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# APPENDIX C

Clinical Protocol

IDE: G200099

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# CLINICAL PROTOCOL

# Supervised Safety and Feasibility Evaluation of the Zone-MPC Control Algorithm Integrated into the iAPS in Pregnant Patients with Type 1 Diabetes with Extension into Outpatient at Home


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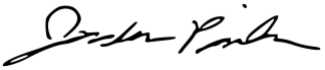
VERSION 2.1
Date: November 30, 2021

| | Name | Function/ Title | Signature | Date |
|---|---|---|---|---|
| **Prepared by** | Dr. Jordan Pinsker, MD | Senior Research Physician, Sansum Diabetes Research Institute |  | 03/15/2021 |
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# SPONSOR


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# Table of Contents

# 1 EXECUTIVE SUMMARY

This clinical trial is a safety and feasibility study to assess the performance of an artificial pancreas (AP) system using the Zone Model Predictive control (Zone-MPC) and Health Monitoring System (HMS) algorithms embedded into the iAPS platform (MAF-1625 1625, Amendment #10) for pregnant patients with type 1 diabetes (T1D).

The system will be evaluated on up to 21 pregnant adult subjects with type 1 diabetes age 18-45 years old at three clinical sites (Sansum Diabetes Research Institute, Mayo Clinic Rochester MN and Mt Sinai Hospital, New York City). We will recruit pregnant patients with T1D between 14-32 weeks gestation. All racial/ethnic groups will be eligible for participation. Subjects will complete a 48-60 hour closed-loop (CL) session in a supervised outpatient environment with medical staff present. During the session, subjects will bolus for all meals and snacks, and will perform their usual daily activities while being accompanied by study medical staff. The AP system to be used consists of an insulin pump, a Continuous Glucose Monitor (CGM), and a phone app as described in MAF-1625, Amendment #10: Master File for Artificial Pancreas System (APS) Platform.

For subjects who wish to continue use of the system, they will then be offered the option of continuing use of the system at home in an extension phase, for the rest of their pregnancy, with weekly remote review of safety and efficacy data.

The **primary endpoint** is time within the target glucose range of 63-140 mg/dL overall as assessed by CGM, determining if the system can provide safe and effective glucose control, as recommended by the current international consensus on time in range for pregnant women with diabetes.

**Secondary safety and efficacy endpoints** will include: sensor glucose time within the target range of 63-140 mg/dL overnight, sensor glucose time within the range of 63-140 mg/dL postprandial within 2 hours following meals; frequency of hypoglycemia below predefined thresholds of 63 mg/dL and 54 mg/dL, and frequency of hyperglycemia above predefined thresholds of 140, 180 mg/dL and 250 mg/dL. Additional secondary outcomes include markers of hypo- and hyperglycemia, as well as safety events, treatments for hypoglycemia, outside interventions needed, and a failure analysis of the devices/connectivity issues that may occur.

The clinical study will also review any serious adverse events that occur: hypoglycemic events, hyperglycemic events, planned and unplanned outside intervention, other Adverse Events, Serious Adverse Events, Unanticipated Adverse Device Effects, and device complaints for the commercial devices used. A root cause analysis of each event will be performed to determine if it is related to the approved devices - the CGM or the Continuous Subcutaneous Insulin Infusion (CSII) pump - the insulin, the AP system, or the control algorithm. Safety of the patient and her fetus will remain the primary goal. The goal of the AP device is to operate without outside intervention apart from Health Monitoring System (HMS) alerts suggesting carbohydrate ingestion due to impending hypoglycemia.

# 2 BACKGROUND INFORMATION

## 2.1 Introduction

### Prior Clinical Evaluations of the Proposed AP System

Several clinical studies involving nonpregnant patients using the novel zone MPC control framework, which is the basis for the proposed research, have shown consistently that the AP system is able to improve glucose regulation in T1D. Dassau et al. (FDA IDE G090129) published in 2013 results of a pilot clinical trial conducted at Sansum Diabetes Research Institute (SDRI), evaluating individualized, fully automated (no premeal bolus) AP using commercial devices (1). Two trials (n= 22, n=17) were conducted using a multi parametric formulation of MPC and an insulin-on-board algorithm. CGM glucose was maintained in the near-normal range 70-180 mg/dL for an average of 70% of the trial time. These results showed the ability of a control algorithm tailored to an individual's physiology to successfully regulate glycemia, even when faced with unannounced meals or initial hyperglycemia. We (FDA IDE G110093) studied the safety and efficacy of a fully automated AP using zone MPC with the health monitoring system (HMS) during unannounced meals and overnight and exercise periods. A fully automated closed-loop AP was evaluated in 12 subjects with T1D and demonstrated 80 and 92% time in the 70–180 mg/dL range for the entire session and overnight, respectively. These results showed that the combination of the zone MPC controller and the HMS hypoglycemia prevention algorithm was able to safely regulate glucose in a tight range with no adverse events despite the challenges of unannounced meals and moderate exercise. The zone MPC algorithm was successfully used in 2015 (FDA IDE G130147), when Drs. Dassau and Doyle AP team, Mayo Clinic and SDRI, among other sites, showed in a randomized clinical trial of 32 subjects in a transitional environment (such as hotel) that algorithmic adjustment of individualized insulin dosing parameters was safe and effective for AP use (2). As part of the DP3DK094331 research project, the fruitful collaboration among Drs. Dassau and Doyle AP team, Mayo Clinic, SDRI and other collaborators yielded a large outpatient clinical trial of the zone MPC and HMS system (FDA IDE G150063), where 30 adult subjects each used AP at home for three months (3). This study resulted in a statistically significant decrease in HbA1c (−0.3, 95% CI −0.5 to −0.2, $p<0.001$) and time spent in hypoglycemia during the day from 5.0 to 1.9% (−3.1, 95% CI −4.1 to −2.1, $p<0.001$) over the three months of AP use (Figure 1).

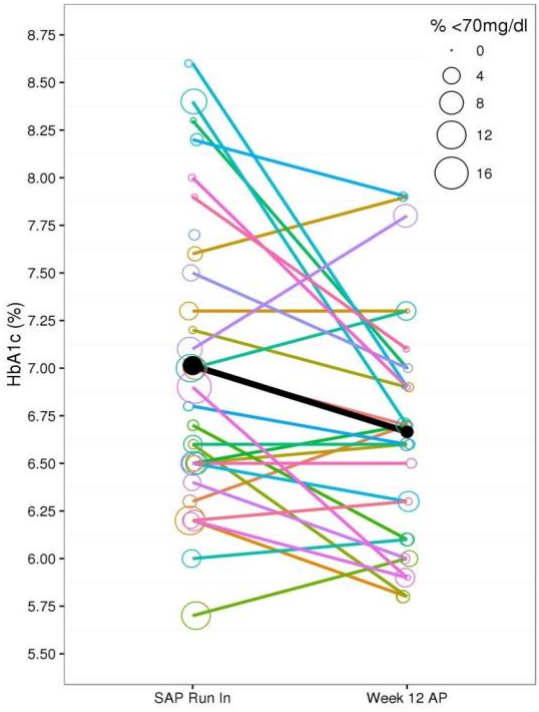



**Figure 1.** Change in HbA1c compared to percent time hypoglycemia in a three-month outpatient study comparing our zone MPC algorithm to SAP use in patients with T1D [3]. Mean HbA1c change and reduction in percent time CGM glucose <70 mg/dL are shown by the black line and filled in black circles. Individual subjects are shown by the colored lines and colored circles.

The zone MPC controller has also been used for outpatient studies in adolescents (FDA IDE G150122), with unannounced exercise and large meals multiple times per day. Mean CGM glucose was significantly lower during AP vs. sensor augmented pump (SAP) use (150±19 vs 173±32, P = 0.042) (4). We also recently concluded a randomized-crossover study comparing glycemic control of the zone MPC AP system versus SAP therapy use at home in which insulin infusion set (IIS) and CGM failures were precipitated in 7 and 21 days of use, respectively, in which results were significantly better for zone MPC compared to SAP use (5). Our second generation target MPC AP system (enhanced MPC, or eMPC) (6) with the addition of a trust index that weights future insulin delivery based on past glucose predictions (7) was evaluated in 15 adult subjects studied for 48 hours in SDRI, and achieved 88% time in the target glucose range 70-180 mg/dL (8).

**Next Generation Artificial Pancreas: zone MPC and HMS on a Smartphone App**

The zone MPC algorithm has been implemented on iAPS (formerly referred to as "APS App"), a novel, user friendly smartphone application and the system was clinically evaluated in a feasibility study (FDA IDE G180011), where it achieved 83% time in glucose range 70-180 mg/dL and mean CGM at 136 mg/dL (9).

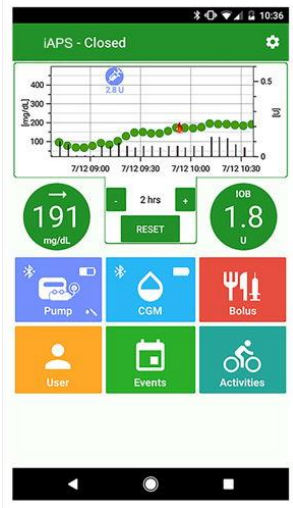



**Figure 2.** iAPS Interface

iAPS is a smartphone-based artificial pancreas platform which provides seamless integration with Dexcom G5 and G6 CGM, and two different insulin pumps: Tandem t:slim and Insulet Omnipod. The app is designed to be cross-platform (Android and iOS), can be used concurrently with typical apps in a smartphone, and is designed to be interoperable and compatible with leading devices for diabetes management. As the app resides in a smartphone and connects wirelessly to the CGM and the insulin pump, the complete system is very portable and user friendly.

In addition to the hardware integration, the iAPS app provides interface to the algorithms for AP glucose regulation namely the zone MPC and the HMS, which provides audio-visual advisory alarm for hypoglycemia. The app has an intuitive user interface (UI) allowing the user to request an insulin bolus for meal/correction and providing ability to log various activities such as exercise (Figure 2). It also provides alarms for system malfunction, e.g. loss of connectivity with devices, including text-messages to the subject's care partners for alarm events such as impending hypoglycemia. A web-based remote monitoring facility complements the app running on the smartphone allowing the clinician to verify salient features of subject's glycemic health.

Our AP algorithms have been clinically evaluated in previous clinical studies (17 IDEs) with over 76,000 hours of human use as shown in Table 1. iAPS is also now being evaluated in a 2-week outpatient trial comparing different stress assessments in the closed and open-loop setting (FDA IDE G180011/S002).

