exceed 5 mg/dL will be called to attention of the study physician to assess the need for immediate recalibration.

Each time a YSI measurement is taken, a finger stick measurement using the CONTOUR® EZ blood glucose monitoring system will be taken for information.

Calibration of the CGM will be performed with a finger stick with the CONTOUR® NEXT EZ glucose meter. On the day of CGM insertion and at the beginning of the CRC visit, QC testing of the standard solution specific to the CONTOUR® NEXT EZ glucose meter will be performed. QC may be repeated any time there is a question about the glucose result from the meter. The labeling of the commercially available standard solution can be found in Appendix 13 of the original IDE submission. The QC testing will be performed with at least two different concentrations of control solution, including a concentration in the hypoglycemic range if the manufacturer provides one. A glucose meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.

Table 10–1: Frequency of glucose monitoring during CRC

Measurement	When	Frequency
CGM	Closed-loop	Every 5 min
Finger stick OneTouch® Ultra®	Calibration of CGM	Per manufacturer's guidelines and before meals & at bedtime
YSI + finger stick CONTOUR® EZ	Closed-loop	Every 30±10 min
YSI + finger stick CONTOUR® EZ	If subject reports symptoms of hypoglycemia	When subject reports symptoms of hypoglycemia
YSI + finger stick CONTOUR® EZ	Hypoglycemia: BG<70 mg/dL per YSI Or if AP device (CGM) predicts <70 mg/dL in the following 15 min	Every 15±5 min until YSI >80 mg/dL
YSI + finger stick CONTOUR® EZ	Hyperglycemia: BG>400 mg/dL	Every 15±5 min Until YSI<300 mg/dL
YSI + finger stick CONTOUR® EZ	During exercise	Every 15±5 min and for 1 hour after starting exercise

The AP device includes multiple visual and auditory alarms that are embedded into the APS© software should the system malfunction. The control algorithm also includes intrinsic safety limits that trigger alarms should the patient's glucose level go too high or too low and which prevents the system from delivering too much insulin.

Should the HMS predict that the glucose level is going to be <70 mg/dL in the next 15 min, the system will alert on the AP device and send a redundant text message to a predefined list of people, which in this study will be only the physician (who will be next to the subject in this study) to notify the subject to eat 16 g of CHO. All warnings issued by the HMS will be documented.

To prevent dehydration secondary to hyperglycemia, the subject will be allowed to consume sugar free beverage during the trial if he/she is thirsty.

Each adverse event will be graded as mild, moderate, or severe as described by Table 15–1~~Table 9–1~~. Should there be any Serious Adverse Event or Unanticipated Adverse Device Effect, immediate action for the safety and welfare of the patient will be taken. An investigation will be promptly conducted and reported to the safety

officer of the IRB. All adverse events will be documented as described in section 159.

10.4.2.2. Blood volume requirements

Maximum amounts:

All subjects are adults between the age of 21 and 65 years old. At the time of admission, the maximum number of blood draws that can be safely performed based on the subject's age, weight, blood draw history and volume per draw will be determined. The amount of blood that may be drawn should not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. It is anticipated that the number of protocol-defined blood draws will not exceed this subject limit and no single blood draw will exceed 1.5 cc. However, if the required number of draws for the admission is determined to exceed the recommended limit for the subject, the admission will be cancelled. If the blood draw limit is reached during the admission for any reason, the admission will be terminated.

Worst case estimate:

It is anticipated that at a minimum, 51 blood draws will be necessary during the admission. The frequency of YSI measurement may be increased following HMS warnings or for any other reason. As a worst case, if the HMS were raising 9 to 10 warnings, hence increasing the frequency of YSI measurements, it would require to perform approximately 80 blood draws. Blood sparing methods will be used. Therefore, each blood draw measurement will require approximately 1.2 cc. However, for the worst case estimate, the calculation will consider that a blood draw may require 1.5 cc. Therefore, if there were between 51 and 80 YSI readings, the total amount of blood drawn would be between:

51_{draws} x 1.5 cc = 77 cc

80_{draws} x 1.5 cc = 120 cc

Finger stick:

Each fingerstick measurement requires 1.5 microliters. As these are minimal, they are not included in the impact of total blood draw volume.

Screening laboratory:

Sampling for screening laboratory will require approximately 10 cc. The laboratory testing is likely going to take place 1 to 8 weeks prior to the CRC clinical session.

10.4.2.3. Safety

The site maintains appropriate equipment for mitigating severe Adverse Events that may occur during this study. The safety equipment at the CRC includes:

- An automated defibrillator
- A standard crash cart including glucagon, intravenous and oral dextrose, oxygen with ambubag.

Sansum Diabetes Research Institute, where the trial will take place, is located 1/2 block from Santa Barbara Cottage Hospital, less than 30 seconds by car, should there be any Serious Adverse Event.

The Sponsor and Principle Investigator of this study is a physician certified in Internal Medicine for more than 19 years. For the last 10 years, he has been part of or led more than seventy clinical studies in the diabetes therapeutic area. All studies were conducted per FDA regulations and ICH/GCP guidelines. These credentials have been summarized in the IDE submission. The Principle Investigator is also the developer of this clinical protocol.

Table 10–2~~Table 4–2~~ describes which actions will be taken for the safety of the patient.

All actions taken will be documented in the CRF. For example, if the investigator initiates a correction bolus or if the patient ingest carbohydrates. Any outside intervention not requested by the device will lead to the termination of the trial for that subject, that day. The trial may be repeated another day after adjustment of the *safety factor*. If the subject is required to ingest carbohydrates following warnings generated by the HMS, these will not be considered a failure of the device and the trial will continue. All outside intervention, requested by the HMS or not, will be documented in the CRFs.

