Tandem PLGS Pivotal Trial:

A randomized clinical trial to assess the efficacy of predictive low glucose suspend versus sensor-augmented pump therapy in the management of type 1 diabetes

IDE Sponsor: Tandem Diabetes Care, Inc.

Version 6.0
21/February/2018

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AUC	Area Under the Curve
BG	Blood Glucose
CFR	Code of Federal Regulations
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
EGV	Estimated Glucose Values
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
ICH	International Conference on Harmonization
IOB	Insulin-on-Board
IRB	Institutional Review Board
IV	Intravenous
JCHR	Jaeb Center for Health Research
MDI	Multiple Daily Injections of insulin
PGV	Predicted Glucose Values
PLGS	Predictive Low Glucose Suspend
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RMB	Risk-Based Monitoring
SAE	Serious Adverse Event
SAP	Sensor-Augmented Pump
SD	Standard Deviation
SMBG	Self-Monitoring of Blood Glucose
T1D	Type 1 Diabetes
UADE	Unanticipated Adverse Device Effect
UI	User Interface

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Tandem PLGS Pivotal Trial: A randomized clinical trial to assess the efficacy of predictive low glucose suspend versus sensor-augmented pump therapy in the management of type 1 diabetes

Protocol Version/Date: v6.0 02-21-2017

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Jaeb Center for Health Research, which serves as the Coordinating Center for the protocol, with complete and timely information, as required in the conduct of the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21, and 21 CFR Part 812).

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel at my site have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature: _____Date: _____ / _____ / _____

dd mmm yyyy

Investigator's Name: _____

Site Name/Number: _____

163 **PROTOCOL SUMMARY**
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PARTICIPANT AREA	DESCRIPTION
Title	Tandem PLGS Pivotal Trial: A randomized clinical trial to assess the efficacy of predictive low glucose suspend versus sensor-augmented pump therapy in the management of type 1 diabetes.
Précis	A 6-week crossover study will compare PLGS to SAP outcomes in adults and youth ≥ 6 years old with type 1 diabetes (T1D). An extension phase listed in CHAPTER 14: will include participants who have completed the crossover study. These participants will use the PLGS pump for two years or when the product becomes commercially available, whichever comes first. Additional details can be found in CHAPTER 14:.
Investigational Device	The intervention arm (use of PLGS feature) will utilize Tandem Diabetes Care's ambulatory insulin infusion pump with integrated Dexcom G5 CGM and predictive low glucose suspend function. This pump is called the "t:slim X2 with Basal-IQ Technology" and is referred to in the protocol as the Tandem PLGS pump. The control arm (SAP only) will utilize an identical pump in functionality as the Tandem PLGS pump except for the lack of the PLGS feature and the associated UI. This pump is called the t:slim X2 Dexcom G5 Mobile CGM Enabled pump, and is referred to in the protocol as the Tandem SAP pump.
Objectives	To assess the efficacy and safety of a predictive low glucose suspend (PLGS) system that uses continuous glucose monitoring (CGM) measurements to suspend basal insulin delivery when hypoglycemia is predicted as well as resume basal insulin delivery once CGM values begin to increase.
Study Design	Multi-center, randomized, crossover design, consisting of two 3-week periods, with the PLGS System used during one period and SAP therapy used during the other period. The crossover trial will be preceded by a run-in phase in which participants may receive training using the study devices. For 10 adult participants, a PLGS Pilot Period will proceed to the crossover trial to ensure safety and usability objectives are met prior to the start of the crossover trial.
Number of Sites	4-6 in the United States
Endpoint	**Primary Efficacy Outcome:** Percentage of sensor glucose values <70 mg/dL **Key Secondary Efficacy Outcomes:** *Hypoglycemia* • Percentage of values <60 mg/dL • Percentage of values <50 mg/dL • AUC <70 mg/dL • Low blood glucose index • Frequency of CGM-measured hypoglycemic events (see below): *Glucose Control* • Mean glucose • Percentage of values 70 to 180 mg/dL *Hyperglycemia* • Percentage of values >250 mg/dL • Percentage of values >180 mg/dL • AUC glucose >180 mg/dL • High blood glucose index

PARTICIPANT AREA	DESCRIPTION
	Key Safety Outcomes: • Diabetic ketoacidosis (DKA), as defined by the Diabetes Control and Complications Trial (DCCT). • Severe clinical hypoglycemic events such that the participant required assistance from another person to actively administer carbohydrate, glucagon, or engage in other resuscitative actions; note severe hypoglycemia could be considered both and efficacy and safety outcome • Ketosis events (blood ketone level >1.0 mmol/L) • All other reported adverse events • Unanticipated adverse device effects
Population	**Key Inclusion Criteria:** • Clinical diagnosis of type 1 diabetes treated with insulin via an insulin pump or injections for at least 1 year • Age ≥6.0 years old • For participants <18 years old, living with one or more parents or guardians committed to participating in training and able to contact the participant in case of an emergency • For females, not currently known to be pregnant **Key Exclusion Criteria:** • Anticipated need to use acetaminophen during study participation • Participation in another pharmaceutical or device trial • A condition, which in the opinion of the investigator or designee, would put the participant or study at risk including any contraindication to the use of any of the study devices per FDA labelling
Sample Size	At least 90 participants completing the crossover trial
Treatment Group	Random assignment (1:1) to (A) PLGS in period 1 and SAP in period 2 or (B) SAP in period 1 and PLGS in period 2.
Participant Duration	2-6 months
Protocol Overview/Synopsis	**1) Screening and Enrollment** • Informed consent will be signed and eligibility will be assessed • History and physical examination • HbA1c measurement • Urine or serum pregnancy test (if applicable) • Evaluation of CGM and pump experience **2) CGM and SAP Training Period at Home** All eligible participants will be assessed based on their CGM and pump experience to determine if the CGM Training Period, the SAP Training Period, or both are required. a. CGM Training Period (10-14 days): Participants currently using a CGM may skip the CGM Training Period per investigator discretion, generally requiring that CGM has been used on at least 85% of days during the prior 4 weeks.

PARTICIPANT AREA	DESCRIPTION
	b. SAP Training Period (14-28 days): Participants currently using a Tandem pump concomitantly with a Dexcom CGM may skip both the CGM Training and the SAP Training periods per investigator discretion. i. The Tandem SAP pump will be used during the SAP Training Period and pump training will be customized based on prior pump experience **3) PLGS Pilot Phase** Prior to the initiation of the crossover trial, 10 adult participants will use the Tandem PLGS pump and CGM system in a 10-day Pilot Period. Data will be evaluated for system usability and predetermined safety metrics before participants ≥12 years old can be randomized into the crossover trial. **4) Randomized Crossover Trial** The crossover trial will begin after the data from the Pilot Period have been reviewed. Enrollment of participants 6 to 11 years old will be deferred until data from 100 post-randomization PLGS participant-days have been evaluated from participants 12 to 17 years old and the same predetermined safety metrics used to evaluate the Pilot Period have been satisfied. At the Crossover Trial initiation visit, the following will be done: • The clinician will confirm the participant's willingness to participate in the crossover trial • The participant's HbA1c level will be measured • Random assignment to Group A or Group B Group A: intervention period first (PLGS), control period second (SAP) Group B: control period first (SAP), intervention period second (PLGS) During each of the two 3-week periods, a phone, email, or text contact will occur at 2 and 14 days, and a clinic visit at 7 and 21 days. HbA1c will be measured at the end of each period.