**Table 1.** Summary of prior studies with the Artificial Pancreas System (APS) in different hardware configurations, as well as different variants of the Model Predictive Control (MPC) and Health Monitoring System (HMS) algorithms.

| Year | IDE # | Components | Platform | Hours of Human Use | Location | PubMed Link |
|---|---|---|---|---|---|---|
| 2020 | G200047 | t:slim-Dexcom (ZMPC and HMS) | iAPS | >75,000 Hours 35 Subjects | Outpatient at Home | In Progress |
| 2019 | G180011/S002 | t:slim-Dexcom (ZMPC and HMS) | iAPS | >4,000 Hours 12 Subjects | Outpatient at Home | 32783473 |
| 2019 | G180011/S001 | t:slim-Dexcom (ZMPC and HMS) | iAPS | >3,500 Hours 10 Subjects | Outpatient at Home | 32319791 |
| 2018 | G160279/S002 | t:slim-Dexcom (ZMPC and HMS) | iAPS | 800 Hours 18 Subjects | Supervised Outpatient | In Progress |
| 2018 | G180011 | t:slim/OmniPod-Dexcom (ZMPC and HMS) | iAPS | 300 Hours 6 Subjects | Supervised Outpatient | 30547670 |
| 2017 | G150063 | Roche-Dexcom (ZMPC and HMS) | DiAs | >60,000 Hours 30 Subjects | Outpatient at Home | 29030383 |
| 2017 | G150122/S003 | Roche-Dexcom (ZMPC and HMS) | DiAs | >6,000 Hours 19 Subjects | Outpatient at Home | 28584075 |
| 2017 | G160281 | OmniPod-Dexcom (PBH algorithm) | pAPS | >50 Hours 10 Subjects | Supervised CRC | 29355439 |
| 2017 | G160281 | OmniPod-Dexcom (Target eMPC and HMS) | pAPS | >700 Hours 15 Subjects | Supervised CRC | 29958023 |
| 2016 | G150122 | Roche-Dexcom (ZMPC and HMS) | DiAs | >700 Hours 10 Subjects | Supervised Hotel | 28459617 |
| 2016 | G160169 | OmniPod-Dexcom (Target eMPC and HMS) | pAPS | >1,950 Hours 54 Subjects | Supervised CRC | 29431513 |
| 2015 | G130147 | Animas-Dexcom (ZMPC and HMS) | pAPS | >1,500 Hours 32 Subjects | Supervised CRC | 26204135 |
| 2015 | G130236 | Animas-Dexcom (Target MPC/PID - HMS) | pAPS | >1,500 Hours 30 Subjects | Supervised CRC | 27289127 |
| 2013 | G110093/S006 | Animas-Dexcom (ZMPC and HMS) | APS | 36 Hours 4 Subjects | Supervised CRC | 24351171 |
| 2013 | G110093/S003 | OmniPod-Dexcom (ZMPC/HMS, Inhaled Insulin) | APS | >200 Hours 9 Subjects | Supervised CRC | 25901023 |
| 2012 | G110093 | Animas-Dexcom (Zone MPC and HMS) | APS | >275 Hours 12 Subjects | Supervised CRC | 24471561 |
| 2012 | G110069 | Animas-Dexcom (ZMPC and HMS) | APS | >250 Hours 13 Subjects | Supervised CRC | 24876535 |

## 2.2 Pregnancy and Automated Insulin Delivery

**Pregnancy in patients with T1D is associated with significant maternal and fetal morbidity linked to suboptimal glycemic control.** Maternal pregnancy complications in patients with T1D include preeclampsia, medically indicated preterm delivery, labor abnormalities, need for cesarean delivery and maternal birth trauma, all linked to hyperglycemia throughout gestation(10-13), as well as severe hypoglycemia. Fetal and neonatal morbidity includes increased risk of congenital malformations, growth and fluid abnormalities (either fetal growth restriction, small [SGA] or large for gestational age [LGA] fetus or neonate) (14; 15), fluid abnormalities (oligo- and poly-hydramnios), stillbirth, birth trauma, neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia, and polycythemia, neonatal intensive care admission, as well as possible seizures. Table 2 shows data from cohort studies in Europe with no similar recent cohort studies from the US. When compared to control pregnancies, mothers with T1D in Sweden had an odds ratio of 4.47 for preeclampsia, 4.86 for preterm birth, 3.08 for very preterm birth, 5.31 for cesarean delivery, 2.5 for fetal congenital malformation, 3.34 for stillbirth, 3.29 for perinatal mortality, and 11.45 for LGA baby. Pregestational and gestational elevated hemoglobin A1c (HbA1c), time in target range, time in hyperglycemia, and perhaps incidence of severe hypoglycemia have been associated with poorer outcomes (16-19). Recent studies on the use of closed-loop systems (artificial pancreas or AP) with T1D patients have shown significant reduction in HbA1c as well as percent time <70 mg/dL and percent time in hyperglycemia; however, research in the pregnant population has been limited (3; 20; 21). This underserved population should benefit from the best in class glucose control provided by an automated insulin delivery using zone MPC and remote safety supervision system via the iAPS.

**Table 2.** Morbidity during Pregnancy in T1D

| Study | Geographic region (number of patient) | Pre-eclampsia | Preterm birth | C-section | Congenital malformation | Still birth | Perinatal mortality | LGA |
|---|---|---|---|---|---|---|---|---|
| **Persson et al 2009 (14)** | Sweden (5089) | 14% | 21% | 46% | 4.7% | 1.5% | 0.02% | 31% |
| **Mackintosh et al 2006 (22)** | UK (1707) | NR | NR | NR | 4.8% | 2.6% | 3.17% | NR |
| **Evers et al 2004(15)** | Netherlands (323) | 12.7% | 32.2% | 44.3% | 8.8% | 1.86 % | 2.8% | 45.1% |
| **Murphy et al 2017 (23)** | England/Wales (1563) | NR | 39.7% | NR | 4.62% | 1.07 % | 0.81% | 46.4% |
| **Jensen et al 2004 (24)** | Denmark (1218) | 18.1% | 41.7% | 55.% | 5% | 2.1% | 3.1% | 62.5% |

(NR=not recorded)

Type 1 diabetes management in pregnancy: Despite the evidence supporting the relationship between glycemic control and pregnancy outcomes, optimal glycemic goals in T1D during pregnancy are still debated. Because there are very few prospective studies available from the US that attempted to control T1D tightly throughout pregnancy, the Endocrine Society Clinical

Guidelines group concluded that the evidence to support tight glucose control is of low quality (25) in contrast to stricter targets recommended by the ADA. The NIH-funded interdisciplinary Diabetes in Pregnancy Program Project Grant (1978-1993) project concluded that programs emphasizing preconception diabetes care and strict glycemic control would significantly decrease the rate of perinatal mortality and congenital malformations in patients with T1D (26). **Despite revolutionary changes in diabetes treatment technologies, there are very few studies testing their impact on patients who are pregnant with T1D or planning pregnancy, the subset of patients who, with their offspring, specifically might benefit the most.**

Data from Sweden, and the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) control group (27), report 50% time-in-range (TIR) in the first trimester, improving to 60% time-in-range (TIR) in the third trimester, reflecting contemporary antenatal care. Of note, these data confirm that the time below range < 63 mg/dL recommendation of 4% is safely achievable, especially after the first trimester. Furthermore, 33% of women achieved the recommendation of 70% TIR 63‑140 mg/dL in the final (>34) weeks of pregnancy. Preliminary data suggest that closed-loop systems may allow pregnant women to safely achieve 70% TIR at an earlier (>24 weeks) stage of gestation. Law et al. analyzed data from two early CGM trials describing the associations between CGM measures and risk of large-for-gestational-age (LGA) infants. Taken together, the Swedish and CONCEPTT data confirm that a 5‑7% higher TIR during the second and third trimesters is associated with decreased risk of LGA and other adverse neonatal outcomes including macrosomia, shoulder dystocia, neonatal hypoglycemia, and neonatal intensive care admissions.

Glucose variability in pregnancy: More stringent glucose targets for pregnant T1D patients, makes it more difficult to achieve glucose goals. The quest to reduce hyperglycemia results in a significantly higher risk of hypoglycemia compared to non-pregnant T1D patients (28). The greatest risk for both hyperglycemia and hypoglycemia often occurs overnight when patients are least able to make insulin dose adjustments. Hypoglycemia in pregnancy leads to greater risk of hypoglycemia unawareness and dangerously low glucose levels. The CONCEPTT study revealed benefits of continuous glucose monitoring (CGM) use in pregnant women with T1D, demonstrating that in the setting of comparable overall good glucose control as reflected in HbA1c level (mean HbA1c 6.35% in CGM group vs 6.53% in non-CGM group; p=0.0207), pregnant CGM users spent more time in target (68% vs 61%; p=0.0034) and less time hyperglycemic (27% vs 32%; p=0.0279) than did pregnant control participants, with comparable severe hypoglycemia episodes (18 CGM and 21 control) and time spent hypoglycemic (3% vs 4%; p=0.10) (27). Fewer fetal adverse outcomes were reported for subjects wearing CGM. CGM wear in this study was reported at 70% using the Medtronic Guardian sensor which requires calibration 4 times a day and has to be replaced every 6 days. This study suggests that other metrics of glucose variability such as TIR and reduced post-prandial hyperglycemia, as opposed to HbA1c, may be stronger predictors of adverse maternal and fetal outcomes.

Artificial pancreas during pregnancy in T1D has been understudied and has significant therapeutic potential: There have been 3 AP studies published from European investigators showing safety and efficacy in pregnant women with T1D. The first study by Murphy et al in 2011 conducted AP studies for 24 hours in an inpatient clinical research center in 10 pregnant women with T1D at 14.8 and 28

weeks of pregnancy (29). The system required data entry by an RN every 15 minutes into a laptop computer that stored the algorithm. Overnight time in range was 84% and 100% (63-140 mg/dL) in the early and late gestation groups, respectively, with no hypoglycemia. Two follow up studies (30; 31) utilized a Sooil insulin pump and freestyle Navigator II CGM. Neither of these off the shelf devices is available in the United States. Subjects (16 in each study) were studied in a randomized crossover fashion and served as their own controls. Subjects wore the system for 4 weeks overnight in Stewart et al., 2016 and wore the system day and night in Stewart et al., 2018. In both studies, subjects used SAP for 4 weeks as the control arm and had an option for study extension. Results (summarized in Table 3) revealed the safety of the system in the home setting with fewer episodes of hypoglycemia and increased overnight time in the target glucose range of 63-140 mg/dL. In the overnight study, time in range (74.7 vs. 59.5% [95% CI 6.1 to 24.2]; P = 0.002) was significantly longer and mean glucose (119 vs. 133 mg/dL, P = 0.009) was significantly lower while using the closed loop system. Time above goal was significantly reduced (>140 mg/dL: 24% vs 38.6%, P= 0.005; >180 mg/dL 7.4% vs 15.7%, P=0.004). In the day and night study, there were significantly fewer hypoglycemic episodes (median [range] 8 [1–17] vs. 12.5 [1–53] over 28 days; P =0.04) and percent time spent below goal was less (<63 mg/dL: 1.6 vs. 2.7%; P = 0.02; <50-mg/dL: 0.24 vs. 0.47%; P = 0.03). The time in range overall for the latter study was comparable between groups, but there was a trend toward higher overnight time in target (67.7 vs. 60.6%; P = 0.06). Maternal glycemia was variable, however. Five (31%) of the study participants spent less time in target range and had higher mean glucose levels during AP therapy. Maternal and fetal outcomes for both studies are shown in Table 4.