Table 10–2: Safety action to take in case of hypoglycemic and hyperglycemic events based on YSI values

CONDITION	ACTION
Hyperglycemia	
Asymptomatic and serum glucose > 250 mg/dL more than 2 hours Or if subject develops nausea, vomiting or abdominal pain	Test the blood for serum ketones. Check the pump, if not running, change pump. If blood ketones exceed 1.0 mmol/L, the study for this subject will be terminated. If a correction bolus needs to be administered by the study staff, it will be administered with a syringe.
Mild polyuria and polydipsia; serum glucose > 250 mg/dL more than 3 hours	If blood ketones were less than 0.6 mmol/L at 2 hours, recheck blood ketones and check the pump. If pump not running or catheter occluded or leaking, change the pump. If blood ketones > 1.0 mmol/L, then the study for this subject will be terminated. If a correction bolus needs to be administered by the study staff, it will be administered with a syringe.
Glucose level ≥300 mg/dL for more than 1 hour	Investigator will give a manual correction dose bolus administered with a syringe. The trial will be terminated for this subject.
Emesis, but with a normal sensorium and glucose > 350 mg/dL	The study for this subject will be terminated. Intravenous fluids would be given at a rate of 3,000 cc/M2/day. A manual correction dose of a short acting insulin analog would be given. The insulin infusion set would be changed. The subject would remain in the CRC until serum glucose is < 200 mg/dL. Subject will be monitored for at least 2 hours post treatment by study investigator. In case of reoccurring symptoms the subject shall be transferred to the emergency room by paramedics. If a correction bolus needs to be administered by the study staff, it will be administered with a syringe.
Decreased sensorium (sleepy, difficult to arouse) with or without emesis: glucose > 350 mg/dL	The study will be terminated for this subject. The subject will be transferred to the emergency room for evaluation with electrolytes and pH and monitoring for possible further deterioration of neurological status as a decrease sensorium may be indicative of electrolyte and/or pH abnormalities that could lead to respiratory or cardiac depression if not detected and treated appropriately.
Blood glucose >400 mg/dL	The study is terminated for this subject. The investigator will give a manual (with a syringe) correction bolus.
No heart rate, no blood pressure	Perform resuscitation. If this occurred all studies would be put on holding pending an investigation of the circumstances leading to this very adverse outcome. Call 911 and transfer the treated subject to emergency room.
Hypoglycemia	
If CGM prediction is <70 mg/dL in	The AP device notifies the physician. The physician treats the

CONDITION	ACTION
the following 15 min	subject with 16 g of oral CHO. The study is not terminated for this subject. This is an anticipated part of the study. YSI frequency will increase to every 15±5 min until YSI >80 mg/dL.
Adrenergic/cholinergic symptoms without neurocognitive changes; YSI<70 mg/dL, but > 60 mg/dL	Subjects would be closely monitored with glucose levels every 15±5 minutes until YSI > 80 mg/dL. The investigator will give CHO if directed by HMS.
Asymptomatic or adrenergic/cholinergic symptoms with serum glucose < 60 mg/dL	If the HMS did not raise hypoglycemic warning, the study will be terminated for the subject. Subject will be treated with oral simple carbohydrates, such as glucose tablets or juice, and glucose by YSI rechecked in 15 minutes, and treatment repeated if glucose remains < 70 mg/dL. With second treatment the insulin infusion will be suspended until glucose is > 70 mg/dL. YSI frequency will continue every 15±5 min until YSI > 80 mg/dL. Subject will be monitored for at least 2 hours post treatment by study investigator. In case of reoccurring symptoms the subject shall be transferred to the emergency room by paramedics.
Moderate neurocognitive change, subject is talking but unable to treat their hypoglycemia without assistance; serum glucose < 50 mg/dL	The study will be terminated for this subject. This is unlikely to occur because treatment would have been given with first glucose < 60 mg/dL and glucose is measured every 15 minutes. Subjects will be treated with oral simple carbohydrates, such as glucose tablets or juice, and serum glucose subsequently rechecked in 15 minutes, and treatment repeated if glucose remains < 70 mg/dL. With second treatment the insulin infusion will be suspended until glucose is > 70 mg/dL. Subject will be monitored for at least 2 hours post treatment by study investigator. In case of reoccurring symptoms the subject shall be transferred to the emergency room by paramedics.
Moderate neurocognitive changes, but subject is incoherent and/or refusing treatment and needs assistance for hypoglycemia treatment; serum glucose < 50 mg/dL	The study will be terminated for this subject. This is unlikely to occur because treatment would have been given with first glucose < 60 mg/dL and glucose is subsequently measured every 15 minutes. Intravenous glucose would be given (0.5 grams/kg intravenous over 3 minutes), and insulin delivery suspended until glucose is > 70 mg/dL. Subject will be monitored for at least 2 hours post treatment by study investigator. In case of reoccurring symptoms the subject shall be transferred to the emergency room by paramedics.
Seizure of loss of consciousness; serum glucose < 50 mg/dL	The study will be terminated for this subject. This is unlikely to occur because treatment would have been given with first glucose < 60 mg/dL and glucose is subsequently measured every 15 minutes. Intravenous glucose would be given (0.5 grams/kg intravenous over 3 minutes), and insulin delivery suspended until glucose is > 70 mg/dL. In the event subject experience loss of consciousness or seizure he / she will be transferred to the emergency room by paramedics.
No heart rate, no blood pressure	Perform resuscitation. If this occurred all studies for all subjects would be put on holding pending an investigation of the circumstances leading to this serious adverse event. Call 911 and transfer the treated subject to emergency room.

10.4.3. Unannounced meals during closed-loop

During the 24-hour closed-loop, the subject will take two meals (evening dinner and breakfast), one snack prior to the exercise segment, and one snack 3 hours after exercise. All meals will be unannounced. This means that the subject will ingest the meal and the AP device will automatically regulate insulin delivery without being given any details about the meal. Therefore, it will react to the increase of glucose level following the meal. Based on the CGM data collected every five minutes, the AP device will quickly react to the meal and deliver correction bolus based on the predictions of future insulin. The objective is to observe the controller's ability to detect the meal and make an appropriate control action. The target glucose is to return to and remain in the range of [70-180] mg/dLduring the 5 hours post-prandial and then to return to [80-140] mg/dL range afterwards.

10.4.3.1. Dinner

Approximately 2 hours (±30 min) after starting the closed-loop (Day 1), i.e. 6:30 pm, once the subject's glucose has been stabilized by the AP device, the subject will be given an evening meal with approximately 50 g of carbohydrates (CHO). The subject will remain under closed-loop control overnight.

10.4.3.2. Breakfast

At approximately 7:00 am (±30 min) on Day 2, the subject will be given a breakfast with approximately 50 g of CHO.

10.4.3.3. Snack before exercising

Just before starting the exercising segment of the trial, at approximately 11:00 am, the subject will eat a snack of approximately 16 g of CHO if his/her glucose level is <120 mg/dL.

10.4.3.4. Snack after exercising

Approximately 3 hours after starting the exercising, at approximately 2:00 pm (±30 min) on Day 2, the subject will eat a snack of approximately 16 g of CHO if his/her glucose level is <120 mg/dL.