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166 **Figure 1 – SCHEMATIC OF STUDY DESIGN**

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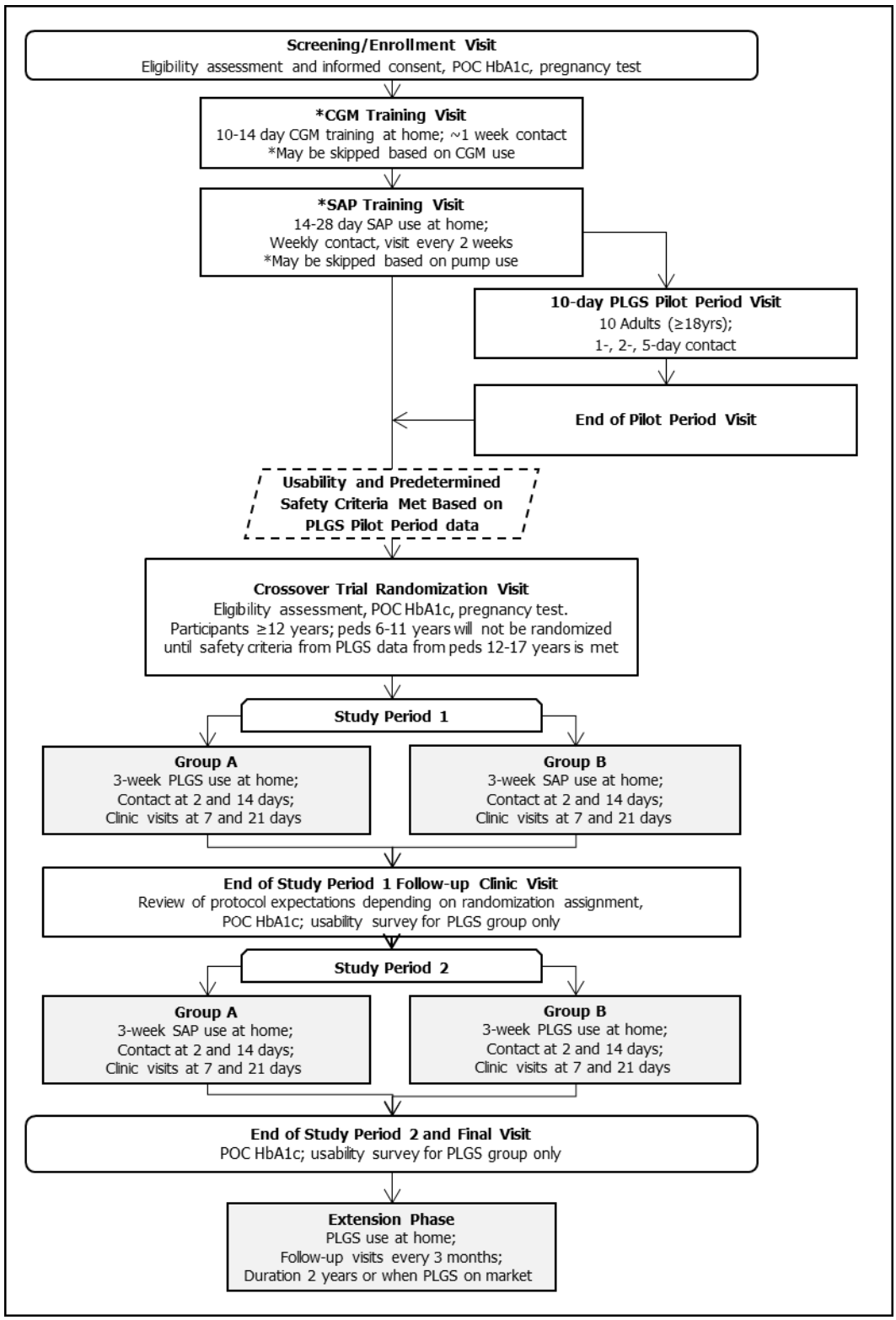

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Table 1 - SCHEDULE OF STUDY VISITS[3], CONTACTS, AND PROCEDURES

Procedure	Screening Visit	CGM and SAP Training-related Visits and Contact	Randomization Visit (Week 0)	Study Period 1 (SP1), Followed by Identical Schedule for Study Period 2 (SP2)			
				Day 2 Follow Up	Day 7 Follow Up	Day 14 Follow Up	Day 21 End of SP1 or SP2
Time from Randomization (SP1) or Crossover (SP2)	0-6w prior	2-6w prior	0	2d ± 1d	7d ± 2d	14d ± 3d	21+7d
Visit (V) or Contact (C)	V	V,C	V	C	V	C	V
Eligibility Assessment	X		X				
Point-of-Care HbA1c	X		X				X
Pregnancy test	X		X				
Device Data Downloads	X	X	X		X		X
PLGS System Training			X				X[1]
System Usability Scale							X[2]

1 – PLGS System Training performed only at end of SP1 for participants who did not use PLGS in SP1
2 – For participants who used PLGS in the preceding study period
3 – Additional visits associated with a study Extension Period are described in Appendix A

CHAPTER 1: BACKGROUND INFORMATION

1.1. Introduction

The goal of this study is to assess the functionality of an integrated predictive low glucose suspend system designed to minimize the incidence and duration of hypoglycemia by suspending insulin delivery if hypoglycemia is projected. The hypothesis is that the system, utilizing CGM and predictive algorithms, can safely reduce hypoglycemia exposure, especially during sleep.

Most episodes of severe hypoglycemia occur during the night, specifically during sleep (1, 2). Even with the advent of real-time CGM, patients do not awaken to over 70% of nocturnal alarms (3). Certain studies have demonstrated that reducing nocturnal hypoglycemia by using a CGM device with hypoglycemic prediction algorithms to suspend basal insulin delivery is both safe and effective (4-6). However, this benefit has been accompanied by modest increases in mean overnight sensor glucose and morning fasting blood glucose. A 10-subject CRC-based pilot study was conducted using a prototype version of the PLGS system to be used in the current study. The pilot study demonstrated that the system suspended and restarted the insulin pump appropriately in response to falling and rising CGM sensor glucose levels (abstract accepted at ADA 2017).

This protocol is designed to test the safety and efficacy of a predictive low glucose suspend system (PLGS) compared to a sensor-augmented pump (SAP) system during day and night use at home under normal conditions. The study data are intended to be used to support a Premarket Approval (PMA) application.

1.2. Hypoglycemia Minimization Strategy

A predictive low glucose suspend algorithm (PLGS) is used to respond to low glucose readings. The Predicted Glucose Values (PGV) are based on current Estimated Glucose Values (EGV) (i.e., glucose readings) produced by the Dexcom G5 CGM System every 5 minutes. Specifically, the last 4 EGVs are combined using linear regression and used to project future glucose values. Using the calculated rate of change, the resulting PGV extends the past trend into the future by 30 minutes. At least 3 of the last 4 EGV data points must be available in order to provide a prediction.