**Table 3.** Reported Glycemic Outcomes in AP Studies

| | Stewart et al, 2016 (overnight) | | Stewart et al, 2018 (day and night) | |
|---|---|---|---|---|
| | CL | SAP | CL | SAP |
| **Time in range** | 74.7%* | 59.5% | 62.3% | 60.1% |
| **Mean glucose (mg/dL)** | 119* | 133 | 131.4 | 131.4 |
| **Standard deviation (mg/dL)** | 25 | 27 | 36 | 37.8 |
| **Time >140mg/dL** | 24%* | 38.6% | 36.1% | 36.6% |
| **Time >180mg/dL** | 7.4%* | 15.7% | 14.6% | 14.8% |
| **Time <63mg/dL** | 1.3% | 1.9% | 1.6%* | 2.7% |
| **Time <50mg/dL** | 0.3% | 0.6% | 0.2%* | 0.5% |
| **Median # of hypo events** | 3 | 2.5 | 8* | 12.5 |

**(*indicates P value<0.05)**

**Table 4.** Reported Maternal and Fetal Outcomes in AP Studies

| | **Stewart et al, 2016** | **Stewart et al, 2018** |
|---|---|---|
| **Baseline HbA1c** | 6.8±0.6% | 8.0±1.1% |
| **Pre-eclampsia** | 31% | 12.5% |
| **Preterm** | 44% | NR |
| **C-section** | 94% | 81% |
| **NICU admission** | 75% | 69% |
| **LGA** | 81% | 44% |
| **Congenital malformations** | Not recorded | 12.5% |

Our consortium also is following a prospective cohort of 30 women who are participating in the Longitudinal Observation of Insulin Requirements and Sensor Use in Pregnancy (LOIS-P) study designed to track glycemic control and insulin pump setting changes throughout pregnancy. All subjects are enrolled before 17 weeks gestation, are using insulin pumps, are provided Dexcom G6 CGM, and are followed prospectively throughout their pregnancy and for 6 weeks post-partum. All subjects are contacted every 2 weeks. Data collected include CGM, insulin delivery, self-monitoring of blood glucose (SMBG), and maternal and fetal outcomes of pregnancy. Activity and diet logs are also being collected during 1 week in the 2nd and 3rd trimesters. This is a unique dataset that will pave the way for better understanding of the dynamic insulin requirements during pregnancy.

As of Jan 15, 2021, we have analyzed results from 25 subjects enrolled in the LOIS-P study referred to above. Only six participants achieved >70% recommended TIR for pregnancy. Between 18-24 and 26-30 weeks, mean daily percentage of CGM TIR was significantly lower, and time above range was significantly higher compared to the reference biweek. Time below target was unchanged. All primary outcomes were statistically significant ($p<0.003$). Daily basal insulin per kilogram was higher during weeks 6-10 and 28-40. Daily bolus and total insulin per kilogram were higher during weeks 22-40. Carbohydrate intake stayed stable. All insulin parameters were significantly increased from 22 weeks onwards. We conclude that insulin dosing changes significantly with advancing gestation and most participants did not achieve >70% TIR. This further illustrates the urgent unmet need for automated insulin delivery systems customized to this population's targets.

These data support the importance of studying AP systems further in pregnant women with T1D. The potential of a system with FDA approved devices (including the Dexcom G6 CGM with high accuracy, mean absolute relative difference (MARD) <10, and no acetaminophen impact (32)) with a smartphone-based operator has not been studied. We believe a system that has adjustable glucose targets and adapts to changes in insulin sensitivity as pregnancy progresses will provide an increased time in glucose target range of 63-140 mg/dL as well as benefit to mother and fetus.

## 2.3 Results of G200099 48-Hour AP in Pregnancy Study Showing Safety and Efficacy

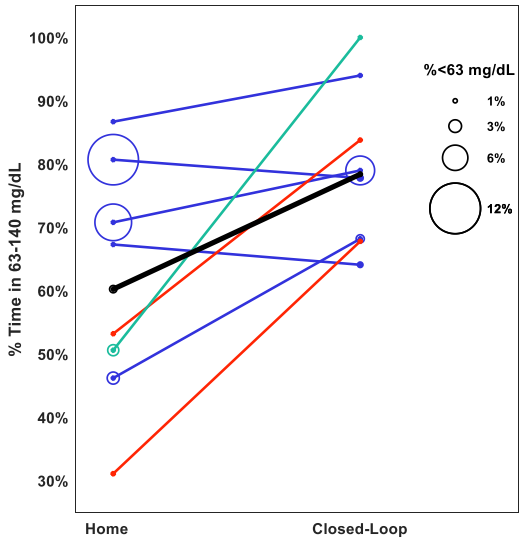
As of Jan 15, 2021, eight pregnant women with T1D from three US sites have participated in the 48-hour clinical trial from this IDE G200099 (NCT04492566). Per protocol, women were enrolled after completing the first trimester period. CL sessions used the iAPS running a Zone-Model Predictive Control algorithm designed for stricter glycemic targets of pregnancy. Glycemic target zones were 80-110 mg/dL during the day and 80-100 mg/dL overnight, with assertive insulin delivery in the postprandial period. All subjects completed the trial. Participants were 29.3±3.5 years, gestational age of 22.2±3.6 weeks, BMI of 28.2±5.1, and had an HbA1c of 5.7±0.5%. Mean CGM TIR was 79.3±12.8% during closed-loop, compared to 60.8±18.8% for the week prior in open loop at home ($p=0.03$, Table 5). All subjects completed the study safely, with almost all showing increased time-in-range compared to their prior care (Figure 3). Unrestricted carbohydrate intake at meals ranged from 7 to 78 grams during the CL sessions. No severe hypoglycemia or adverse events occurred.

**Table 5.** Mean±SD continuous glucose monitoring (CGM) metrics for the closed-loop control (CLC) sessions, compared to the week prior for 8 pregnant women with type 1 diabetes.

| Sensor Glucose Metric (mg/dL) | 48 Hour CLC Session | Week Prior CGM Use at Home | p-value |
|---|---|---|---|
| **Percent time 63-140** | 79.3±12.8 | 60.8±18.8 | 0.03* |
| **Percent time 70-180** | 89.3±5.8 | 78.1±11.8 | 0.02* |
| **Mean CGM Glucose** | 112.5±11.9 | 131.9±26.4 | 0.05 |
| **Percent time <54** | 0.4±0.5 | 1.2±1.4 | 0.11 |
| **Percent time <63** | 1.6±2.2 | 3.5±4.5 | 0.2 |
| **Percent time >140** | 19.1±12.5 | 35.7±21.0 | 0.06 |
| **Percent time >180** | 6.1±4.4 | 15.6±13.7 | 0.07 |
| **Percent time >250** | 0.4±1.0 | 3.7±4.9 | 0.09 |
| **SD CGM Glucose** | 33.1±9.2 | 43.6±12.7 | 0.07 |
| **CV CGM Glucose (%)** | 29.1±7.1 | 32.8±5.8 | 0.21 |

* Statistically significant with p<0.05 (paired t-test)

**Figure 3.** Change in the percentage of time spent in target range (TIR, 63-140 mg/dL) and below range per participant during the open-loop management at home vs. 48-hour closed loop study. Median change in the TIR and percent time CGM < 63 mg/dL are shown by the black line and filled in black circles.




## 3 DESCRIPTION OF DEVICES

### 3.1 Overview and hardware

The interoperable Artificial Pancreas System (iAPS) is an artificial pancreas system (as described in MAF-1625, Amendment #10), comprised primarily of an insulin pump, a continuous glucose monitor (CGM), and a cellular phone device to connect the components. The portable AP device is intended to adjust insulin doses when glucose concentration is, or is predicted to be, outside the

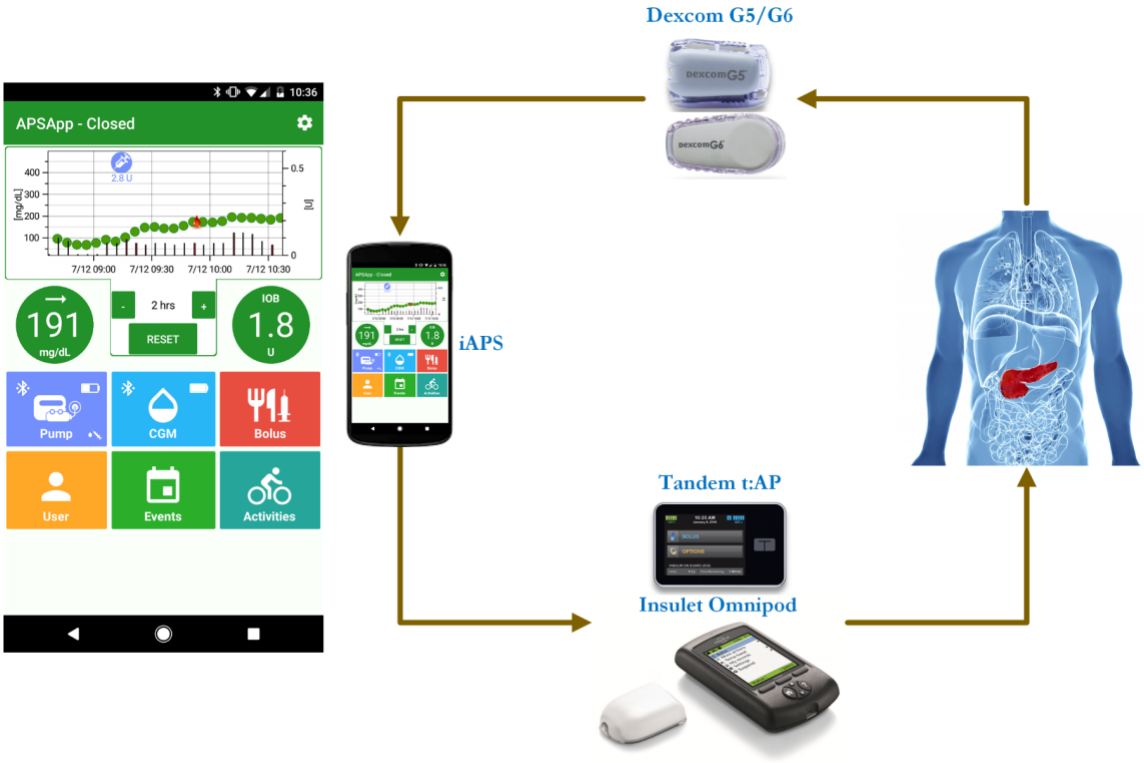
specified target range of 80-100 mg/dL. It includes a redundant safety control that will send warnings of impending hypoglycemia and recommend ingesting carbohydrates immediately to prevent hypoglycemia (Health Monitoring System).