10.4.4. Exercising

Approximately 5 hours after the breakfast (11:00 am ± 30 min), the subject will undergo exercise for 30 minutes (±5 minutes) at 50% of his /

her predicted heart rate reserve (HRR). The subject will be monitored for approximately 6 hours following the end of the exercise segment or until his/her blood glucose has stabilized within the [80-140] mg/dL range. During and for 3 hours after exercise, the subject will be monitored to verify that his/her glucose level returns and remains within the range of [70-150] mg/dL.

If the subject's blood level is >270 mg/dL the subject will not go through the exercising segment of the trial, but will continue the closed-loop until the end of the 24-hour trial. Subjects whose glucose level is below 120 mg/dL at (11:00 ± 30 min) will be given 16 g CHO tablets and will not start exercise until glucose is greater than 120 mg/dL.

Exercise will be done by cycling on a recumbent stationary bicycle or by walking on a treadmill for 30 minutes (15 minutes of exercise, 5-minute break, followed by15 additional minutes of exercise) at approximately 50% predicted heart rate reserve (HRR). HRR is calculated using the following formulas. The calculation is different for men and women.

HRR: Heart Rate Reserve

RHR: Resting Heart Rate

MHR: Maximum Heart Rate

$THR_{X\%}$: Target heart rate to be at X% of HRR

Smoking code: "1" if the subject is a smoker and "0" if the subject is not a smoker

Equation 1 provides the MHR for men. The Target Heart Rate is provided by equation 3.

$MHR=203.9 - (0.812 \times Age) + (0.276 \times RHR) - (0.084 \times Weight_{kg}) - (4.5 \times \text{smoking code})$ (1)

Equation 2 provides the MHR for women.

$MHR = 204.8 – (0.718 \times Age) + (0.162 \times RHR) – (0.105 \times Weight_{kg}) – (6.2 \times \text{smoking code})$ (2)

Target Heart Rate for exercise (at 50%) is provided by equation 3:

$THR_{50\%} = [(MHR – RHR) \times 50\%] + RHR$ (3)

References:
Whaley MH, et al, *Predictors of over- and underachievement of age-predicted maximal heart rate*, Med Sci Sports Exerc 1992;24(10):1173-9;
Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study.Ann Med ExpBiolFenn. 1957;35(3):307-15;
Davis JA, Convertino VA.A comparison of heart rate methods for predicting endurance training intensity.MedSci Sports. 1975;7(4):295-8.

Subjects with high risks factors for cardiac disease and Type 1 diabetes, as recommended by the American Diabetes Association will be monitored with continuous electrocardiography throughout exercise to monitor for potential arrhythmias. The risks factors are:

- Age > 35 years
- Type 1 diabetes for > 15 years' duration
- Presence of any additional risks factor for coronary artery disease
- Presence of microvascular disease (proliferative retinopathy or nephropathy, including microalbuminuria)
- Peripheral vascular disease
- Autonomic neuropathy

All subjects will wear a Polar RS400 heart rate monitor. The resistance on the bicycle or the speed and grade on the treadmill will be adjusted to keep subjects close to the target heart rate.

Exercise may be discontinued at the request of the subject or at investigator discretion if there is concern for the subject's safety.

Blood glucose (YSI) will be sampled every 15±5 minutes for one hour beginning at the start of exercise. Additional YSI blood glucose values may be requested by the study physician as deemed necessary for safety.

Exercise will be discontinued and the subject will be given 16 mg CHO if the system predicts unavoidable impending hypoglycemia as determined by the HMS (i.e. when CGM glucose level is predicted to be <70 mg/dL in the following next 15 min). Treatment with 16 mg CHO may be repeated as necessary.

If the subject feels hypoglycemic subject will perform finger stick and YSI measurement will be taken. If YSI value below 60 mg/dL, juice or

glucose tablets will be used to return the glucose to >80 mg/dL and exercise may be discontinued**.** Closed-loop will be discontinued. This will mark the end of the trial for this subject.

Following the exercise segment, the subject will be monitored for approximately 5-6 hours (end of the 24-hour period). During that time, the insulin delivery for the subject will continue to be controlled by the AP device. The patient may have a snack of 16 g CHO approximately 3 hours after the start of exercise. The patient will not be discharged until blood sugar value, based on YSI is >90 mg/dL for at least an hour.

10.4.5. Discharge from the CRC

At the end of the 24-hour period and once the glucose level of the subject has stabilized within the desired zone (>90 mg/dL for at least 1 hour), the AP device will be disconnected. The IV line and the two CGMs will be removed. The subject will be connected to his/her own insulin pump. The investigator or study staff will verify that the insulin pump of the subject has been restarted successfully. Glucose check will be performed after new infusion set or the pump of the subject has been inserted, as per standard care. Subject will return all supplies to study staff. On the subject's blood glucose is >90 mg/dL and <180 mg/dL with ketones <0.6 mmol/L, the subject will be discharged from the CRC.

This marks the end of the study day after using the AP device for approximately 24-hour (as a closed-loop).

10.5. Follow-up call

A brief contact with the subject, typically by phone, will take place within 24 hours (±12 hours) to verify that the subject has no further questions or has any problems related to his/her participation in the study. The contact will be documented in the subject file.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

Twelve to twenty subjects will be enrolled in the study.

11.1. Inclusion criteria

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

- Clinical diagnosis of type 1 diabetes for at least one year and using an insulin pump for at least 6 months with commercially available rapid acting insulin

- The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed.
- Age 21 to 65 years
- For females, not currently known to be pregnant or nursing
- HbA1c between 5.0% and 10%, as measured with DCA2000 or equivalent device
- Willing to perform the calibration of the study CGMs using a finger stick only and willing to follow instructions for insulin pump and CGM wear.
- Willing to use the study CGM and study insulin pump during closed-loop.
- Able to and agrees to avoid the following medication starting 24 hours before sensor wear through completion of CRC visit: acetaminophen, prednisone, and pseudoephedrine.
- Forced expiratory volume in 1 second (FEV1) ≥ 70% Third National Health and Nutrition Examination Survey (NHANES III) predicted
- Forced vital capacity (FVC) ≥70% NHANES III predicted
- Forced expiratory volume in 1 second as a percentage of forced vital capacity(FEVl/FVC)≥NHANES III lower limit of normal (LLN)
- An understanding of and willingness to follow the protocol and sign the informed consent.