Both EGV and PGV values are used to regulate insulin delivery. If the PGV is less than 80 mg/dL the system will suspend insulin delivery. If the observed EGV falls below the suspension threshold (70 mg/dL), the system will also suspend insulin delivery, even if a PGV cannot be generated. Insulin will resume when the system detects that EGVs are rising (i.e., when the most recent EGV is 1 mg/dL greater than the previous EGV). Additionally, the insulin will resume if the system has been suspended for more than 120 minutes in the last 150 minutes. These specific rules for suspension and resumption of insulin are applied after each 5-minute CGM reading, are active 24-hours a day, and have been adopted from previously published clinical studies by Buckingham et al. (4-6).

1.2.1. PLGS System

Tandem Diabetes Care's ambulatory insulin infusion pump with integrated Dexcom G5 CGM and predictive low glucose suspend (PLGS) function, "t:slim X2 with Basal-IQ Technology," is

intended for subcutaneous delivery of insulin, for the management of diabetes mellitus in persons requiring insulin. The PLGS System includes the Dexcom continuous glucose monitoring (CGM) device indicated for detecting trends and tracking patterns in persons with diabetes. The PLGS System is able to stop and resume basal insulin delivery automatically in response to low sensor glucose values, thereby reducing the incidence and duration of hypoglycemic episodes.

The system used in this study is a modified version of the previously approved t:slim G4 system (P140015) and is comprised of a CGM sensor and transmitter along with an insulin pump with user interface (UI) for display of system information. The sensor is inserted subcutaneously and transmits data every 5 minutes to the pump via the transmitter. The pump includes the hypoglycemia minimization strategy described in Section 1.2 that will issue insulin delivery commands.

Figure 2 - The Tandem insulin infusion pump with integrated Dexcom G5 CGM and predictive low glucose suspend function (PLGS): t:slim X2 with Basal-IQ Technology

1.3. Rationale

Hypoglycemia is a significant problem for adults and children with type 1 diabetes (T1D). A system that can reduce insulin delivery when the hypoglycemia is predicted will be very beneficial to reduce the risk of severe hypoglycemia and improve quality of life.

1.4. Potential Risks and Benefits of the Investigational Device and Study Participation

1.4.1. Risk of Hyperglycemia

The main risk of using the PLGS system is hyperglycemia, which could occur if insulin delivery is suspended for an extended period during the operation of the PLGS system. Prior studies have demonstrated that an increase in mild hyperglycemia is likely with prolonged pump suspension (4-6). With prolonged pump suspension, ketonemia may occur, but the risk of DKA should not be increased (7-8). A CGM functioning poorly and significantly underestimating glucose concentrations could lead to inappropriate suspension of insulin delivery.

1.4.2. Known Potential Benefits

One purpose of this research is to reduce the frequency and duration of hypoglycemia in addition to severe hypoglycemic events. Hypoglycemia is a major fear of many individuals with T1D and their families and this fear often prevents optimal glycemic control.

It is expected that this protocol will yield increased knowledge about using a predictive low glucose suspend system to control blood glucose level in persons with T1D. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the participants and general benefit to others with T1D.

1.4.3. Risk Assessment

Based on the facts that (1) adults and adolescents with diabetes experience frequent hypoglycemia as a consequence of the disease and its management, (2) the study intervention is expected to reduce hypoglycemia without a substantial increase in hyperglycemia, and (3) a similar system has been extensively tested in prior studies, the investigators believe that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents the prospect of direct benefit to the participants and general benefit to others with T1D.

1.5. General Considerations

The study is being conducted in compliance 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 (GCP).

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

The protocol is considered a significant risk device study, due to the fact that the predictive low glucose suspend system is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

CHAPTER 2: STUDY RECRUITMENT, ENROLLMENT, AND SCREENING

2.1. Participant Recruitment and Enrollment

Enrollment will proceed with the goal of at randomizing approximately 100 participants so that least 90 participants complete the crossover trial with sufficient data to include in the primary analysis. A maximum of 200 individuals may be enrolled in the study in order to achieve this goal and potentially support an increase in sample size per the interim analysis described in Chapter 10. Participants who have signed consent and started the screening process will be permitted to continue into the trial, if eligible, even if the trial completion goal has been reached.

Study participants will be recruited from 4-6 clinical centers in the United States. All eligible participants will be included without regard to gender, race, religion, or ethnicity. There is no restriction on the number of participants to be enrolled by each site towards the overall recruitment goal.

The approximate distribution of participants completing the crossover trial is as follows:

- 45 participants ≥18 years old
- 45 participants <18 years old, with the goal of recruiting a target of:
    - At least 15 participants 12-17 years old
    - At least 15 participants 6-11 years old

The above numbers generally will be minimums but could vary depending on the need for participants to successfully complete the run-in, training phase, or both and to complete the crossover trial.

The crossover trial will include the following minimum numbers of participants:

- 15 pump users
- 15 multiple daily injection of insulin (MDI) users
- 15 CGM naïve users (may be pump or MDI)
- 15 experienced CGM users (may be pump or MDI)

Each participant's percentage of sensor glucose values <70 mg/dL during an approximate two-week period prior to initiation of the crossover trial will be assessed, with a study goal that no more than 25% of crossover trial participants will have a value <3%. As the study progresses, participation in the crossover trial may be restricted to participants with values ≥3% if crossover trial participation is projected to exceed the 25% threshold.

Ten eligible adult participants ≥18 years old will use the PLGS system in a 10-day Pilot Period.

2.1.1. Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained.

For potential study participants ≥18 years old, the study protocol will be discussed with the potential study participant by study staff and an Informed Consent Form will be given. Potential

study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

For potential participants <18 years old, a parent or legal guardian (referred to subsequently as "parent") will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Potential participants meeting the IRB's minimum age of assent will be given a Child Assent Form to read and discuss with their parents and study personnel. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form will be signed. A copy of the consent form(s) will be provided to the participant and their parent and another copy will be added to the participant's study record.

As part of the informed consent process and described in either the same document or a separate document, the potential participant will be informed with respect to the study-specific information that will be collected and to whom that information will be disclosed (i.e., HIPAA requirements).

A participant is considered enrolled when the informed consent form and assent form, if applicable, have been signed.

2.2. Participant Inclusion Criteria

Individuals must meet all of the following inclusion criteria to be eligible to participate in the study:

1. Clinical diagnosis, based on investigator assessment, of T1D treated with insulin via an insulin pump or injections for at least 1 year, with no major change in the intensity of insulin therapy in the past 3 months (e.g. switching from injections to pump)
2. Age ≥6.0 years old
3. For participants <18 years old, living with one or more parents or guardians committed to participating in training and able to contact the participant in case of an emergency
4. For females, not currently known to be pregnant
    - *If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.*
5. Investigator has confidence that the participant can successfully use all study devices and is capable of adhering to the protocol

2.3. Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria will be excluded from study participation:

1. Anticipated need to use acetaminophen during study participation
2. Participation in another pharmaceutical or device trial at the time of enrollment or plan to participate in another study during the time period of participation in this study
3. Employed by, or having immediate family members employed by Tandem; or 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

4. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk including any contraindication to the use of any of the study devices per FDA labelling
    - Individuals should not be enrolled with uncontrolled thyroid disease, renal failure (e.g., dialysis or eGFR <30), hemophilia or another major bleeding disorder, or unstable cardiovascular disease.
    - Laboratory testing and other work up needed to determine that an individual is a suitable candidate for the study should be performed as part of usual care.

2.4. Screening Procedures

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

Participants who do not initially meet study eligibility requirements may be rescreened once later per investigator discretion.