The interoperable Artificial Pancreas System (iAPS) used in this study is described in MAF-1625, Amendment #10, and includes:

- A cellular phone device to connect to the insulin pump and CGM transmitter (Google Pixel 1, 2 or 3/3a)
- Dexcom G6 Sensor & Transmitter (G160069)
- Tandem t:AP insulin pump (San Diego, CA) (MAF-2032-A003)
- The same control algorithm successfully used with iAPS in G180011/002 and G200047 (Zone MPC with HMS), with modifications to the tighter target glucose range as recommended for pregnant women with diabetes to achieve increased time in range 63-140 mg/dL, and reduce postprandial hyperglycemia.
- The same Health Monitoring System (HMS) algorithm used in G180011/002 and G200047, which issues safety notifications to the subject and support personnel to prevent impending hypoglycemia, with minor modifications to the algorithm as noted above.

A schematic of the iAPS system being used in the study is shown in Figure 4.

**Figure 4:** Schematic of the representative principal system hardware components. The iAPS works with both Dexcom G5/G6 and with OmniPod and Tandem t:AP pumps. In this study we will only be using Dexcom G6 and Tandem pumps.




Letters of authorization for all devices used as part of iAPS system are included in MAF-1625, Amendment #10.

### A. Dexcom G6 (Study CGM)

The AP System will be integrated with the Dexcom G6 (study CGM). The G6 transmitter sends data points directly to iAPS.

### B. Tandem t:AP Pump

The Tandem t:AP insulin pump is a modified version of the Tandem t-slim insulin pump that is modified to work with an AP controller. It otherwise functions identically to the commercially available product. No other pumps will be used in this study.

### C. Study Glucometer and Ketone Meter

Subjects will use the Contour NEXT blood glucose monitoring system (K150942 - Ascensia Diabetes Care US, Inc., 5 Wood Hollow Rd, Parsippany, NJ 07054 USA) to measure capillary blood glucose for CGM calibration and confirmation of CGM readings.

Subjects will use the Precision Xtra® ketone meter (K040814 - Abbott Diabetes Care Inc., 1360 South Loop Road, Alameda, CA 94502 USA) to test blood ketones as needed during the study.

### D. Phone Device

The phone device that will run the iAPS in this study is a stock Google Pixel 1, 2 or 3/3a Phone, with the iAPS as described in MAF-1625, Amendment #10. The version of Android used in the phone for this study is version 7.1.2, 8.1, 9, 10 or 11. The phone is set to not allow automatic upgrades of the OS. However, if a phone OS upgrade does occur, study staff will not allow subject use of the device and will not release the interlock on the study RM website if the OS version upgrades past the last version that has been tested and verified to support full AID functionality. In that case, the subject's study phone will be replaced.

## 3.2 Control Algorithm with HMS

A detailed description of the Zone-MPC and HMS control algorithms, meal bolus strategy, and insulin-on-board calculations are provided in Appendix B of the IDE.

The meal bolus strategy used in this study uses full meal boluses for each meal as long as sensor glucose is above 70 mg/dL, as this is necessary for achieving tight glycemic control in pregnancy. The user may adjust the bolus dose up or down at the time of the bolus and needs to approve and confirm the bolus before it is given. This is similar to how boluses are performed in all current insulin pumps, with the dose adjusted, reviewed and confirmed by the user.

The HMS algorithm is also incorporated into the system to provide alerts to the user and clinician of impending hypoglycemia that may require treatment such as fast-acting carbohydrate consumption. Although the HMS algorithm uses the same CGM data as the MPC algorithm, it utilizes a separate algorithm for predicting glucose values. This HMS algorithm was also developed by engineers at Harvard University in collaboration with Sansum Diabetes Research Institute, and the same algorithm was successfully used in G150063, G150122, G160281, G130236, G130147, G180011, G180011/S001, G180011/S002, and G160279/S002. In this study, the HMS will produce an alert on the phone screen when it predicts a glucose value below 65 mg/dL within the next 15 minutes. Treatment will be given at the discretion of the investigator and subject when confirmatory fingerstick glucose is ≥ 63 mg/dL to prevent hypoglycemia as per the subject's usual routine and investigator direction. Treatment with carbohydrates is mandated for hypoglycemia, which is defined as fingerstick glucose < 63 mg/dL and/or symptomatic.

# 4 STUDY OVERVIEW

## 4.1 Study Overview

In this study, subjects will use the iAPS for ~48-60 hour period in a supervised outpatient environment. All meals will be bolused for as per usual care. In addition, subjects will perform their usual daily activities (excluding intense exercise) while being accompanied by study medical staff. This includes following a lower carbohydrate diet that women are normally prescribed in pregnancy.

Extension Phase

For subjects who wish to continue use of the system beyond the 48-hour session, they will be trained on use of the study pump and the iAPS during the 48-hour study, and staff will complete the study training checklists. Subjects will then be able to continue with home use of the system all the way through to delivery if they desire, with a 24-hour, 48-hour and 72-hour follow up call, and then at least weekly follow up during the course of the study. The outpatient studies will be closely supervised with easy access for subjects to clinical study teams at each site. High risk obstetrics physician will be available at each site for the clinical research study team.

## 4.2 Primary Objective

The **primary endpoint** is time within the target glucose range of 63-140 mg/dL overall as assessed by CGM.

## 4.3 Secondary Endpoints

**Secondary safety and efficacy endpoints** will include: time within the target range of 63-140 mg/dL overnight, within the range of 63-140 mg/dL postprandial within 2 hours following meals; frequency of hypoglycemia below predefined thresholds of 63 mg/dL and 54 mg/dL, and frequency of hyperglycemia above predefined thresholds of 140, 180 mg/dL and 250 mg/dL. Additional secondary outcomes include markers of hypo- and hyperglycemia, as well as safety events, treatments for hypoglycemia, outside interventions needed, and a failure analysis of the devices/connectivity issues that may occur.

The clinical study will also review any serious adverse events that occur: hypoglycemic events, hyperglycemic events, planned and unplanned outside intervention, other Adverse Events, Serious Adverse Events, Unanticipated Adverse Device Effects, and device complaints for the commercial devices used. A root cause analysis of the event will be performed to determine if it is related to the approved devices - the Continuous Glucose Monitor (CGM) or the Continuous Subcutaneous Insulin Infusion (CSII) pump - the insulin, the AP system, or the control algorithm. Safety of the patient and the fetus will remain the primary goal. The goal of the AP device is to operate without outside intervention apart from HMS alerts suggesting carbohydrate ingestion due to impending hypoglycemia.

# 5 BACKGROUND INFORMATION

## 5.1 General Background

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

Informed consent will be obtained before the study procedures are conducted.

Data for this study will be collected on a combination of paper and electronic case report forms, which will be considered the source data. If possible, data will be directly entered into the eCRF as applicable.

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

## 5.2 Description of Population Studied

The system will be evaluated on up to 21 pregnant adult subjects with type 1 diabetes age 18-45 years old at three clinical sites (Sansum Diabetes Research Institute, Mayo Clinic Rochester MN and Mt Sinai Hospital, New York City). We will recruit pregnant patients between 14-32 weeks gestation. All racial/ethnic groups will be eligible for participation. Subjects will complete a ~48-60 hours closed-loop (CL) session in a supervised outpatient environment with medical staff present, and then have the option to use the CL system at home throughout the remainder of their pregnancy if desired.

# 6 TRIAL DESIGN

## 6.1 Overview

This study is a 3-site early feasibility study of pregnancy-specific AP in which we will recruit a total of 21 pregnant women with T1D for a complete 48-60 hours of AP control in a supervised outpatient environment. After completing the 48-hour session, we will offer continued use of the system at home, through as far as delivery if desired, to each subject. Subject data will be reviewed for safety at 24 hours, 48 hours and at 72 hours of home use, and then weekly before being extended a week at a time for the rest of the pregnancy.

### 6.1.1 Limitations on the Number of Subjects that can be Enrolled

Enrollment will be limited to a maximum of 4 active subjects **across all clinical sites** at any given time. This will allow for subjects to finish the study before the next is enrolled, and assure available resources for the maximum of 4 possible subjects who may run concurrently.

Enrollment is also limited to only 3 active subjects at a given clinic site at any one time, and each site may only enroll 2 subjects per week maximum.

These limits will remain in place throughout the study.

## 6.2 Eligibility and Exclusion Criteria

### 6.2.1 Inclusion Criteria

To be eligible to enroll in this study, subjects must meet all of the following including criteria:

1) Age ≥ 18 and ≤ 45 years at the time of screening.
2) Clinical diagnosis of type 1 diabetes
3) Currently using an insulin pump at the time of screening.
4) HbA1c ≤ 9%, as performed by point of care or central laboratory testing. A1c will be assessed at the screening visit.
5) Pregnant $14^{0/7}$ to $32^{6/7}$ weeks gestation.
6) Singleton pregnancy without any other significant known complications, such as preeclampsia, premature rupture of membranes, 2nd/3rd trimester bleeding, fetal growth or fluid abnormalities.
7) No proven or suspected fetal malformations diagnosed in the current pregnancy.
8) Bolus for all meals and snacks that contain ≥ 5 grams of carbohydrate.
9) Willing to switch to Novolog or Humalog, or continue Novolog or Humalog for the duration of closed-loop use.
10) Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial.
11) Willing to abide by the study protocol and use study-provided devices.
12) Have a care partner with the following responsibilities: knowing subject whereabouts and being promptly available for contact by study staff during the day and night, residing in the same dwelling as subject during the night, being agreeable to all device training during the supervised HCL session and additional training on hyper- and hypoglycemia treatment, and assisting with emergency care if needed, such as transportation to the hospital or emergency department.