11.2. Exclusion criteria

The presence of any of the following, the subject will be excluded from the study:

- Pregnancy (as determined by a positive blood pregnancy test performed in females of childbearing capacity during screening visit and urine test at time of admission for in-patient visit) or nursing mother.
- Diabetic ketoacidosis in the past 6 months prior to enrollment requiring emergency room visit or hospitalization
- Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment
- Current treatment for a seizure disorder;
    - Subjects with a history of seizures may be included in the study if they receive written clearance from their neurologist

- Cystic fibrosis
- Active infection
- A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as cognitive deficit.
- Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation, including subjects not able to read or write.
- Coronary artery disease or heart failure.
    - Subjects with a history of coronary artery disease may be included in the study if they receive written clearance from their cardiologist
- Presence of a known adrenal disorder
- Active coronary artery disease or heart failure
- 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
    - Adequately treated thyroid disease and celiac disease do not exclude subjects from enrollment
- Abuse of alcohol
- 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 exercise protocol
- Current use of a beta blocker medication
- Laboratory results:
    - Hematocrit < 30% or >55%
    - A1C > 10%
    - Abnormal liver or renal function (Transaminase >2 times the upper limit of normal, Creatinine> 1.5 mg/dL)
    - Labs drawn at screening visit or within one month prior to screening (for other purposes) will suffice for enrollment purposes related to hematocrit

- Subject has skin conditions that, in the determination of the investigator, would preclude wearing the study devices (infusion set and sensor), in the abdomen. Examples include but are not limited to: psoriasis, burns, scaring, eczema, tattoos, and significant hypertrophy at sites of device wear; any known allergy to medical adhesives.
- Currently on long-term treatment using prednisone.
- If subject had been on short term treatment of prednisone, defer enrollment until underlying condition and prednisone treatment have resolved.
- Allergy to study drug, food or other study material.
- History of asthma, COPD (chronic obstructive pulmonary disease), or any other clinically relevant chronic lung disease.
- Respiratory track infection within 4 weeks before screening.
- Clinically significant screening ECG, physical examination, laboratory test, or vital sign abnormality.
- Exposure to any investigational drug within 30 days.
- History of malignancy within the 5 years before screening (other than basal cell carcinoma).
- Inability, in the opinion of the investigator, to adequately inhale Technosphere® Insulin Inhalation Powder.
- Abnormal spirometry.
- Currently smoking or discontinued smoking (including cigarettes, cigars, pipes) over the past 6 months.
- Highly sensitive to insulin: insulin-to-carbohydrate ratio I:C > 1:12
- Current participation in another investigational trial (unless participation to original protocol of IDE G110093) or has previously participated to this study.

11.3. Starting rules

For the in-clinic days, the subject is to arrive in the clinic around 4 pm. The last meal of the subject, prior to arrival to the clinic should have occurred no later that noon of that day. The subject should not have any insulin bolus after 2:00 pm or ingest any carbohydrate after the lunch, unless it is for treatment of hypoglycemia, i.e. if the subject glucose level is < 70 mg/dL.

The clinical staff may reschedule the subject if the above directions are not followed. If the subject has questions on the day of admission, they should contact the study staff.

11.4. Stopping rules

11.4.1. Criteria for individual subject withdrawal

The termination of a subject from the study will be documented in the subject source documents and on the CRF. The reason for the termination and possible following effects must be documented. Subjects that have discontinued participation will not be replaced. Should a subject be lost-to-follow-up (LTF), i.e. no return for the on-site 24-hour closed-loop after enrollment, a reasonable effort will be made to contact the subject to determine why the subject failed to return. Any investigator-decided outside intervention will trigger termination of the trial for the subject. If the investigator treats the subject with 16 g of carbohydrates following the recommendation of the HMS, then the trial will not be terminated, this is anticipated and part of the trial. If a trial is terminated, the same subject may be rescheduled and the trial repeated. Rules for terminating a visit for an individual subject are as follows (glucose levels measured by YSI).

- Outside intervention (bolus or carbohydrate treatment) from the investigator that did not follow recommendation from HMS.
- Gross system malfunctions such as:
    - Pump failure
    - Failure of both study sensors
    - System or controller malfunctions that may have an impact on the safety of the subject
- Any correction bolus initiated by the investigator.
- Glucose YSI > 250 mg/dL for more than 2 hours and blood ketones exceed 1.0 mmol/L.
- Subject develops nausea, vomiting, or abdominal pain and blood ketones exceed 1.0 mmol/L.
- Glucose YSI > 350 mg/dL with decreased sensorium with or without emesis.
- Glucose level YSI > 400 mg/dL at any point if the investigator decides to treat with a correction bolus.

- Glucose YSI < 60 mg/dL without having received a HMS warning
- Glucose YSI < 50 mg/dL.
- Severe Hypoglycemia or Hyperglycemia as defined by Table 9-2.
- The subject or physician requests the trial be stopped.
- Failure of YSI equipment.
- Subject withdraws his/her consent.
- Adverse Event which necessitates termination of the study as decided by the investigator, such as DKA.
- Protocol violation: subject is no compliant with procedures, becomes pregnant, violates study entry criteria, or use unacceptable medication.

11.4.2. Criteria for suspending / stopping the study

In case of a recurring system malfunction or subject safety issue observed across multiple subject visits, the overall study will be suspended (no further subjects at any site) while the problem is diagnosed.

In the event of a UADE, the Sponsor/investigator will evaluate the event and follow-up procedure, including the possible suspension and / or termination of the study.

In the event of a Serious Adverse Event, the Sponsor/investigator will evaluate the root cause of the event and will determine appropriate action, including termination of the study.

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. Any change to the protocol or the system will need to be approved by the Agency prior to implementation.

The study may also be suspended or terminated if the FDA, IRB or other regulatory authority discontinues the approval of the study protocol or Sansum clinical site participation.

The IRB and FDA will be notified if the study is stopped and permission to resume will be obtained from the IRB and FDA prior to restarting.

12. EXPECTED SAMPLE SIZE

This is a feasibility clinical study; therefore, only approximately 12 to 20 adult subjects will take part to this trial.