2.4.1. Data Collection and Testing

After enrollment (informed consent signed), the following procedures will be performed/data collected/eligibility criteria checked and documented:

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race, ethnicity, socioeconomic status)
- Contact information (retained at the site and not entered into study database)
- Diabetic history, including CGM, insulin, and pump use
- Medical history
- Concomitant medications
- Standard physical exam (including vital signs and height and weight measurements) by the study investigator or designee (a physician, nurse, nurse practitioner or a physician assistant).
- Blood draw for HbA1c measurement (point-of-care measurement acceptable)
    - HbA1c within 4 weeks of screening visit is acceptable
- Urine or serum pregnancy test for all women of child-bearing potential

Screening procedures will last approximately 1 hour.

CHAPTER 3: CGM AND SAP TRAINING PHASES

3.1. Introduction

The run-in phase consists of a CGM training period and SAP training period. The CGM training period will last approximately 10-14 days followed by the SAP training period, which will last approximately 14-28 days.

Eligible participants may complete the CGM training period and the SAP training period, or may skip one or both based on the participants' device use at the time of enrollment, as described in the table below.

- Participants currently using a CGM may skip the CGM Training Period per investigator discretion, generally requiring that the CGM has been used on at least 85% of days during the prior 4 weeks.
- Participants currently using a Tandem pump concomitantly with a Dexcom CGM may skip both the CGM Training and the SAP Training periods per investigator discretion.
    - These participants will proceed to the next visit, which can either be the Crossover Trial Randomization Visit, or the 10-day PLGS Pilot Period (see Chapter 4).
- Participants must complete the SAP Training Period if they are either:
    - Not using a CGM
    - Not currently using a Tandem insulin pump

Table 2 - CGM and SAP Training Requirements Based on Device Status at Enrollment

	CGM Use	Insulin Delivery Mode	CGM Training Period: 10-14 days	SAP Training Period: 14-28 days
Device Use	Current use of CGM	Current use of pump	Skip per investigator's discretion, generally requiring that CGM has been used on at least 85% of days during the prior 4 weeks.	Skip if participant's personal pump is Tandem; else participate using Dexcom study CGM and Tandem study pump
		MDI (No current use of pump)		Participate using Dexcom study CGM and Tandem study pump
	No current use of CGM	Current use of pump or MDI	Participate using Dexcom study CGM while continuing personal pump or MDI	Participate using Dexcom study CGM and Tandem study pump

3.2. CGM Training Period (10-14 Days)

Participants not currently using a CGM as described above will complete 10-14 days of study CGM use at home with their current form of insulin therapy (personal pump or MDI).

CGM training will include the following:

- Approximately 1-2 hours of training on sensor insertion, transmitter placement, sensor calibration, and the use of CGM in daily diabetes management per manufacturer guidelines

- Participants will be provided with information regarding the potential risk of sensor site infection and bleeding, sensor needle fracture and sensor failure
- Participants will be provided with written instructions on using the CGM

Participants will be provided with a CGM system and sensors; a blood glucose meter, test strips, lancets, and control solution; and a blood ketone meter, test strips, and control solution.

3.2.1. CGM Training Contact and Visit Schedule

Participants will be contacted after 6±1 days to review any issues with CGM use.

Participants will use the CGM for at least 10 days and will return to the clinic after 10+4 days. Participants may continue in the study if the investigator judges that the participant can use the CGM safely and consistently in the remainder of the study.

3.3. SAP Training Period (14-28 days)

Participants not currently using a CGM or not currently using a Tandem insulin pump must complete the SAP Training Period. Participants will use the study Dexcom CGM and the Tandem pump called the "t:slim X2 Dexcom G5 Mobile CGM Enabled (referred to subsequently as the Tandem SAP pump) at home for 14-28 days.

For participants currently on insulin pump therapy, the Tandem SAP pump will be programmed so that basal insulin delivery and other settings match the participant's personal pump settings. Participants will be expected to use the Tandem SAP pump daily.

Participants may use commercially available features of the study CGM system related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose.

For participants not currently on insulin pump therapy, an initial basal insulin profile will be customized on a per-participant basis. Total daily insulin dose will be reduced by approximately 20% as a general rule, with a recommended method outlined in a separate procedures manual. Further adjustments to total daily dose and intraday basal rate profile may be made during the course of the SAP Training Period.

Pump training will take approximately 1-2 hours and will be customized based on participant's pump experience. General guidelines are as follows:

- Participants who are pump-naïve will receive standard insulin pump therapy training including use of the bolus wizard, and will provide a return demonstration of use of the major features of the pump. For participants who are already pump users, differences from their personal pump will be reviewed.
- Training topics will include calculation of insulin-on-board (IOB) and correction boluses, infusion site initiation, cartridge/priming procedures, setting up the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the participant in study pump infusion site insertion and initiation of the pump. The Tandem SAP pump will be programmed with the participant's

usual basal rates and pump parameters, if available. The participant will be observed using the Tandem SAP pump during at least one meal or snack bolus.

Participants will be provided with an insulin pump, cartridges, and infusion sets and insulin if they are not already using an insulin that can be used in the Tandem pump. Participants will also be given the appropriate CGM supplies for the SAP Training Period.

3.3.1. SAP Training Contact and Visit Schedule

Participants will be contacted via email, phone, or text after 7±1 day (preceded by an upload of the pump and sensor data if possible) and have a visit after 14+3 days to review use of the study CGM and Tandem SAP pump. Adjustments may be made to optimize pump settings during the SAP Training Period per investigator discretion.

If the investigator deems it necessary, an additional two-week SAP Training Period may occur, with the same contact and visit schedule as above.

3.3.2. Assessment of SAP Training Period

The CGM data will be downloaded and reviewed to assess whether the participant had used the CGM on at least 85% of possible days and the Tandem SAP pump was used every day unless extenuating circumstances existed.

Participants who do not meet these criteria after an additional two-week SAP Training Period will be withdrawn from the study, unless the investigator believes that there were extenuating circumstances that prevented successful completion.

Participants will continue to use the study CGM and Tandem SAP pump until the 10-Day Pilot Period initiation visit or crossover trial randomization visit, unless the visit is concomitant with an SAP Training Assessment visit.

CHAPTER 4: PLGS PILOT PERIOD

4.1. PLGS Pilot Period Overview

Prior to the initiation of the crossover trial, 10 adult participants will use the study CGM and Tandem's t:slim X2 with Basal-IQ Technology system that includes the predictive low glucose suspend function (referred to subsequently as "Tandem PLGS pump") in a 10-day Pilot Period. Data will be evaluated for system usability and predetermined safety metrics before participants ≥12 years old may be randomized into the crossover trial.

4.2. Initiation of PLGS

Participants will be trained on the use of the PLGS feature of the pump and instructed to use the Tandem PLGS pump and study CGM daily until returning to the clinic. Participants will be provided with all CGM and pump supplies, including insulin if needed.

4.3. Visit and Contact Schedule

Contact via phone, email, or text will occur on days 1, 2, and 5 (±1 day) to assess for adverse events and system issues.

Participants will use the PLGS system for at least 10 days and then return to the clinic after 10+4 days. Participants may use commercially available features of the study CGM system related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose.

Device data will be downloaded at the day 10 clinic visit. Participants will be transitioned to a study Tandem SAP pump (no PLGS feature) and may continue study CGM use until data review from all Pilot Period participants has been completed. Participants will then return to the clinic to participate in the crossover trial as described below when that part of the study begins.