### 6.2.2 Exclusion Criteria

Subjects would not be eligible to enroll in this study if they meet any of the following exclusion criteria:

1) Known unstable cardiac disease or untreated cardiac disease, as revealed by history or physical examination.
2) Concurrent use of Afrezza or any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).
3) Hemophilia or any other bleeding disorder
4) Prior history of Preterm Premature Rupture of Membranes (PPROM)

5) Significant hyperemesis interfering with carbohydrate intake
6) Laboratory results:
    a. A1C > 9%
    b. Abnormal liver or renal function (Transaminase >2 times the upper limit of normal, creatinine > 1.5 mg/dL)
    c. Liver and renal function testing drawn at screening visit or within three months prior to screening (for other purposes) will suffice for enrollment purposes
7) Dermatological conditions that would preclude wearing a CGM sensor or infusion site.
8) Any condition that could interfere with participating in the trial, based on investigator judgment.
9) Participation in another pharmaceutical or device trial at the time of enrollment or during the study.
10) Having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial
11) History of severe hypoglycemia in the past 6 months
12) History of DKA requiring hospitalization in the past 6 months
13) Significant chronic kidney disease (eGFR < 60) or hemodialysis
14) Significant liver disease
15) History of adrenal insufficiency
16) History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated
17) History of high dose steroid use in the past 8 weeks

## 6.3 Schedule of Events

The trial consists of:

1) A screening visit to assess eligibility

2) One to two week open-loop data collection while wearing Dexcom G6 CGM

3) A 48-60 hour closed-loop session in a supervised outpatient environment with at least one licensed medical provider present at all times

4) A follow up phone call 2 hours after discharge from the closed-loop session to assure subject safety and safe transition back to the subject's home insulin pump if they are not continuing in the extension phase.

5) Continued use of the system at home, optionally though the end of pregnancy, for subjects who wish to continue use of the system. To achieve this,

a. Subjects must consent to training for the extension phase at the time of signing their informed consent form.

b. Subjects will be trained on use of the study pump and phone while attending the 48-hour study session. Study staff will complete the study pump and phone training checklists, and the site investigator will sign off attestation that the subject is ready to use the study devices at home.
c. Subjects will have a documented 24-hour, 48-hour and 72-hour check in after taking the system home, requiring the study team to review the remote monitoring system data, and then at least weekly documented contact with each subject. Providers may adjust insulin delivery settings as clinically indicated.
d. During the first two weeks of home use of the study device, subjects will continue to perform scheduled fingersticks (SMBG) prior to meals, 2 hours after meals, and at bedtime, in addition to fingersticks mandated by the hyperglycemia and hypoglycemia study safety plan. After two weeks, the study glucometer will be downloaded, and if ≥90% of CGM values are within 20%/20 mg/dL of SMBG readings, this will be documented in a study contact CRF and the scheduled SMBG requirement for the remainder of that particular participant's time in the study may be removed. However, the participant will still be instructed to perform the confirmatory fingerstick requirements for safety criteria. If a subject's particular data set does not support removing this requirement, that subject will continue to perform scheduled fingersticks per protocol in addition to following the confirmatory fingerstick requirements for safety criteria. This analysis will be repeated for each subject in the study.
e. Subject's glycemic data will be reviewed and a documented contact will be completed at least weekly after the 72-hour check. If there is a significant deterioration of glycemic control as determined at any time or during the scheduled weekly contacts, leading to a significant worsening time in range compared to baseline (10% or more worsening of time in target range) and time in range consistently below 50%, the site clinical investigator will end the subject's participation in the study (Stopping criteria, section 8.4)
f. After ~4 weeks, the study Data Safety and Monitoring Board (DSMB) will review a summary of the subject's glycemic data, to include any adverse events, to approve continued use of the system through the remainder of pregnancy if the subject desires. Success criteria based on CGM glycemic metrics, to be presented to the DSMB, before approval can be granted to move beyond three subjects, are the following:
    a. CGM % Time ≤ 54 mg/dL = 2% or less
    b. CGM % Time 63-140 mg/dL = greater than or equal to 50%
    c. No Unanticipated Adverse Device Effects (UADE's)
g. Follow up visit after delivery: Subjects will be called or seen in person before hospital discharge to ensure they have transitioned safely to their home devices. Maternal and neonatal outcomes will be recorded.

Subjects will be considered enrolled when, after completing the screening visit, the investigator has reviewed all enrollment criteria and signed off on the subject's enrollment. Up to 21 subjects may be enrolled.

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

Study schedule and interventions are summarized in the table below:

**Table . Schedule of Assessments Including Extension**

| | Screening | Open Loop Data Collection | Hybrid Closed-Loop Phase | End of Study Phone Call (Last study visit) | Extension Phase |
|---|---|---|---|---|---|
| Informed Consent | X | | | | |
| Demographics | X | | | | |
| Medical History | X | | | | |
| Diabetes History | X | | | | |
| Medication Use | X | | | | |
| Vital Signs[1] | X | | X | | |
| Skin inspection (Sensor/Infusion Set Sites) | X | | | | |
| Fetal Doptones | | | X | | |
| Laboratory | X | | | | |
| Point-of-care HbA1c | X | | | | X[4] |
| Insulin pump/CGM/glucometer data download | X | | X | | |
| CGM Training | | X | X | | |
| CGM Placement | | X | X | | |
| iAPS & Study Pump Closed-Loop Use | | | X | X | X |
| Fingersticks BG as required per protocol[2] | | X | X | X | X |
| CGM Calibrations[3] | | X | X | X | X |
| Competency assessment prior to discharge home with iAPS | | | X | | |
| 24, 48, and 72 hour contact, then a minimum of weekly contact with subjects. | | | | | X |

1 – Vital signs at admission, Q12 hours, discharge, and per investigator discretion during the closed-loop phase.

2 – Fingersticks per protocol criteria for hypo and hyperglycemia during closed-loop use.

3 – As required per manufacturer's instructions.

4 – A1c and/or fructosamine may be performed via point-of-care or by central laboratory testing every 4 weeks during the extension phase.

## 6.4 Screening Visit

Subjects must sign the consent form prior to any screening procedures. Each subject will have the opportunity to ask questions and receive answers from study personnel prior to signing the consent.

The following will be evaluated/performed and documented during the screening visit:

1) Informed consent form (signed and dated)
2) Inclusion and Exclusion criteria
3) Demographic information (e.g., date of birth, gender, race)
4) Medical history to include any relevant data related to the current pregnancy, to specifically include common conditions in pregnancy such as heartburn, headaches and nausea, asthma, diet plan and how subjects are managing this during pregnancy and how they will manage it during the closed-loop session.
5) Diabetes history (diabetes type, diabetes duration, pump use duration, past/current CGM use, total daily insulin dose, basal rates, carbohydrate ratios, correction factors).
6) Current medication use
7) Vital signs to include blood pressure, heart rate, height and weight.
8) Physical examination, including skin inspection of potential sensor and infusion set insertion sites.
9) Recording of duration of pregnancy (Gestational Age).
10) HbA1c via point-of-care or laboratory testing.
11) Screening liver and renal function testing, if not completed within prior 3 months.
12) Insulin pump, CGM (if available) and glucometer (if available) data download.

## 6.5 Open Loop Data Collection

Approximately 1-2 weeks prior to the planned closed-loop session, study subjects will first undergo Dexcom G6 training as per the study CGM training form, and then wear Dexcom G6 for CGM for 1-2 weeks.

Study clinicians will evaluate skin prior to sensor placement and upon removal for appropriateness of site as well as any skin findings or reactions. Sensors will be worn for up to 10 days. For the study, clinicians will review that CGM use is not currently approved for pregnant women, and that there is no approved wear site in pregnancy. As such, participants will be instructed that CGM will be worn in the posterior upper arm during the study, as this site is the approved wear site for the clinical study. Staff will also review the need to make all treatment decisions based on fingerstick SMBG.

Subjects with no prior experience with the Dexcom CGM will be taught by study staff on how to use the CGM, including how to insert the sensor and transmitter and to calibrate the CGM as necessary per manufactures instructions.

Participants will be advised to continue daily activities and food consumption as usual and continue to make diabetes management decisions (e.g., insulin dosing adjustments, hypoglycemic/hyperglycemic management, lifestyle modifications, etc.) as per clinician recommendations. Participants who are naïve to CGM will undergo training on CGM use (similar to CGM training in nonpregnant person new to CGM), including use of trend arrows, alerts, alarms and historical trend information. During this instruction, emphasis will be made on the use of fingerstick SMBG to confirm low or high readings before making treatment decisions, as well as using fingerstick SMBG to make meal bolus and correction dose decisions. Clinicians will decide on an individual basis the appropriate glucose thresholds and alarm settings with the aim of safely achieving pregnancy specific glucose targets and reducing hypoglycemia. Participants' CGM data will be reviewed on a daily basis for the first 3 days of wear followed by at least two times per week for safety.

Subjects will also be provided with a glucose meter and test strips for home use. Subjects will be instructed that if CGM calibration is required, the best time to calibrate the CGM is when glucose levels are not rapidly changing, generally before breakfast and before dinner.

Subjects will be given a Contour NEXT glucose meter. The glucose test strip bottle given to the subject will pass quality control (QC) testing with at least one control solution prior to being given out to subjects. A glucose meter and/or test strips will not be used in a study if it does not read within the target range of the QC solution testing per manufacturer labeling.

Study staff may contact the subjects more frequently, use the Dexcom Follow app to monitor subjects, and/or simply review their diabetes care on the phone. During this phase, the subjects' basal rates, carbohydrate ratios and/or insulin sensitivity factors may be adjusted as needed based on clinician discretion to optimize pump settings prior to entering the hybrid closed-loop phase.

### 6.6 Hybrid Closed-Loop Phase (~48-60 Hours)

Subjects will be instructed to insert a new CGM sensor at least 24 hours prior to arrival to the supervised outpatient environment. Study staff will verify that the subject has changed out their CGM sensor at least 24 hours prior to the start of closed-loop session and document this on the study case report forms.

Prior to arriving for the closed-loop visit, subjects will be reminded to bring all their usual medication, to include PRN medications especially those needed for asthma and other chronic illnesses should an exacerbation occur. Subjects will also be reminded to stay well hydrated even prior to arrival, and to bring their own supportive tools they are already using such as pillows or lumbar support to the session.

Prior to initiating the closed-loop study, fetal heart rate will be documented using a portable Doptone. Vital signs to include blood pressure will also be taken at admission and every 12 hours, at investigator discretion, and will be performed for development of new symptoms such as headache or nausea.

During the closed-loop session, subjects will be supervised at all times by study staff who are clinically trained in treating hypoglycemic and hyperglycemic emergencies per the clinical study protocol. In addition, a clinician (MD/NP) will be present.

At the start of closed-loop use, subjects will be advised that use of the iAPS, in particular entering boluses, may only be performed with direct study staff supervision, until training on the system is complete.

Fingerstick glucose measurements will be performed as required by manufacturer's instructions to calibrate the CGM. Fingerstick glucose measurements will also be performed before all meals, 2 hours after meals, and at bedtime. In addition, subjects can perform additional fingersticks upon their request, upon request of the investigator, when prompted by the HMS, as per evaluation and treatment of hyper- and hypoglycemia guidelines in the protocol, during exercise, for CGM calibration or for any other reason.