13. DESCRIPTION OF THE CLINICAL CENTER

Sansum Research Diabetes Institute, a nonprofit research center founded in 1944 devoted to the prevention, treatment and cure of diabetes, is located ½ block from Santa Barbara Cottage Hospital, approximately 30 seconds by car to the emergency room. It is a research center devoted to the prevention, treatment and cure of diabetes. It is a nonprofit organization that was founded in 1944. The Institute has gained international recognition for its work to develop an artificial pancreas, in developing protocols to increase the incidence of healthy babies born to women with diabetes, and its work with people at risk for type 2 diabetes. Physicians and researchers continue to develop new treatment protocols for peoples with diabetes. New drugs and medical devices are clinically tested to ensure their efficacy and safety.

Sansum Diabetes Research Institute is led by Lois Jovanovič, M.D. who is renowned internationally through her work. She has published extensively in particular in relation to developing formulae for insulin dosing in subjects using either insulin infusion pumps or multiple daily injections. Her formulae not only succeeded in normalizing blood glucose levels but in a randomized trial, the computer based insulin delivery systems fared better than daily interactions with a physician to adjust insulin doses. She has directed multiple clinical trials involving continuous glucose monitoring and insulin infusion pumps. Her expertise and leadership have brought Sansum Research Diabetes Institute to the frontline of diabetes research, nutrition, education and diabetes prevention. Her research has already, and will continue to improve the lives of people worldwide who suffer from this serious disease.

Sansum Diabetes Research Institute
2219 Bath Street
Santa Barbara, CA 93105
Ph: 805-682-3332
Email: info@sansum.org

14. ASSESSMENT OF EFFICACY

The goal of the study is to evaluate the feasibility of the artificial pancreas device, not to measure its efficacy. However, as described in the statistical section, several outcomes will be measured that may give some indication of the possible efficacy of the device.

15. ASSESSEMENT OF SAFETY

15.1. Reporting to regulatory agencies

The study will be conducted after receiving IDE approval by FDA and Cottage Health System IRB approval.

- All anticipated Adverse Events will be reported in details to both the IRB and FDA with the results of the study within 3 months of the completion of the trial.
- Unanticipated Adverse Device Effects (UADE) will be thoroughly investigated and as required by 21 CFR 812.46, they will be reported to FDA and IRB no later than 10 working days after the sponsor first receives notice of the effect, i.e. 10 days after it occurs since the Sponsor is also the investigator (Sansum).
- The CGM Dexcom® G4® or the insulin pump (OneTouch® Ping®) malfunctions which are not related to the modifications of the interface to include them as components of the AP device or the glucose meter (OneTouch ®Ultra® blood glucose meter) will be reported to their respective manufacturers as a complaint per MDR requirements (Animas Corp for the insulin pump and the glucose meter and Dexcom for the G4® CGM).
- Malfunctions related to the interfaces of the CGM or insulin pumps with the APS© platform will also be reported to their respective manufacturers.

15.2. Definitions

15.2.1. Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence in a study subject, irrespective of the relationship between the adverse event and the device(s) under investigation. Anticipated adverse events, such as skin irritation from sensor wear will be recorded in specific sections of the case report forms. However, a severe skin irritation is not anticipated and would be reported on the AE form.

All adverse events may be graded from mild to severe as defined by Table 15–1~~Table 9–1~~.

15.2.2. Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any untoward occurrence that is:

- Results in death.
- Life threatening, even if temporary in nature;
- Results in permanent impairment of a body function or permanent damage to a body structure;

- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. "Permanent impairment" means irreversible impairment or damage to a body structure or functions, excluding trivial impairment damage.

15.2.3. Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

15.2.4. Device complaints

Those only apply to the approved devices used in the AP device, i.e. the CGM and the insulin pump. Those devices are not being used as they were intended to be used. Effectively, these devices are being used beyond their original intended use when included in a closed-loop. However, their intended output and performance specifications are not being modified: the purpose of the CGM in the closed-loop is still to provide subcutaneous glucose values, while the purpose of the pump in the closed-loop is still to deliver controlled amount of insulin. A device complaint also applies to CONTOUR® NEXT EZ Glucose meter used to calibrate the CGM. It is used per the manufacturer's instructions.

A complaint means any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. The complaint may or may not be associated with an adverse event.

Should there be any malfunction of the device related to the original intended use for which the device is marketed for, it will be reported to the manufacturer per 21 CFR 803.3. For example, problems with the infusion set (Inset®), or the subcutaneous needle would be independent of the closed-loop trial and will be reported.

Because both Dexcom® and Animas are close partners in the development of an artificial pancreas, they will informally be notified of any other malfunction of their device related to their use in the AP device. This will

be valuable information for further product development of an artificial pancreas.

15.2.5. Anticipated adverse events

Each adverse event is graded for its severity from mild to severe as described by Table 15–1~~Table 9–1~~. This is a measure of intensity only. An adverse event may be severe, but not clinically serious.

Table 15–1: Severity of adverse events

Intensity level	Description
Mild	Usually transient, requires no special treatments, and does not interfere with the subject's daily activities
Moderate	Usually causes a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorate by simple therapeutic measures.
Severe	Interrupts a subject's usual daily activities and generally requires system drug therapy or other treatment.

Hypoglycemia and hyperglycemia are intrinsic risks and adverse events associated with type 1 diabetes. The level of severity of such events follows a more detailed description as described by Table 15–2~~Table 9–2~~: it varies from negligible, mild, moderate, severe and very severe. Only hyperglycemia or hypoglycemia that is rated moderate or worse will be documented in a CRF.

Table 15–2: Levels of hyperglycemia and hypoglycemia as defined by YSI

Severity	YSI	Clinical symptoms	Description
Hyperglycemia			
Negligible	200<BG<300 mg/dl for <1 hr or BG>300 mg/dl for <1 hr	Asymptomatic	Little or no potential injury, pain or discomfort
Mild	200<BG<300 mg/dl	Mild polydipsia and mild polyuria	Potential of minor injury, pain, or user discomfort
Moderate	BG> 300 mg/dl	Symptoms of ketosis (nausea, polyuria, polydipsia, vomiting) with normal mental status	Potential of non-life threatening injury, pain, or direct or indirect exacerbation of existing non-life threatening condition
Severe	BG>300 mg/dL requiring intravenous fluids to correct	Altered mental state Subject in critical condition	Major injury requiring medical intervention
Very severe	N/A	No heart rate, no blood pressure Subject in critical condition	Potential of death or serious injury
Hypoglycemia			
Negligible	60<BG<70 mg/dL	Asymptomatic or adrenergic/cholinergic symptoms without neurocognitive changes	Little or no potential injury, pain or discomfort
Mild	BG<60 mg/dL Or HMS indicates impending hypoglycemia (<70mg/dL in the next 15 min per CGM measurements)	Asymptomatic or adrenergic / cholinergic symptoms without neurocognitive changes	Potential of minor injury, pain, or user discomfort
Moderate	BG<60 mg/dL	Subject is talking, but early neurocognitive changes such as slow speech, mild affect changes	Non-life threatening injury, pain, or direct or indirect exacerbation of existing non-life threatening condition
Severe	BG<60 mg/dL	Require assistance of another individual due to loss of consciousness, seizure or the inability to administer treatment to self due to neuroglycopenia	Major injury requiring medical intervention
Very Severe	N/A	No heart rate, no blood pressure Subject in critical condition	Potential of death or serious injury

Table 15–3~~Table 9–3~~ is a list of anticipated adverse events. These will be reported on the CRF found in Appendix 9 of the IDE submission.