4.4. PLGS Pilot Period Data Review

After the 10th participant completes the Pilot Period, data from approximately 100 participant-days will be evaluated for system usability and predetermined safety metrics.

Predetermined safety metrics are the following:

- No PLGS-related DKA
- No severe hypoglycemia related to system malfunction

All instances of DKA or severe hypoglycemia will be adjudicated by the Medical Monitor to determine whether the events were related to system performance. If the predetermined safety metrics are not satisfied, the study will be stopped for system evaluation as described in Section 8.6.

Usability will be assessed on participant and investigator feedback. If system changes are required due to safety or usability issues, any necessary regulatory or IRB reviews will be performed. Then the Pilot Period will be repeated, and the results will again be evaluated for safety and usability prior to the crossover trial.

CHAPTER 5: CROSSOVER TRIAL

5.1. Crossover Trial Overview

The main part of the study, a six-week crossover trial, consists of two arms which will receive different treatments. Participants will be randomly assigned to one treatment option, then cross over to the other treatment option after three weeks. The two treatment options are:

- Intervention (PLGS Group): Use of the Dexcom G5 CGM with an insulin pump that has a PLGS feature (t:slim X2 with Basal-IQ Technology)
- Control (SAP Group): Use of the Dexcom G5 CGM with an insulin pump that does not have a PLGS feature (t:slim X2 Dexcom G5 Mobile CGM Enabled)

The two Tandem pumps, referred to as the Tandem PLGS and the Tandem SAP pumps, respectively, are identical in functionality and user interface (UI) with the exception of the PLGS feature and associated UI component.

5.2. Crossover Trial Initiation

The crossover trial will begin after successful completion of the Pilot Period (see Chapter 4).

Initially, participants ≥12 years old can be entered into the crossover trial. Initiation of the crossover trial by participants 6 to 11 years old will be deferred until data from 100 post-randomization PLGS participant-days have been evaluated from participants 12 to 17 years old (of which at least 50 participant-days will come from participants 12 to <15 years old) and the same predetermined safety metrics used to evaluate the Pilot Period have been satisfied.

- If the safety criteria to proceed to the younger age group are not met, then there will be a hold on initiating the crossover trial in this age group until either additional data are collected from the active participants or a revision is made to the risk mitigation plan and approved by FDA before proceeding

Randomization into the crossover trial may be restricted to participants with at least 3% of sensor glucose values <70 mg/dL during an approximately two-week period prior to randomization if the crossover trial is projected to include fewer than 75% of such participants.

5.2.1. Crossover Study Periods

- Study Period 1: 3-week period of PLGS (Group A) or SAP (Group B)
- Study Period 2: 3-week period of PLGS (Group B) or SAP (Group A)

5.3. Home Procedures during the Study Periods

During the two study periods, participants will be asked to:

- Use the study pump and study CGM every day
- Keep the PLGS feature activated if using the Tandem PLGS pump
- Not change pump settings related to insulin delivery (such as basal rate, correction factor, and carb ratio) without first discussing with study staff
- Ensure proper calibration of the CGM at all times, using the study-provided glucose meter
- Measure blood ketones with the study-provided ketone meter when CGM glucose is >300 mg/dL on awakening or for at least one hour at other times, or >400 mg/dL at any time. CGM glucose >300 mg/dL should be confirmed by self-monitoring of blood glucose (SMBG) readings
- Participants may use commercially available features of the study CGM system related to

mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose. Participants will be encouraged to be consistent with their use of any such features between the two periods of the crossover study.

- Contact the study staff if:
  - Blood ketone readings are ≥1.5 mmol/L
  - There are any technical issues with the system
  - There are any symptoms or occurrences of DKA, severe hypoglycemia, or development of other medical problems
  - Pregnancy is possible
  - Discontinuation of study participation is desired

Participants will also receive study staff contact information to ask any questions they may have during the study.

5.4. Prohibited Medications, Treatments, and Procedures

Participants will be instructed that acetaminophen must be avoided during the study. If acetaminophen is inadvertently taken, the participant will be instructed to disable the PLGS feature for 4 hours and to not use the CGM measurements for diabetes management during this time.

Participants will be instructed not to add any new glucose-lowering agents during the study.

5.5. Study Visits and Contacts

The schedule for follow-up visits and contacts is the same during both periods of the crossover trial.

- 2±1 day: Contact via phone, email, or text
- 7±2 days: Visit
- 14±3 days: Contact via phone, email, or text
- 21+7 days: Visit

At each contact and visit, the occurrence of device issues and adverse events will be solicited. Device data will be uploaded at the day 7 visit (and from home if possible) and are needed to assess issues that may arise.

Additional visits and contacts may occur at investigator discretion.

5.6. Crossover Trial Randomization Visit (Beginning of Study Period 1)

The following procedures will be completed at the crossover trial randomization visit:

- Eligibility criteria will be reviewed to verify that there have been no changes that could affect eligibility since enrollment
- The individual's understanding of the protocol and willingness to participate in the crossover trial will be reviewed
- HbA1c will be measured using the DCA Vantage or similar point-of-care (POC) device or local lab if not already measured on the same day during the screening visit
- A pregnancy test will be performed if not already performed on the same day during the screening visit
- All needed study supplies will be given to the participant

Study personnel will enter data on the study website to verify eligibility and obtain random assignment

to Group A or Group B

- Group A: intervention period first (PLGS), control period second (SAP)
- Group B: control period first (SAP), intervention period second (PLGS)

Group A participants will receive PLGS training (if not previously received through participation in the Pilot Period).

5.6.1. End of Study Period 1 Follow-up Clinic Visit and Beginning of Study Period 2

The following procedures will occur during this visit:

- Data will be reviewed for potential safety issues, and if none pump settings will not be adjusted prior to initiation of Study Period 2
- HbA1c level will be measured using the DCA Vantage or similar point-of-care device or local lab
- Group A participants will complete the PLGS usability survey (see Chapter 7)
- Initiation of Study Period 2
  - Group A participants will return the Tandem PLGS pump and receive the Tandem SAP pump with all needed supplies.
  - Group B participants will return the Tandem SAP pump and receive the Tandem PLGS pump with all needed supplies, and will receive training (or refresher training if applicable) on the PLGS feature of the pump.