During the closed-loop phase, subjects will be allowed to snack at any time and bolus appropriately per their home routine, with the goal to prebolus 15-30 minutes of ahead of time to minimize postprandial hyperglycemia. Each subject will be provided with the same rapid-acting insulin (e.g., Novolog or Humalog) as they customarily use. The carbohydrate content of all meals/snacks that a subject would normally bolus for will entered into the iAPS by the subjects while supervised by the study staff for all meals and snacks requiring insulin.

If a CGM sensor fails or comes loose at any point during this phase, the sensor will be replaced and closed-loop mode will resume once the sensor has completed warm-up. Skin Tac or other similar agents may be used to ensure adequate adherence of the CGM sensor to the skin.

Subjects will be allowed to perform light exercise (e.g., walking, stretching, yoga) per their usual home routine at any time during the closed-loop phase, and may take additional carbohydrates for exercise as per their usual home routine. Any additional carbohydrates or activity will be documented in the subjects' chart.

Subjects will eat their usual prescribed diet while using the system. They will be encouraged to hydrate well as well.

In the case of maternal assessment of decreased fetal movement, fetal kick count will be assessed (at least 10 movements within 2 hours) if gestational age appropriate (>28w gestation). Research medical staff will assess and as needed research staff will stop the session and request subject contact her obstetrician and/or send subject to appropriate acute care setting for immediate evaluation.

For new onset vaginal bleeding, hypertension >140/90 mm Hg, uterine cramping (regular and/or painful) or contractions, PPROM, headache related to new onset hypertension, nausea with significant vomiting and any other medical concern that may cause a safety concern, research medical staff will stop the session and request subject contact her obstetrician and/or facilitate transport of subject to appropriate acute care setting for immediate evaluation. Fetal doptones will also be performed.

Treatment for hypo- and hyperglycemia that occur during the closed-loop phase will follow the hypo- and hyperglycemia treatment plan as detailed in Table 8.

### 6.6.1 Monitoring Frequency in the Closed-Loop Session

The frequency of glucose monitoring during closed-loop use is described above and summarized below:

**Table 7. Frequency of glucose monitoring during Closed Loop**

| Measurement Device | When | Frequency |
|---|---|---|
| **CGM** | Entire Closed-Loop Session | • Every 5 minutes |
| **Fingerstick SMBG** | Calibration of CGM During Closed-Loop | • As required by CGM manufacturer instructions. |
| **Fingerstick SMBG** | Closed-loop | • Scheduled before all meals, 2 hours after meals, and at bedtime<br>• Every 15 minutes once BG is below 63 mg/dL until BG ≥ 63 mg/dL<br>• Every 30 minutes once BG > 250 mg/dL for at least 1 hour until BG ≤ 250 mg/dL |
| **At home CGM** | | Every 5 minutes |

Multiple visual and auditory alarms are embedded into the iAPS 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 <54 mg/dL in the next 15 min, the system will alert on the iAPS and send a redundant text message to a predefined list of people, which in this study will include the medical staff (who will be on stand-by and in close physical proximity to the subject in this study) to notify the subject to consume 4-16 grams of carbohydrate, at the discretion of the investigator (Table 8). All warnings issued by the HMS will be documented. The study personnel monitoring the study will confirm that the subject has responded to the hypoglycemia alert and has taken corrective action. If the subject is asleep or

has not heard or noticed the alert, the study medical staff will wake the subject, inform her of the alert and confirm that proper action is taken.

To prevent dehydration secondary to hyperglycemia, the subject will be encouraged to consume water or sugar free beverages during the trial if she is thirsty.

Photographs and/or videos of participants may be used in presentations at conferences and shown to potential subjects, as well as research donors. Subjects will be given the option consent to be photographed and/or videotaped while participating in the study. Subjects may decline to consent to photograph and video, and this will not impact their participation in the study. Photographs and videotape will be full body portrait with study devices, and subjects will have the have the option upon consent of choosing to have their face blurred. Subject names will not be associated with any photograph(s) or video(s) used.

Upon session completion, prior to discharge, subjects who are not continuing with closed-loop use will transition back to their personal diabetes management devices after having been determined safe for discharge by the study clinician. Prior to discharge from the closed-loop study, fetal heart rate will be documented using a portable Doptone and vital signs will be repeated.

A follow up phone call will be performed 2 hours after discharge to make sure the subject is doing well and has safely transitioned back to their home pump.

### 6.6.2 Extension Phase

For subjects who wish to continue use beyond the 48- hour observed session, they may continue use of the system at home if the following criteria are met:

1) CGM training refresher completed: At investigator discretion, applicable elements of the CGM system training may be completed as refresher training. The participant will be provided with a supply of CGM sensors, a backup CGM transmitter, and blood glucose strips to last until the next study visit.

2) Blood ketone meter training completed and supplies issued: The participant will be provided with a study blood ketone meter and strips and instructed on the use of this device.

3) Home Glucagon Emergency Kit: Participants will be required to have a home glucagon emergency kit. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

4) Completion of formal study pump training and study phone training, using the study checklists, as per sections 6.6.3 and 6.6.4 below.

5) No severe hypoglycemic or hyperglycemic adverse events during the 48-hour training visit, as defined in sections 8.1.2.1 and 8.1.2.2, respectively.

6) No UADE's or reportable device issues, as defined in section 8.2.

7) Completion of care partner training.

### 6.6.3 Pump Training

For extension phase continued use of the system, subjects will complete study pump training during their 48-hour study session:

- The participant will be fully instructed on the study insulin pump. A member of the study research team will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board and correction boluses. Additional topics not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.
- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.
- The appropriate study pump training checklist will be used to document and facilitate the training process; a physical or electronic copy of the pump user guide will be provided for the participant to take home.
- Participants will be provided with sufficient insulin infusion supplies to last until the subsequent visit.

### 6.6.4 Study Phone Training

For extension phase continued use of the system, subjects will complete study phone training during their 48-hour study session:

- The study team will confirm the subject's parameters are entered in the system (APS RM) with the study physician.
- How to switch the system between Pump mode (open-loop, preprogrammed basal insulin delivery) and Closed Loop mode depending on circumstances.
- How to calibrate the CGM unit during the study as per manufacturer's instructions and per clinical need.
- How to access the CGM trace from the sensor on the phone screen. Study staff will also explain the concept of "safe basal" to the subjects which can be activated after CGM connectivity is interrupted to the study phone.

- How to activate the meal bolus screen of the phone system any time insulin will be given with a meal or any time additional correction insulin is desired.
- Specifically, study staff will follow inform the subject that:
    - The bolus screen correction calculation is based on the last CGM value.
    - Fingerstick glucose measurements are required prior to all meals, 2 hours after meals, and at bedtime, in addition to confirmatory fingersticks for hyperglycemia (> 180 mg/dL) and hypoglycemia (<63 mg/dL) as per the study safety plan. After 2 weeks, the accuracy of fingerstick measurements will be reviewed as compared to CGM, and the requirement for scheduled fingersticks may be able to be removed. Fingersticks for the study safety plan will always be required.
    - They can add a fingerstick value into the bolus screen, and this will adjust the correction slider calculated correction dose. If there is any concern about the accuracy of the current CGM value, a fingerstick is generally more accurate and should be performed instead of relying on the current CGM value.
    - They can adjust the correction slider calculated correction dose.
    - They can use the total dose box to adjust the final dose to be delivered, regardless of what settings are entered into the other boxes (glucose value, carbohydrates, correction). The amount shown in this box will be delivered.
    - CGM trend information is not used in the meal bolus or correction bolus calculation.
    - Study staff will observe them using all buttons and boxes on the meal bolus screen to show us they understand how to use the meal bolus screen.
- How to inform the system of hypoglycemia treatment via a hypoglycemia treatment button on the phone UI after each hypoglycemic treatment is consumed.
- What to do when exercising while using the system.
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.
- How to perform blood ketone testing.
- Review of the iAPS App User Guide; a physical or electronic copy will be provided for the participant to take home.
- The study iAPS training checklist will be used to document and facilitate the training process.

### 6.6.5 General Usage Training and System Initiation

For extension phase continued use of the system, subjects will be instructed to use the system in closed-loop mode except 1) when no CGM sensor is available or 2) if insulin is delivered by any means other than the study pump (e.g. injection of subcutaneous insulin via syringe in the event

of infusion site failure). If insulin is delivered by any means other than the study pump, participant will be instructed to turn off closed-loop mode for approximately four hours.

The participant will also be instructed to contact study staff during periods of illness with an elevated temperature >101.5 degrees Fahrenheit (38.6 degrees Celsius), periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reaction or asthma attack in addition to use of oral or injectable glucocorticoids to determine if closed-loop use should be temporarily discontinued. Participants will be specifically instructed:

1) Not to upgrade the phone operating system.
2) Not to plug headphones into the study phone or alerts will be silenced.
3) Not to put the phone on vibrate mode or alerts will be silenced.
4) Not to use any manufacturer provided (e.g. Dexcom G6 Mobile App) or third-party components for CGM connectivity and monitoring, as this will interfere with connectivity to the study phone.

During the 48 hour training session, the subject's care partner must be trained on the following:
- Review device training including the alerts that are sent to the participant.
- Review study staff contact information.
- Mixing and giving glucagon, turning subject to the side, and call 9-1-1.
- Disconnecting the study pump.
- Review symptoms of hypoglycemia that can include sweating, jitteriness, and not feeling well, as well as the possibility of fainting or seizures (convulsions).
- Review symptoms of hyperglycemia to include increased thirst, urination, headaches, not feeling well, nausea, vomiting, and ultimately diabetic ketoacidosis.
- Review disconnecting the study devices.

Training of the care partner will be completed either in person or via video visit during a portion of the 48-hour study session, prior to discharging the subject home with the system for home use.

After study system training and the 48-hour closed-loop session has been completed, participants will proceed with home use of the study system. Participants may use the study pump and study phone without closed-loop and study CGM during periods of component disconnections or technical difficulties. In order to continue on in the outpatient extension phase of the study, subjects must have a care partner/other responsible adult, willing to share their contact information with the study team and who has ready access to the subject, who can be available to physically find the subject and assist if the subject does not respond to contacts from the study team.

## 6.7 Remote Monitoring

The study providers on site will monitor all subjects on the web interface for the iAPS (Appendix A - Device User Manual) so they can see ongoing data from all current subjects at once.

Required real-time alerts, for the duration of the outpatient study, are to be set as follows:

- CGM > 180 mg/dL for more than 1.5 hours
- CGM > 250 mg/dL for 20 minutes
- CGM < 54 mg/dL for more than 20 minutes
- No CGM data for 2 hours.
- Out of closed loop for 2 hours

Additional text notifications to providers may be added and continued at investigator discretion to assure subject safety.