Table 15–3: Anticipated Adverse Events

Adverse event	Description
Hypoglycemia	Refer to details in Table 9-2. Only report if moderate or worse.
Hyperglycemia	Refer to details in Table 9-2. Only report if moderate or worse.
Skin irritation	From sensor wear or insulin pump infusion set. Only considered an AE if the irritation is severe or meets definition of SAE
Bruising at the side of insertion of CGM, infusion set, IV	Only considered an AE if bruising is severe or meets definition of SAE.
Infection at the side of insertion of CGM, infusion set, IV	Only considered an AE if infection is severe or meets definition of SAE.
Pain or bleeding at the side of insertion of CGM or infusion set	Only considered an AE if pain or bleeding is severe or meets definition of SAE.
Infection at side of finger stick	Only considered an AE if infection is severe or meets definition of SAE
Glucose sensor break	Glucose sensor rupture leaves a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site

15.3. Adverse event reporting and protocol monitoring

The first concern will be the safety of the subject, and appropriate medical intervention will be made to address any adverse event.

All adverse events will be recorded on the CRF (Appendix 9 of the IDE), including those that may have occurred during the outpatient phase of the trial (the investigator will elicit reports of adverse events from the subject).

In case of a Serious Adverse Event, the study will be put on hold until a thorough investigation is performed and documented to determine the root cause of the event. Based on the results, the Sponsor/investigator will determine appropriate action, including changes to the protocol or termination of the study, and notify the appropriate regulatory authorities if required.

Intensity: The intensity of the adverse event will be recorded based on Table 15–1~~Table 9–1~~. The term severe is a measure of intensity, not clinical severity. A severe AE is not necessarily a serious AE. For example, itching for several days may be rated as severe, but may not be clinically serious.

Causality: The study investigator will assess the relationship of any adverse event to be related or unrelated to participation in the protocol by determining if

there is a reasonable possibility that the adverse event may have been caused by the study device or study procedures.

Outcome: 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.

16. DATA ANALYSIS

16.1. Overview

This section presents the statistical analysis that will be used to evaluate the primary and secondary end-points of the non-randomized feasibility study. These are based on CGM data. The primary endpoints consist in measuring the percentage of time the glucose level of the subject is in the safe zone [80-140] mg/dL, including overnight and excluding 5 hours postprandial and during exercises and 3 hours post-exercise. The expected glucose levels during those periods are:

- 5 hours postprandial: [70-180] mg/dL
- During exercise and for 3 hours after exercise: [70-150] mg/dL

The secondary endpoints consist in measuring the glucose extremes and the need for outside intervention to address hypoglycemia and hyperglycemia. The restoration of glucose level to a safe range, i.e. within [80-140] mg/dL after the two unannounced meals and the exercise without the need of intervention to address hypo- or hyperglycemia, i.e. no physician override to inject insulin or give carbohydrate to the subject, will be considered a successful outcome.

If outside intervention is the result of notification from the Health Monitoring System algorithm (HMS), then it will be considered a successful outcome as well.

There is no control group since the patient is his/her own control. In addition, a more refined data analysis will be performed as discussed below.

16.2. Control Variability Grid Analysis

The overall performance of the control algorithm will be visualized via the Control Variability Grid Analysis (CVGA), which is built on a mix/max plot of glucose values. For each subject , a point is plotted with the X-coordinate defined as the minimum blood glucose and the Y-coordinate defined as the maximum blood glucose level for an observation period. In this trial, the

observation period is the 24-hour closed-loop including the unannounced meals and exercise segments.

In order to reject sensor errors, the minimum glucose level is set at the 2.5th percentile and the maximum glucose level is set at the 97.5th percentile of the glucose level distribution, in other words, the Y-X coordinate difference corresponds to the 95% spread of the observed distribution. The plot is then split into zones defined by their X and Y coordinate ranges as follows. The zones are color coded to facilitate the visual interpretation of the results:

- the green zone is safe and acceptable,
- the orange/yellow zone is not desirable, and
- the red-zone would be considered failure of the safety of the Artificial Pancreas device.

Numerically, the information contained in the CVGA, can be described as the percentages within each zone. For example, in Figure 3–1~~Figure 3–1~~ which present the preliminary results of IDE G090129, there were 40% of the data points in zone A, 60% in zone B and 0% in zones C or D. In other words, the CVGA can be interpreted as a display of event-based clinical characteristics of the control algorithm. **Table 16–1**~~**Table 10–1**~~ shows the interpretation of the various zones in the CVGA representation.

Table 16–1: Interpretation of the CVGA zones

Zone ID	Clinical impact	X coordinate	Y coordinate
A-zone	Accurate control	110-90 mg/dL	110-180 mg/dL
Lower B	Benign deviations from hypoglycemia	90-70 mg/dL	110-180 mg/dL
B-zone	Benign control deviation	90-70 mg/dL	180-300 mg/dL
Upper B	Benign deviation into hyperglycemia	110-90 mg/dL	180-300 mg/dL
Lower C	Over-correction of hypoglycemia	<70 mg/dL	110-180 mg/dL
Upper C	Over-correction of hypoglycemia	110-90 mg/dL	>300 mg/dL
Lower D	Failure to deal with hypoglycemia	<70 mg/dL	180-300 mg/dL
Upper D	Failure to deal with hyperglycemia	90-70 mg/dL	>300 mg/dL>300 mg/dL
E-zone	Erroneous control	<70 mg/dL	

16.3. Primary end-points

Table 16–2~~Table 10–2~~ is an outline of the analysis of the performance of the AP device primary end-points some of which are more qualitative than quantitative. All measures will be performed using CGM values. Below the table, the listed questions will be used as a guidance to perform the qualitative review of the AP device.