5.6.2. End of Study Period 2 and Final Visit

The following procedures will occur at the end of Study Period 2:

- Data will be reviewed for potential safety issues
- HbA1c level will be measured using the DCA Vantage or similar point-of-care device or local lab
- Group B participants will complete the PLGS usability survey (see Chapter 7)
- All applicable study supplies will be returned to the clinic

CHAPTER 6: STUDY DEVICES

6.1. Description of the Investigational Device

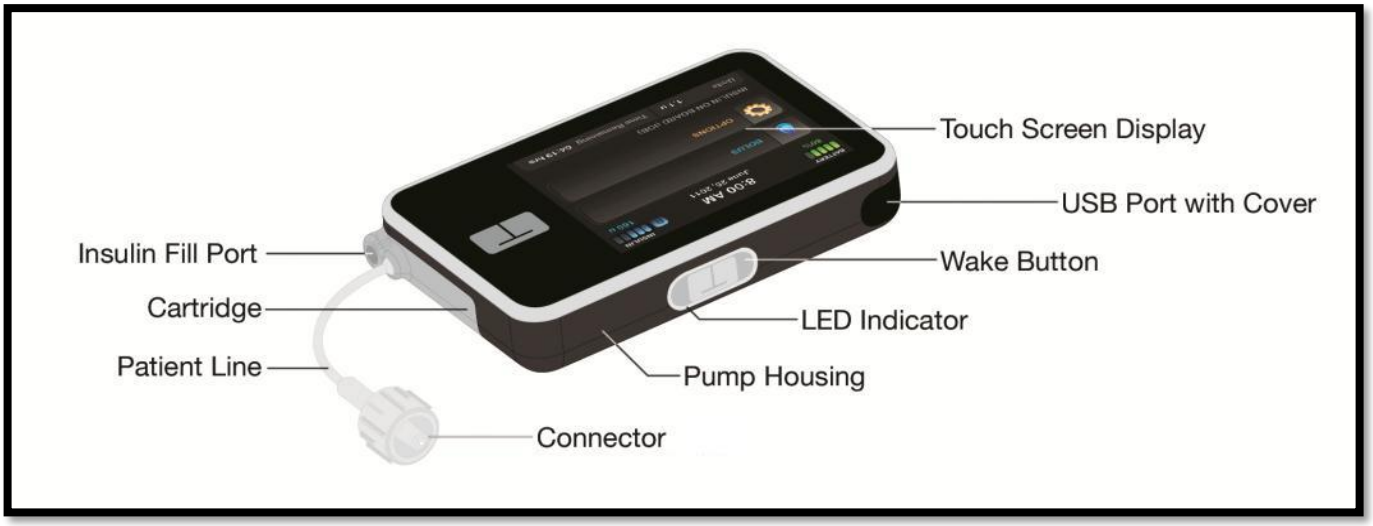
6.1.1. Insulin Pump

The Tandem Diabetes ambulatory infusion pump with PLGS (t:slim X2 with Basal-IQ Technology) is intended for the subcutaneous delivery of insulin for the management of diabetes mellitus in persons requiring insulin. A touch sensitive Liquid Crystal Display (LCD) provides both the pump information to the user as well as the interface for the user to program insulin delivery timing and quantity, both basal and bolus delivery of insulin at set and variable rates.

Additionally these pumps are integrated with and display continuous glucose data (CGM) and contain a Predictive Low Glucose Suspend (PLGS) algorithm which allows the user to set the system to automatically suspend delivery of insulin when the predicted glucose value falls below a predefined threshold.

The device system components include an insulin pump and cartridge, infusion catheter, CGM sensor and transmitter, and a blood glucose meter for CGM calibrations.

Figure 3 - Tandem Pump Showing Labeled Components



6.1.2. Continuous Glucose Monitoring

The study CGM will included an unmodified Dexcom G5 Mobile transmitter and sensors. This is an FDA-approved device system with no changes to its hardware or firmware components. The CGM sensor will be replaced at least once every seven days.

6.1.3. Blood Glucose Meter and Strips

Blood glucose levels will be measured and the CGM device will be calibrated using the Accu-Chek Guide Blood Glucose Monitoring System in accordance with the manufacturer labeling.

6.1.4. Ketone Meter and Strips

Blood ketone levels will be measured using the Abbott Precision Xtra meter and strips in accordance with the manufacturer's labeling. The blood glucose meter component of the Precision Xtra device will not be used.

6.2. Study Device Accountability Procedures

Device accountability procedures will be detailed in the study procedures manual.

6.2.1. Blood Glucose Meter Testing

- Participants will be provided with instructions to perform QC testing per manufacturer guidelines.
- All study blood glucose meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The Participant will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
- Participants will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.

6.2.2. Blood Ketone Testing

- Participants to perform QC testing at home per manufacturer guidelines.
- All study blood ketone meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The Participant will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
- Participants will be instructed on how to perform blood ketone testing
- Participants will be given guidelines for treatment of elevated blood ketones

6.3. Safety Measures

6.3.1. CGM Calibration

Throughout the study, participants will be instructed to calibrate the study CGM in accordance with manufacturer labelling.

6.3.2. PLGS Suspend and Resume Alerts

By default, the Tandem PLGS pump's audible PLGS suspend and resume alerts will be disabled when the participant receives the pump. The participant will be permitted to enable these audible alerts if desired during system use.

6.3.3. Low Glucose Alert and Safety Protocol

Participants will be required to set the CGM low glucose alert level between 60 mg/dL and 70 mg/dL during the course of the study, and not to change this setting during the crossover trial.

If a participant receives a CGM low glucose alert or notes that the CGM glucose is below the low glucose threshold alert value, confirmatory fingerstick testing will be performed if required by CGM

765 labelling and the participant will be instructed to treat hypoglycemia with ~16 grams of fast-acting oral
766 glucose.
767
768 **6.3.4. High Glucose Alert and Safety Protocol**
769 Participants will be required to set the CGM high glucose alert level between 200 mg/dL and 300
770 mg/dL during the course of the study, and not to change this setting during the crossover trial.
771
772 If a participant receives a CGM hyperglycemia threshold alert or notes that the CGM glucose is above
773 the hyperglycemia threshold alert value, confirmatory fingerstick testing will be performed if required
774 by CGM labelling.
775
776 If a participant's CGM reading is ≥300 mg/dL when fasting in the morning upon awakening, ≥300
777 mg/dL for over 1 hour during the day, or ≥400 mg/dL at any point, the participant will be instructed to
778 take the following steps:
779 - Perform a blood glucose meter check.
780 - If the blood glucose is ≥300 mg/dL, then blood ketones should be measured with the study
781 ketone meter.
782 - Correction insulin may be taken per the participant's usual routine.
783 - Participants will be instructed to change their pump site and administer correction insulin via
784 insulin syringe or pen for ketones ≥0.6 mmol/L and to additionally notify study staff for
785 ketones ≥1.5 mmol/L.

CHAPTER 7: TESTING PROCEDURES AND QUESTIONNAIRES

7.1. Testing Procedures

The following tests and test procedures will be performed during the study:

1) Hemoglobin A1c (HbA1c) will be tested using a DCA Vantage or similar point-of-care device or local lab
2) Pregnancy tests will be performed using a urine or serum pregnancy test

7.2. Questionnaire

The following questionnaire will be completed by each participant after the crossover study period during which the PLGS system was used. The procedures for administration are described in the study procedures manual.

7.2.1. Usability Questionnaire

The System Usability Scale (SUS) is a 10-item questionnaire that measures the overall usability of a system that will be administered to all participants. It is a valid and reliable measure of the perceived usability of a system and is technology-agnostic. The questionnaire presents statements with five response options (anchoring the options from strongly disagree to strongly agree) and asks users to rate their agreement to the statements. User scores are transformed into a composite score, from 0 to 100, and this score is taken as an overall measure of the system's usability; higher scores indicate better perceived usability.

Administration time is approximately 5 minutes.

CHAPTER 8: ADVERSE EVENTS, REPORTING, AND STOPPING RULES

8.1. 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.

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

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in 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 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: A device complication or complaint is something that happens to a device or is 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.

Device Malfunction: 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)

8.2. 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, unless excluded from reporting in Section 8.3
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

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.

Pregnancy occurring during the study will be recorded.

8.2.1. 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.

8.2.2. Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following criteria is met: (1) the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or (2) in the absence of DKA if 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.