# 7 ASSESSMENT OF SAFETY

## 7.1 Blood Volume Requirements

Finger stick:

Each fingerstick measurement requires 1.5 microliters for accurate measurement. There is no significant blood loss. There are only screening blood draws for the study, which require < 10 mL of blood. Screening Hemoglobin A1c will be performed by fingerstick point-of-care testing if not performed as a serum sample as part of routine clinical care. These screening blood draws are also the typical evaluation done in the routine care of a pregnant woman with T1D.

## 7.2 Hypoglycemia and Hyperglycemia Prevention and Treatment

Table 8. Hypoglycemia and Hyperglycemia Prevention and Treatment

| Condition | Action Taken – Inpatient Study | Action Taken – Outpatient Extension |
|---|---|---|
| HMS alert for impending hypoglycemia | Study staff will closely monitor the subject's CGM readings for potential hypoglycemia during the 48-hour session.<br><br>A confirmatory fingerstick measurement will be performed.<br><br>If fingerstick glucose ≥ 63 mg/dL, treatment may be initiated by the investigator (~4-16 g fast acting carbohydrate) per investigator discretion. Subjects will then perform a follow-up fingerstick measurement 15 minutes after | Subject is instructed to perform a confirmatory fingerstick measurement for all predictive low alarms.<br><br>If fingerstick glucose ≥ 63 mg/dL, treatment may be initiated with ~4-16 g fast acting carbohydrate. Subjects will then perform a follow-up fingerstick measurement 15 minutes after treatment if CGM < 63 mg/dL. This protocol will be repeated until the HMS alert stops alarming.<br><br>If fingerstick glucose < 63 mg/dL, treatment will be initiated with ~4-16 |

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| | treatment if CGM < 63 mg/dL. This protocol will be repeated until the HMS alert stops alarming.<br><br>If fingerstick glucose < 63 mg/dL, treatment will be initiated by the investigator (~4-16 g fast acting carbohydrate) per investigator discretion. Subjects will then perform a follow-up fingerstick measurement 15 minutes after treatment if CGM < 63 mg/dL. This protocol will be repeated until the HMS alert stops alarming. | g fast acting carbohydrate). Subjects will then perform a follow-up fingerstick measurement 15 minutes after treatment if CGM < 63 mg/dL. This protocol will be repeated until the HMS alert stops alarming. |
| CGM reading <63 mg/dL | Same as above treatment. This protocol will be repeated until the fingerstick is >63 mg/dL per standard clinical treatment for hypoglycemia. | Same as above treatment. This protocol will be repeated until the fingerstick is >63 mg/dL per standard clinical treatment for hypoglycemia.<br><br>During the first two weeks of outpatient use, study investigators will receive alerts for prolonged states of hypoglycemia. |
| Any time a subject has subjective symptoms of hypoglycemia | A fingerstick blood glucose measurement will be performed. Fast-acting carbohydrates may be given to any subject who is symptomatic or requests treatment. | Subject is instructed to perform a fingerstick blood glucose measurement for symptoms of hypoglycemia. Fast-acting carbohydrates may be taken at any time for hypoglycemia symptoms. |
| CGM reading is >180 mg/dL for more than 1 hour | A confirmatory fingerstick measurement will be performed.<br><br>If the subject's BG is confirmed to be >180 mg/dL, then ketones will be checked using the study-approved ketone meter. | Subject is instructed to perform a fingerstick blood glucose measurement.<br><br>If the subject's BG is confirmed to be >180 mg/dL, then ketones will be checked using the study-approved ketone meter.<br><br>Study investigators will receive alerts for prolonged states of hyperglycemia. |
| BG confirmed >180 mg/dL for more than 1 hour and | A manual correction bolus with a target of 140 mg/dL may be delivered via the pump. Fingerstick BG and ketone measurements will be repeated after 1 hour. The correction | Subject will deliver a manual correction bolus with a target of 140 mg/dL via the pump. Fingerstick BG and ketone measurements will be repeated after 1 hour. The correction |

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| ketones are <1.0 mmol/L | dose given may be adjusted by the investigator, or by the subject during extended use of the system at home.<br><br>If BG fails to decrease by a minimum of 50 mg/dL in 1-2 hours, then study staff will replace the subject's infusion set with a new infusion set and the correction bolus will be repeated per the investigator's discretion. Subjects will change out their own infusion set during extended use of the system at home. | dose given may be adjusted by the subject during extended use of the system at home.<br><br>If BG fails to decrease by a minimum of 50 mg/dL in 1-2 hours, then subject will replace their infusion set with a new infusion set and the correction bolus will be repeated as needed.<br><br>During the first two weeks of outpatient use, study investigators will receive alerts for prolonged states of hyperglycemia. |
| BG confirmed >180 mg/dL for more than 1 hour and ketones are >1.0 mmol/L | A manual correction bolus with a target of 140 mg/dL may be delivered via injection to assure proper absorption in the setting of likely infusion set failure. Fingerstick BG and ketone measurements will be repeated after 1 hour. The correction dose given may be adjusted by the investigator, or by the subject during extended use of the system at home.<br><br>The study staff will replace the subject's infusion set with a new infusion set and the correction bolus will be repeated per the investigator's discretion. Closed-loop will be disabled by the investigator for the next 2-4 hours and until BG has returned to < 180 mg/dL. Subjects will change out their own infusion set and stop closed-loop use during extended use of the system at home. | Subject is instructed that with positive ketones, a manual correction bolus with a target of 140 mg/dL is to be given via injection to assure proper absorption in the setting of likely infusion set failure. Fingerstick BG and ketone measurements will be repeated after 1 hour. The correction dose given may be adjusted by the subject during extended use of the system at home.<br><br>The subject will replace their infusion set infusion with a new infusion set and the correction bolus will be repeated as needed. Closed-loop will be disabled for the next 2-4 hours and until BG has returned to < 180 mg/dL. Subjects will report all positive ketone measurements to the investigators.<br><br>Study investigators will receive alerts for prolonged states of hyperglycemia. |
| Subject loses consciousness or has a seizure, or subject is unable to take | 1 mg of glucagon will be administered and 911 will be called. The study will be stopped immediately until sponsor conducts a full investigation to determine the root cause for the compromised system performance and is able to | 1 mg of glucagon will be administered by the subject's care partner/other responsible adult and 911 will be called. The study will be stopped immediately until sponsor conducts a full investigation to determine the root cause for the |

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| oral carbohydrates | address all issues. Sponsor will also communicate the results of this root cause investigation to FDA and to study investigators. | compromised system performance and is able to address all issues. Sponsor will also communicate the results of this root cause investigation to FDA and to study investigators. |
| No heart rate, no blood pressure | Perform resuscitation, call 911, and transfer subject to ER.<br><br>Study will be stopped immediately until sponsor conducts a full investigation to determine the root cause for the compromised system performance and is able to address all issues. Sponsor will also communicate the results of this root cause investigation to FDA and to study investigators. | Perform resuscitation, call 911, and transfer subject to ER.<br><br>Study will be stopped immediately until sponsor conducts a full investigation to determine the root cause for the compromised system performance and is able to address all issues. Sponsor will also communicate the results of this root cause investigation to FDA and to study investigators. |

Study staff will monitor the subject's sensor glucose and insulin delivery throughout the study using the iAPS on the subject's phone, the web interface and CGM. All blood glucose measurements will be performed with the study-approved glucometer.

Manual correction boluses may also be administered via the iAPS as needed throughout the hybrid closed loop phase.

For the extension phase (at home use) of the study device, study staff will follow the following detailed plan in response to notifications from the study system or contacts from subjects. Failure to document these actions in response to a notification or subject contact will be considered a protocol deviation.

Safety Monitoring Contact Plan for At Home Portion of Study

| Plan | Team notifications | Plan |
|---|---|---|
| Hyperglycemia Mitigation plan | The study team will receive real time text alerts for CGM values:<br><br>>180 mg/dL for >1.5 hours or >250 mg/dL for >20 minutes. | A study team member will contact participant to review fingerstick and ketone values, discuss etiology of hyperglycemia, and review with participant mitigation strategies including insulin coverage for hyperglycemia, ketone testing, set change, and/ or subcutaneous injection as indicated based on clinical scenario. A licensed |

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| | | professional on the study team (MD or NP) will make these clinical decisions.<br><br>A study team member will recheck CGM remotely in 1 hour to ensure reduction in hyperglycemia. |
| Severe hyperglycemia mitigation plan | The study team will receive real time text alerts for CGM values:<br><br>>180 mg/dL for >1.5 hours or >250 mg/dL for >20 minutes. | A study team member will speak with the participant. If ketones are >1.5 mmol/L, or >0.6mmol/L for more than 90 minutes, and not decreasing after an injection of insulin, the site PI or delegated investigator will ascertain whether the participant has the capacity to care adequately for themselves with guidance. If based on clinical expertise and judgement, it appears the participant may not be adequately able to care for themselves without assistance, then the investigator will either directly communicate with someone on the scene whom they judge to have that capacity, or call 911, or both. |
| Hypoglycemia Mitigation Strategy | The study team will receive real time text alerts for CGM values <54 mg/dL for >20 minutes | A study team member will contact participant to review fingerstick values, discuss etiology of the hypoglycemia, and review with participant the appropriate treatment of the hypoglycemic episode based on glucose level and active insulin on board. A licensed professional on the study team (MD or NP) will direct these clinical decisions. |
| Severe Hypoglycemia mitigation plan | The study team will receive real time text alerts for CGM values <54 mg/dL for >20 minutes | If the investigator upon contacting a participant due to hypoglycemia notes that she is unable to treat herself or she is unable to be contacted, the |

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| | | study investigator will contact her care partner to evaluate the participant and administer glucagon 1mg IM if needed. The investigator or care partner will call 911. |
| Emergency Care plan | Study team contacts participant or care partner because of alert or study team is contacted by the study participant or care partner or another individual onsite for an emergent glucose event or a potential ADE or UADE event with a study device | The event will be reviewed by a licensed professional (MD or NP) on the study team. If the investigator concludes that the participant needs emergency care, the participant will be told to go to an emergency department. Study staff will determine which emergency department the participant will be taken to and follow up within 15 minutes of the expected arrival time to ensure the participant arrived.<br><br>If the study staff (MD or NP) calls 911, they will remain on the telephone with the participant until the ambulance arrives and speak to the Emergency Medical Technician to provide history and determine where the participant will be taken. |
| Emergency room visit plan | Study team contacts participant or care partner because of alert or study team is contacted by the study participant or care partner or another individual onsite. | The PI or designated investigator will speak directly to the emergency room staff caring for the participant.<br><br>The PI or designated investigator will inform the participant's obstetrician of the emergency room visit |
| Loss of CGM connectivity | Team will receive a real time text alert for lack of CGM data for > 2 hours | A study team member will speak with the participant. A fingerstick will be performed and troubleshooting will be |

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| | | performed as needed to resume CGM activity/connectivity. During this time, the insulin pump with automatically deliver insulin according the pump's programmed basal insulin delivery settings. |
| Insulin pump malfunction | Participant will be alerted by loud beeps from the insulin pump if there is a pump malfunction or a low pump battery. Participant will contact study team if malfunction cannot be remedied within 30 minutes.<br><br>Real time text alerts will also be sent to study staff for out of closed-loop for 2 hours for any reason. | Participant will perform a fingerstick. Troubleshooting will be performed by the study team as needed to resume pump functioning. If the malfunction is not resolved, participant will be instructed to resume her personal pump or initiate subcutaneous insulin treatment as guided by the study MD or NP until the pump is replaced. |

## 7.3 Potential Risks and Benefits of the Investigational Device

Risks and Benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with T1D and participants will be monitored for this. As subjects will be pregnant, there are also potential unknown risks to the mother or fetus. Since no new medications are being used, and subjects are already actively managing their type 1 diabetes during their pregnancy, we believe any additional risk from using the study devices is minimal.