Table 16–2: Primary end-point measures

Measure	Description
Review qualitatively profile of predictions and actual CGM values	Ability of the zone-MPC and HMS algorithms to predict fall and rise of glucose value beyond the zone [80-140] mg/dL (1)
Review qualitatively actual data of insulin pump delivery	Capacity of the control algorithm to command the pump to increase or decrease the insulin pump to keep the subject within the zone [80-140] mg/dL (2)
Review all warning events of HMS. Review of events that required outside intervention but was not raised by HMS.	Capacity of the HMS in raising appropriate warnings and alarms to require outside intervention to prevent hypoglycemia (3)
% of time within zone [80-140] mg/dL except 5 hours post-prandial and during exercise and 3 hours post-exercise	Measures ability of AP device to maintain glucose level within a safe zone and to return to save zone following unannounced meals and exercises.
% of time within zone [80-140] mg/dL during night between 12:00 am and 7:00 am	Measures ability of AP device to maintain glucose level with a safe zone during the night and prevent hypoglycemia.
% of time within zone [70-180] mg/dL 5 hours after unannounced evening meal, and breakfast	Measures ability of AP device to react to small meal and to prevent glucose level from dangerous excursions.
% of time within zone [70-150] mg/dL during the 30 min exercise	Measures ability of AP device to maintain safe glucose level during 30 minutes of non-strenuous exercise
% of time within zone [70-150] mg/dL during the 3 hours following exercise	Measures ability of AP device to address exercise and to prevent glucose level from dangerous excursions

Guiding questions:

(1) Did the algorithm deliver insulin in a pattern conducive to causing or maintaining within-zone CGM measurements?

(2) Did the algorithm deliver reasonable size insulin amounts? Did the algorithm deliver the basal amount of insulin in quiescent, within-zone period? When CGM measurements were predicting values higher than the upper zone limit of [80-140] mg/dL, did the algorithm increase insulin infusion? When CGM measurements predicted values lower than the lower zone limit of [80-140] mg/dL, did the algorithm decrease insulin infusion? After glucose excursion above the upper zone limit or below the lower zone limit, when the CGM

measurements predicted measurement was reentering the zone, did the algorithm resume the basal amount of insulin infusion?

(3) When prediction of BG glucose was to be <70 mg/dL in the following 15 minutes, did the HMS send a warning text to physician? Did the HMS system send unnecessary warning text messages when the BG was not predicted to be <70 mg/dL? Did the investigator need to give CHO to the subject without receiving notification from the HMS either because of CGM failure or HMS system failure?

16.4. Secondary end-points

16.4.1. Analyses

In addition to the qualitative evaluation of the performance of the AP device, the percentage of time spent in each zone, and the visual evaluation provided by CVGA plots, other quantitative measures will be reported, analyzed and interpreted. They are presented in Table 16–3~~Table 10–3~~. Unless indicated otherwise, the calculations are performed using CGM values.

Table 16–3: Secondary end-points measures

Measure	Description
Averages	
Mean glucose level during the 24-hour closed-loop	Computed from CGM and then YSI values
Mean-pre meal glucose value	Computed 0-60 minutes before unannounced evening and morning meal
Mean-post meal glucose value	Computed 0-5 hrs after the evening and morning meal
Mean exercise glucose value	Computed value during the 30 min of exercise
Mean-pre-exercise glucose value	Computed 0-60 minutes before exercise
Mean-post exercise glucose value	Computed 0-3 hrs after end of exercise
Extremes	
% of time of glucose > 400 mg/dL	Computed from CGM and YSI values: analysis during 24 hour closed-loop, during night (12:00 am to 7:00 am) and during exercise
% of time of glucose ≥ 300 mg/dL	Computed from CGM and YSI values if duration is more than 1 hour: analysis during 24 hour closed-loop, during night (12:00 am to 7:00 am) and during exercise
% of time of glucose < 60 mg/dL	Computed from CGM and YSI values: analysis during 24 hour closed-loop, during night (12:00 am to 7:00 am) and during exercise
% of time of glucose ≤ 70 mg/dL	Computed from CGM and YSI values if duration is more than 1 hour: analysis during 24 hour closed-loop, during night (12:00 am to 7:00 am) and during exercise
Area under the curve per gram CHO	Computed from the beginning of a meal and continued for 5

Measure	Description
	hours
Area under the curve during exercise	Computed during exercise and for 3 hours following exercise
Area between the curve and nearest zone limit when outside the range [80-140] mg/dL	This will measure how much deviation from the zone. The analysis may be performed for the 24-hour closed-loop, for the night (12:00 am to 7:00 am), and during/following exercise and meals.
Total amount of insulin delivered and standard deviation of delivery amounts during the 24-hour closed-loop	Correspondence of total insulin delivered to total daily insulin (TDI)
Variability and risk assessment (*)	
Interquartile range	It measures the spread around the center of the desired zone, i.e. 110 mg/dL
LBGI: Low blood glucose index	Measures the frequency and extend of low blood glucose readings using CGM data
HBGI: High blood glucose index	Measures the frequency and extend of high blood glucose readings using CGM data
Blood glucose index: LBGI+HBGI	Measure the overall variability and the associated risk with hypoglycemia and hyperglycemia.
Standard deviation of glucose rate of change	Measures the stability of the closed-loop over time

(*) See details of calculations in section 16.4.2~~10.4.2~~.

The review of the secondary end-points will also include the review of all AEs, SAEs, UADE, and complaints. It will also include the review of the need of outside intervention to safely manage the subject.

Data will be presented in table or graphs or both. Data of all subjects may be pooled together or may be presented individually. Should it be warranted, data may also be pooled in different sub-groups.