8.2.3. 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.

8.2.4. 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.

8.2.5. 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.

8.2.6. Outcome of Adverse Event

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

- RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- 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.
- 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).
- 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.

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.

8.3. 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 <u>not</u> 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 7 days
- 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 don't meet criteria for AE reporting

8.4. Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study and a final visit will be conducted. The occurrence of pregnancy will be reported on an AE Form.

8.5. Timing of Event Reporting

Serious or unexpected device-related adverse events must be reported to the Coordinating Center within 24 hours via completion of the online serious adverse event form.

Other reportable adverse events and device malfunctions (with or without an adverse event) will be reported within 3 days of the investigator becoming aware of the event by completion of an electronic case report form.

Device complaints not associated with device malfunction or an adverse event must be reported within 7 days of the investigator becoming aware of the event.

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

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 Sponsor 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 the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor 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 Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

Device malfunctions will be handled by the Sponsor or designee as described below. In the case of a CGM transmitter or sensor device malfunction, the Coordinating Center will be contacted and the Sponsor will be notified accordingly.

8.6. Stopping Criteria

8.6.1. Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

1. 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; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
2. The participant requests that the treatment be stopped
3. Two distinct episodes of DKA
4. Two distinct severe hypoglycemia events as defined in Section 8.2

Even if the study device system is discontinued, the participant will be encouraged to remain in the study through the final study visit.

Participants who become pregnant will be discontinued from the study with a final clinic visit and no subsequent use of study device components.

8.6.2. 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 8.2), use of the study device system will be suspended while the problem is diagnosed.

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 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.

8.7. Risks

The potential risks associated with use of the study device are described in Section 1.4.

Additional risks are minor and/or infrequent and include

- Pain, bruising, redness, or infection from blood draws
- Loss of confidentiality
- Stress from completing quality of life questionnaires
- Skin irritation, infection, or bleeding from CGM sensor or pump infusion set or adhesive tap
- Breaking of CGM sensor with small portion retained under skin causing redness, swelling, or pain

The risk of hypoglycemia should be no greater and possibly less than it is in everyday living for someone with T1D.

CHAPTER 9: MISCELLANEOUS CONSIDERATIONS

9.1. Participant Compensation

Participants will be compensated $50 for each protocol-specified clinic visit during the study. Participants will typically receive these amounts at the end of each clinic visit. For completing all required study visits, participants will be compensated a minimum of $300 and a maximum of $600 due to additional study visits that may be required for some participants.

9.2. 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.

9.3. 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 shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may be provided to research sites involved in the study.

CHAPTER 10: STATISTICAL CONSIDERATIONS

10.1. Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

10.2. Statistical Hypotheses

- Null hypothesis: There will be no difference in percentage of CGM-measured glucose values <70 mg/dL between PLGS and SAP
- Alternate hypothesis: PLGS will improve the percentage of CGM-measured glucose values <70 mg/dL over SAP.

10.3. Sample Size

Data from the JDRF Continuous Glucose Monitoring Randomized Clinical Trial was used to estimate SD and the frequency of time <70 mg/dL for the pump or MDI population. Assuming a crossover design with two 3 weeks periods, a 2-tailed test, a 33% relative reduction in 24-hour time <70 mg/dL, standard deviation of the paired differences = 3%, a type I error = 5%, and 90% power; a sample of 52 participants is required.

With a sample size of 90 participants, the primary analysis will have 99% power. The larger sample size will provide increased precision for safety analyses and subgroup analyses.

10.4. Outcome Measures

Primary Efficacy Endpoint:

- Percentage of sensor glucose values <70 mg/dL

Secondary Efficacy Endpoints:

Hypoglycemia

- Percentage of values <60 mg/dL
- Percentage of values <50 mg/dL
- AUC <70 mg/dL
- Low blood glucose index
- Frequency of CGM-measured hypoglycemic events (see below):

Glucose Control

- Mean glucose
- Percentage of values 70 to 180 mg/dL

Hyperglycemia

- Percentage of values >250 mg/dL
- Percentage of values >180 mg/dL
- AUC glucose >180 mg/dL
- High blood glucose index

Each of the metrics listed will be calculated over 24 hours and separately for daytime (6am – 10pm) and nighttime (10pm – 6am). Secondary outcomes will also include the percentage of sensor glucose values <70 mg/dL calculated separately for daytime and nighttime.

A CGM-measured hypoglycemic event will be defined as at least 2 sensor values <54 mg/dl that are 15 or more minutes apart plus no intervening values >54 mg/dl; at least 2 sensor values >70 mg/dl that are 30 or more minutes apart with no intervening values <70 mg/dl, are required to define the end of an event, at which point the study participant becomes eligible for a new event..

10.5. Description of Statistical Methods

10.5.1. General Approach

This is a crossover study where each participant is randomized to treatment order. All analyses will compare the 3-week period of PLGS to the 3 week period of SAP and will follow the intention-to-treat principle with each period analyzed according to the treatment assigned by randomization regardless of actual PLGS utilization. All participants who have at least one CGM reading in each 3-week period will be analyzed. All p-values will be two-sided.

10.5.2. Analysis Cohorts

- All randomized participants who have at least one CGM reading in each 3-week period will be analyzed for the Intention-to-Treat (ITT) Analysis.
- Safety outcomes will be reported for all enrolled participants, irrespective of whether the study was completed.
- A per-protocol analysis restricted to participants with at least 200 hours of CGM data in each 3 week period will also be conducted provided that there are at least 5 participants with less than 200 hours of CGM data in both treatment periods.

10.6. Analysis of the Primary Efficacy Endpoint

The percentage of sensor glucose values <70 mg/dL will be calculated for each participant in each 3-week treatment period by pooling all sensor glucose readings that occur within each 3-week period. All sensor glucose readings will be weighted equally in the pooled percentages regardless of how they distribute across weeks. The percentage in the PLGS period will then be compared to the percentage in the SAP period for the same participant.

Summary statistics appropriate to the distribution will be calculated for % time below <70 mg/dL separately by treatment arm. A repeated measures regression model with an unstructured covariance structure will be fit for percent time below below <70 mg/dL to compare the two treatments. The model will adjust for period as a covariate. If residual values from the regression model have a skewed distribution then an appropriate transformation or a nonparametric analysis based on ranks will be performed.

There will be no imputation of missing CGM data.

10.7. Analysis of the Secondary Endpoints

Analysis of the secondary endpoints and additional CGM metrics will parallel the analysis of the primary endpoint above.

10.8. Safety Analyses

The following safety outcomes will be tabulated by participant within each 3-week treatment period. The summary statistics will include start date, stop date, severity, relationship, resolution, and duration.

- Diabetic ketoacidosis (DKA), as defined by the Diabetes Control and Complications Trial (DCCT).
- Severe clinical hypoglycemic events such that the participant required assistance from another person to actively administer carbohydrate, glucagon, or engage in other resuscitative actions; note severe hypoglycemia could be considered both and efficacy and safety outcome
- Ketosis events (blood ketone level >1.0 mmol/L)
- All other reported adverse events
- Unanticipated adverse device effects

10.9. Other Analyses

The following outcomes will be tabulated separately over 24-hour period, daytime, and nighttime where applicable:

- Insulin delivery including total insulin, basal insulin, and bolus insulin
- Frequency of insulin suspension events and duration of events, including individual suspensions and cumulative suspension time
- CGM glucose nadir during suspension events and peak within 2 hours after events
- The amount of CGM use in both 3-week periods.
- Percentage of time PLGS is active.