### 7.3.1 Known Potential Risks

#### *7.3.1.1 Venipuncture Risks*

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

#### *7.3.1.2 Fingerstick Risks*

About 1 drop of blood will be removed by fingerstick for measuring blood glucose and sometimes Hemoglobin A1c (HbA1c) or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

#### *7.3.1.3 Subcutaneous Catheter Risks (CGM)*

Participants using the CGM will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a catheter is left under the skin for more than 24 hours, it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causes a bruise (1 in 10 risk).
Study staff should verbally alert the participant that on rare occasions, the CGM may break and leave a small portion of the sensor probe under the skin that may cause redness, swelling or pain at the insertion site. The participant will be instructed to notify the study coordinator immediately if this occurs.

#### *7.3.1.4 Risk of Hypoglycemia*

As with any person having T1D and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days the participant may not be as aware of symptoms of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery. Fetal growth restriction or small for gestational neonates has been reported in pregnant women with excessive hypoglycemia using multiple daily injections or sensor augmented or standard insulin pump therapy.

#### *7.3.1.5 Risk of Hyperglycemia*

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. Stress can also induce hyperglycemia. A CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery. In this study, subjects will take full insulin boluses for all their meals, whether or not they are using the closed-loop system. In addition, subjects will be medically supervised when undergoing stress assessments, with medical staff present who will increase insulin doses as needed if this proves necessary during the stress assessments. All subjects will be issued a ketone meter and ketone strips to use to carefully monitor for hyperglycemia and be given instructions on how to mitigate hyperglycemia should it occur. Chronic hyperglycemia can increase the risk of fetal macrosomia or large for gestational age neonate, polyhydramnios and neonatal hypoglycemia in the newborn fetus at the time of delivery. These are the same risks occur in pregnant women utilizing MDI or sensor augmented or standard insulin pump therapy. Acute hyperglycemia can lead to DKA that puts the fetus at

acute risk of acidosis and demise. Furthermore, DKA in pregnancy can occur at lower glucose levels than in the non-pregnant state, hence the need to be vigilant and intervene when the glucose level approaches 180 mg/dL

#### *7.3.1.6 Risk of Device Reuse*

The study CGM system is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter is attached to the sensor but does not enter the skin and the receiver is a handheld device. Participants will be informed that Food & Drug Administration (FDA) or relevant national authorities have approved these devices for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The study insulin pump is labeled for single-patient use. During the study, this device may be reused after cleaning adhering to a hospital-approved cleaning procedure. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.).

Participants will be informed that FDA or relevant national authorities typically approve the insulin pump device for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The study phone may be reused after cleaning adhering to a hospital-approved cleaning procedure.

The study blood glucose meter and blood ketone meter are labeled for single-patient use. During the study, only one person can use each device as there are rare risks that bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

#### *7.3.1.7 Cleaning Procedure*

All devices being reused in this study as noted above (i.e. the Tandem t:AP pump, the CGM receiver and transmitter, and the phone running the iAPS App) will be thoroughly cleaned prior to reuse. The person performing the cleaning will sanitize their hands and then put on gloves prior to cleaning.

CGM receivers/CGM Transmitters and/or Insulin pumps/Cellular Devices: Sanitize hands, and then put on gloves before opening 70% isopropyl alcohol pads. Thoroughly wipe the device with the alcohol pad. Then use 2 Clorox Healthcare®35309 Bleach Germicidal Wipes, one for pre-cleaning and one for disinfecting. After pre-cleaning wipe the device thoroughly and wet the exterior with a 2nd wipe. Allow the surface to stay wet for 3 minutes and then let air dry. Dispose of used pad and gloves. Equipment will be stored in a clean Ziploc bag.

Equipment will be allowed to dry completely. All cleaned equipment will be stored in a clean zipped bag until ready for reuse.

# 8 ADVERSE EVENTS, DEVICE ISSUES, AND STOPPING RULES

## 8.1 Adverse Events

### 8.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation (see section 8.1.2 for reportable adverse events for this protocol).

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death of the mother or the fetus.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or fetus or may require medical/surgical intervention to prevent one of the outcomes listed above).

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or 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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form).

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3). Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

### 8.1.2 Reportable Adverse Events

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

1. A serious adverse event
2. An Adverse Device Effect as defined in section 8.1.1, unless excluded from reporting in section 8.2
3. An Adverse Event occurring in association with a study procedure
4. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
5. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

#### *8.1.2.1 Hypoglycemic Events*

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met: the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

#### *8.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis*

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 4 criteria is met:

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis

Hyperglycemic events are classified as DKA if the following are present:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

All reportable Adverse Events—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an adverse event form online. Each adverse event form is reviewed by the Medical Monitor to verify the coding and the reporting that is required.

### 8.1.3 Relationship of Adverse Event to Study Device

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

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes
There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

### 8.1.4 Intensity of Adverse Event

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

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

### 8.1.5 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

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.

### 8.1.6 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents. If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

### 8.2 Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.
The following device issues are anticipated and will not be reported on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labeling
- CGM tape adherence issues
- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that do not meet criteria for AE reporting

### 8.3 Timing of Event Reporting

SAEs and UADEs must be recorded within 24 hours via completion of the serious adverse event form.

Other reportable adverse events, device malfunctions (with or without an adverse event), and device complaints should be reported promptly by completion of the relevant case report form, but there is no formal required reporting period.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a UADE report, the study principal investigators will investigate the UADE and if indicated, report the results of the investigation to the sites' IRBs, and the FDA within ten working days of becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitors must determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitors must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitors makes this determination and no later than 15 working days after first receipt notice of the UADE.

In the case of a device system component malfunction (e.g. pump, CGM, control algorithm), information will be forwarded to the responsible company by the site personnel, to be handled by its complaint management system.

## 8.4 Stopping Criteria

### 8.4.1 Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition for the mother or fetus; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- Significant deterioration of glycemic control as determined at any time or during the scheduled weekly contacts, leading to a significant worsening time in range compared to baseline (10% or more worsening of time in target range) and time in range consistently below 50%.
- The participant requests that the treatment be stopped
- One distinct episode of DKA related to system function (includes infusion set failure/occlusion leading to DKA)
- One episode of severe hypoglycemia related to system function
- Subject's must discontinue all investigation device (to include study phone and pump) should glucocorticoids be administered to the subject (i.e., Betamethasone for fetal lung maturity).
- Investigation device use (to include study phone and study pump) will be discontinued upon hospital admission for any reason, to include for labor and delivery, and subjects will return to their standard of care or IV insulin drip per hospital protocols and hospital team directed management.

### 8.4.2 Criteria for Suspending or Stopping Overall Study

In the case of a system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 8.1.2.2), use of the study device system will be suspended while the problem is diagnosed.

Further, study enrollment will be stopped, and all investigation device use will be immediately discontinued, if:

- Two subjects have an episode of DKA related to system function (includes infusion set failure/occlusion leading to DKA)
- Two subjects have an episode of severe hypoglycemia related to system function
- Two subjects have at any time met criteria to stop the study by showing significant deterioration of glycemic control as determined at any time or during the scheduled weekly contacts, leading to a significant worsening time in range compared to baseline (10% or more worsening of time in target range) and time in range consistently below 50%.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected

study activities 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.

The medical monitor for the study will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The medical monitor will request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available. The study medical monitor will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The medical monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

### 8.5 Independent Safety Oversight

The medical monitor will review all reported adverse events and adverse device events. Additionally the engineering team at Harvard University will be informed of any UADEs that require FDA reporting as defined in section 8.3.

The medical monitor for the study is Dr. Carl Rose, Maternal Fetal Medicine at Mayo Clinic.

For the extension phase of the study, we have convened a Data and Safety Monitoring Board (DSMB). The DSMB will provide safety oversight. The DSMB will be informed of all cases of severe hypoglycemia and diabetic ketoacidosis irrespective of device relationship, all device-related SAEs, and all UADEs at the time that they occur during the study and will review compiled safety data at periodic intervals. The DSMB also will be informed of any ADEs not meeting criteria for a UADE if the Medical Monitor requests the DSMB review. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding the DSMB's role will be documented in a separate DSMB charter.

# 9 MISCELLANEOUS CONSIDERATIONS

## 9.1 Drugs Used as Part of the Protocol

Participants will use either lispro or aspart insulin for the closed-loop session.

## 9.2 Prohibited Medications, Treatments, and Procedures

Treatment with any non-insulin glucose-lowering agent (including GLP-1 agonists, Pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals) or Afrezza will not be permitted during the trial.

The investigational study devices (study insulin pump, study phone, study CGM systems) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the treatments above..

## 9.3 Participant Compensation

Participant compensation will be specified in the informed consent form.

## 9.4 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time.
For participants who withdraw, their data will be used up until the time of withdrawal.

## 9.5 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be securely stored at the study clinic sites. De-identified participant information may also be provided to research sites involved in the study.

# 10 DATA COLLECTION AND MONITORING

## 10.1 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 10.2 Quality Assurance and Monitoring

Designated personnel from the study clinical center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol,

Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will be prioritized for monitoring. Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812.

### 10.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

Further details about the handling of protocol deviations will be included in the monitoring plan.

## 11 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

### 11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

### 11.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

### 11.3 Informed Consent Process

#### 11.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw

consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 11.3.2 Participant and Data Confidentiality

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or authorized representatives from Sansum Diabetes Research Institute, Mt. Sinai Hospital, Mayo Clinic or Harvard University may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted from Sansum Diabetes Research Institute, Mt. Sinai Hospital and Mayo Clinic and sent to and stored at Harvard University. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Sansum Diabetes Research Institute, Mayo Clinic, Mt. Sinai and Harvard University. Permission to transmit data will be included in the informed consent.

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