16.4.2. Details for calculations

Inter-quartile range (IQR): It is a measure of the glucose variability. It is more appropriate than the glucose standard deviation because the glucose distribution is highly asymmetric; the hypoglycemic range is numerically narrower than the hyperglycemic range, so the distribution of the glucose values of a subject is typically skewed. The standard deviation of glucose values would be predominantly influenced by hyperglycemic excursion and would not be sensitive to hypoglycemia. Therefore, the inter-quartile range will be calculated. It is also called the mid-spread or middle fifty. It is a statistical dispersion being equal to the difference between the third and first quartile. It is a robust statistic.

$$IQR = Q_a - Q_1 \qquad (1)$$

Where: Q_3 is the 75th percentile and Q_1 is the 25th percentile

Risk index (LBGI and HBGI): In order to capture the glucose variability and its associated risks for hypoglycemia and hyperglycemia, the low blood glucose index (LBGI) and high blood glucose index (HBGI) will be calculated as follows:

Compute (2):

$$f(BG) = 1.509 \times [(\ln(BG))\ 1.084 - 5.381] \quad (2)$$

The BG risk function is r(BG) using equation (3):

$$r(BG) = 10 \times f(BG)^2 \quad (3)$$

The left and right branches are separated as described by (4) and (5):

$$rl(BG) = r(BG) \quad if\ f(BG) < 0\ and \quad 0\ otherwise \quad (4)$$

$$rh(BG) = r(BG) \quad if\ f(BG) > 0\ and \quad 0\ otherwise \quad (5)$$

Given a series of CGM readings BG_1, BG_2, ….BG_n, the Low and High BG indices (LBGI and HBGI) are computed as the average of rl(BG) and rh(BG) respectively.

$$LBGI = \frac{1}{n}\sum_{i=1}^{n} rl(BG_i) \quad (6)$$

$$HBGI = \frac{1}{n}\sum_{i=1}^{n} rh(BG_i) \quad (7)$$

The BG risk index is then defined as:

$$BGRI = LBGI + HBGI \quad (8)$$

In essence, the LBGI and the HBGI split the overall glucose variation into two independent sections related to excursions into hypo- and hyperglycemia, and at the same time equalize the amplitude of these excursions with respect to the risk they carry.

17. ACCESS TO SOURCE DATA / DOCUMENT

17.1. Electronic data

After the insertion of the 2 CGMs, the subject will be an outpatient for 2 to 3 days before the CRC closed-loop trial. Data from the CGM and insulin data during those few days will be collected for information purpose only.

There are two types of data collected from the in-patient phase of the study:

- Manually entered data in APS© MATLAB® file:
  - Time stamps meal, exercise, other events
  - YSI values transferred from paper print out
- Automatically generated:
  - APS© generated MATLAB® file with continuous glucose CGM and insulin data.

The MATLAB® file generated during the closed-loop, including the time stamped events can be converted into Excel for analysis once the trial has been completed. Patients are identified by numbers, and only the study coordinator is able to correlate the electronic file with the name of the patient. Data analysis is blind to the patient's name. There will be a Master Patient Log.

At the end of each trial with each subject, the electronic file is copied onto a Sansum computer which is backed up daily to an outside location. The Sansum computer is password protected and all the data are saved to a dedicated folder. Data are saved with an appropriate filename. Access to the data is controlled via password. Only restricted personnel has access to the data and there is an audit trail associated with all data entry, data changes and manipulations. Raw data are protected and cannot be altered. Hard copy print-out of the data are also generated as a back up at the time of completion of the trial (prior to conversion of the file into Excel).

17.2. Hard copy records

All forms for the screening visit, the monitoring form, the clinical research forms (CRFs) and the informed consent are completed using a hard copy document. The record is the original hard copy document. All records are kept at Sansum in the study file. The records are kept indefinitely.

18. RECORD KEEPING

All clinical hard copy forms and records are maintained by Sansum Diabetes Research Institute. They are locked and kept indefinitely.

All electronic records will be stored both on the study computer and will be transferred to a Sansum computer that is connected to a backup server at the end of each closed-loop session.

19. ETHICS COMMITTEE

Sansum Diabetes Research Institute uses the Cottage Health System IRB for this study. IRB approval for the initial design of this clinical study was obtained under

the reference number #10-36 prior to this submission. Any change resulting from this IDE will be resubmitted to the IRB before proceeding to the initiation of the clinical trial.

Cottage Health System IRB
Chair, CHS IRB: Laurel J. Mehler, M.D.
Post Office Box 689
Pueblo at Bath Street
Santa Barbara, CA 93102-0689

20. FINANCIAL DISCLOSURE

This clinical trial is partly funded by the JDRF grant #17-2010-765. It is also actively supported by the Chemical Engineering department of the University of California, Santa Barbara, and Sansum Diabetes Research Institute.

Subjects will be paid $400 to participate in this study; and there will be no cost to the subjects to participate in this study.

Study supplies are provided at no cost by Dexcom® Corporation for CGMs (Dexcom® G4® System) and Animas Corporation for insulin delivery pumps (OneTouch® Ping®) and finger stick glucose meter (OneTouch® Ultra®).

Financial disclosure of the Principle Investigator will be kept in the study file.

21. INVESTIGATOR'S BROCHURE

The AP device User Manual to be used by the investigator can be found in Appendix 1 of the IDE application.

22. INVESTIGATOR'S CONTACT INFORMATION

The Sponsor is SDRI and the Principal Investigator is Howard Zisser, M.D. He is the Director of Clinical Research and Diabetes Technology at the Sansum Diabetes Research Institute (SDRI) where he conducts clinical trials on new and innovative therapies for type 1, type 2 and gestational diabetes. He is also an Adjunct Professor in the Department of Chemical Engineering of the University of California, Santa Barbara. Dr. Zisser has been recognized worldwide for his work with continuous glucose sensors, insulin delivery systems and intensive glucose management. He has directed numerous clinical studies.

Principal Investigator:

Howard Zisser, M.D.
Sansum Diabetes Research Institute
Director of Clinical Research and Diabetes Technology
2219 Bath Street
Santa Barbara, CA 93105

Email: hzisser@sansum.org
Phone: 805-682-7640, X255
Fax: 805-682-3332

The co-investigators are:

Francis Doyle III, Ph.D.
Associate Dean for Research, Engineering
Duncan and Suzanne Mellichamp Chair in Process Control
UCSB-MIT-Caltech/ARO Institute of Collaborative Biotechnologies

Eyal Dassau, Ph.D.
Senior Investigator & Diabetes Team Research Manager

University of California
Department of Chemical Engineering
Santa Barbara, CA 93106-5080

Email: doyle@engineering.ucsb.edu
Email: dassau@engineering.ucsb.edu
Phone: 805-893-8133
Fax: 805-893-4731

Lois Jovanovič, M.D.
Sansum Diabetes Research Institute
Chief Scientific Officer
2219 Bath Street
Santa Barbara, CA 93105

Email: ljovanovic@sansum.org
Phone: 805-682-7640, X227
Fax: 805-682-3332

23.LIST OF TABLES