10.10. Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the study cohort including CGM metrics will be tabulated. For continuous variables, summary statistics appropriate to the distribution will be given. For discrete variables, number and percentage will be reported for each category.

10.11. Planned Interim Analyses

An interim analysis to re-estimate sample size will be conducted approximately when the 90th subject is enrolled into the screening phase of the study. The objective is to assess whether the observed rate of hypoglycemia in the control arm matches the value assumed in the original sample size calculation.

A longitudinal regression model will be fit using CGM data from SAP use during run-in and available outcome data from the control arm during Period 1 (for subjects randomized to control-first) and during Period 2 (for subjects randomized to control-second). The dependent variable will be CGM measured hypoglycemia to match the primary outcome described above. This model will be used to estimate the amount of hypoglycemia in the control arm.

The required sample size is roughly proportional to the amount of hypoglycemia in the control arm. The adjusted sample size will therefore be calculated as:

*52*4% / estimated hypoglycemia rate in control arm*

where the estimated rate in the denominator is calculated from the regression model described above. This new sample size would be restricted to be a minimum of N=90 and a maximum of N=150 subjects completing the crossover trial with sufficient data to include in the primary analysis. If conditional power is <20% even with a sample size of N=150, the study may be stopped and limited to the subjects who have already been randomized (N not to be less than approximately 100).

Simulations show that basing the sample size on the estimated control arm rate in this manner does not materially inflate the type 1 error rate.

10.12. Sub-Group Analyses

The primary outcome will be tabulated by:

- age
- diabetes duration
- baseline HbA1c
- baseline CGM hypoglycemia

These analyses are considered exploratory and are not being evaluated as independent hypothesis tests.

10.13. Multiple Comparison/Multiplicity

The primary analysis involves a simple treatment arm comparison for a single outcome measure so no correction for multiple comparisons will be performed.

For the secondary analyses described above, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure for multiple comparisons. Note that this procedure can handle correlated outcome metrics and does not assume independent hypothesis tests.

10.14. Exploratory Analyses

No additional exploratory analyses are planned.

CHAPTER 11: DATA COLLECTION AND MONITORING

11.1. Case Report Forms and Device Data

The main study data are collected through a combination of electronic case report forms (CRFs) and electronic device data files obtained from the study software and individual hardware components. These electronic device files and electronic CRFs from the study website are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

11.2. 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.

11.3. Quality Assurance and Monitoring

Designated personnel from the Coordinating 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.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion

- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

11.4. 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.

CHAPTER 12: ETHICS AND PROTECTION OF HUMAN PARTICIPANTS

12.1. 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.

12.2. 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 may require 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.

12.3. Informed Consent Process

12.3.1. 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.

12.3.2. Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or

hospital) and pharmacy records 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 to and stored at the Jaeb Center for Health Research. 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 clinical sites and by Jaeb Center for Health Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Jaeb Center for Health Research.

12.3.3. Future Use of Stored Specimens

Not applicable

CHAPTER 13: INVESTIGATOR AND SPONSOR OBLIGATIONS

13.1. Role of Sponsor

As the study sponsor of this clinical trial, Tandem Diabetes Care, Inc. has the overall responsibility for the conduct of the study, including the assurance that the study meets regulatory requirements and is conducted according to Good Clinical Practice.

13.2. Medical Supervision and Investigator Responsibility

Medical supervision is the responsibility of the investigator named on the Investigator Agreement. The investigator may delegate day-to-day activities to a sub-investigator or study staff member, but retains overall responsibility for ensuring that the study is conducted properly and in accordance with the study protocol. A delegation list is to be maintained that includes all qualified persons to whom the investigator may delegate significant study-related duties. The investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies, or that emergency medical facilities are available and accessible. The investigator is responsible for ensuring that the study is conducted according to Good Clinical Practice (GCP), other applicable regulatory guidelines, and sound medical practices.

13.3. Study Initiation and Sponsor Discontinuation

Prior to initiation of the study, the investigator must provide the Sponsor or designee with the following documents (copies of which must be maintained by the investigator):

- Completed and signed original Investigator Agreement
- Current curriculum vitae, signed and dated; also required is a state license for the investigator and for other medically qualified sub-investigators
- Completed Financial Disclosure information
- Signed copy of the Institutional Review Board (IRB) approval letter that lists the approved items
- List of the IRB members who voted on the approval, including their specialty and affiliation, or the IRB assurance numbers if the roster cannot be obtained
- Copy of the IRB-approved informed consent
- Copy of the IRB-approved Authorization to Use and Disclose Protected Health Information form, consistent with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) legislation (if separate from the informed consent form)

Upon receipt of all necessary paperwork, the Sponsor or designee will arrange for all study material to be delivered to the clinical study site. The Sponsor or designee will conduct an initiation conference call or visit to orient and provide in-depth training for all personnel expected to be involved in the study. Study protocol procedures, instruction for data capture, and overall responsibilities, including device accountability and study file maintenance, will be reviewed.

The Sponsor has the right to terminate the study for any of the following reasons:

- Non-adherence to the protocol
- Unavailability of the investigator or the study personnel to the sponsor's monitoring personnel (or their designee)
- Inability to recruit the expected participant population
- Other administrative reasons

Throughout the course of the study, the investigator is to make a reasonable effort to maintain the enrollment rate that was agreed upon with the Sponsor. The investigator will also make a reasonable effort to enroll appropriate participants. The sponsor may elect to terminate the study at a given site if the enrollment rate lags or if significant numbers of non-evaluable participants are enrolled.

CHAPTER 14: APPENDIX A – EXTENSION PHASE

Introduction

The Tandem PLGS Pivotal Trial is being extended to allow interested trial participants to continue to use the Tandem PLGS pump system after completion of the main trial.

Study Design

All participants will be assigned the Tandem PLGS pump and will return to the clinic approximately every 13 weeks (±2 weeks). The Extension Phase will continue until the system is commercially available or two years after the initial regulatory approval date, whichever comes first.

Participant Eligibility and Informed Consent

Participants who completed the PLGS Pivotal Trial within the previous 6 months will be eligible for the Extension Phase.

Study sites will inform the participants regarding the Extension Phase. Interested participants, parents/guardians, or both will sign new consent/assent forms.

Extension Phase Procedures

At the initial visit after the consent (and assent if applicable) is signed, the participant will be provided with study supplies and device training as needed. Study supplies include: study pump and related supplies, study CGM and related supplies, and study blood glucose and ketone meters and test strips.

The home procedures will be the same as described in sections 5.3 and 5.4. Device use will be as described in Chapter 6.

At each 13-week (±2 weeks) follow-up visit and for the final visit, device data will be uploaded. The occurrence of adverse events and device issues will be solicited, as well as any new medications or medical conditions since the previous visit. Other testing and changes in diabetes management will be performed as part of usual care. Additional supplies will be distributed as needed. The System Usability Scale (SUS) will also be completed by each participant at each visit. Administration time is approximately 5 minutes.
There will be no compensation to participants for completion of visits.

Statistical Analyses

CGM data will be compiled across visits and the metrics listed in section 10.4 will be descriptively reported. Frequency of pump use, CGM use, adverse events, and device issues will be tabulated.

CHAPTER 15: REFERENCES

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