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Automated Insulin Delivery in Elderly with Type 1 Diabetes (AIDE T1D):

A Randomized Cross-over Trial Evaluating Automated Insulin Delivery Technologies on Hypoglycemia and Quality of Life in Elderly Adults with Type 1 Diabetes

Sponsor: Jaeb Center for Health Research

Version Number: 5.0

05 May 2021

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AP	Artificial Pancreas
AUC	Area Under the Curve
BG	Blood Glucose
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCL	Hybrid Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
NIH	National Institutes of Health
PLGS	Predictive Low Glucose Suspend
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled/Clinical Trial
RMB	Risk-Based Monitoring
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Sensor-Augmented Pump
SD	Standard Deviation
SH	Severe Hypoglycemia
SMBG	Self-Monitoring of Blood Glucose

ABBREVIATION	DEFINITION
TDI	Total Daily Insulin
UADE	Unanticipated Adverse Device Effect
UI	User Interface

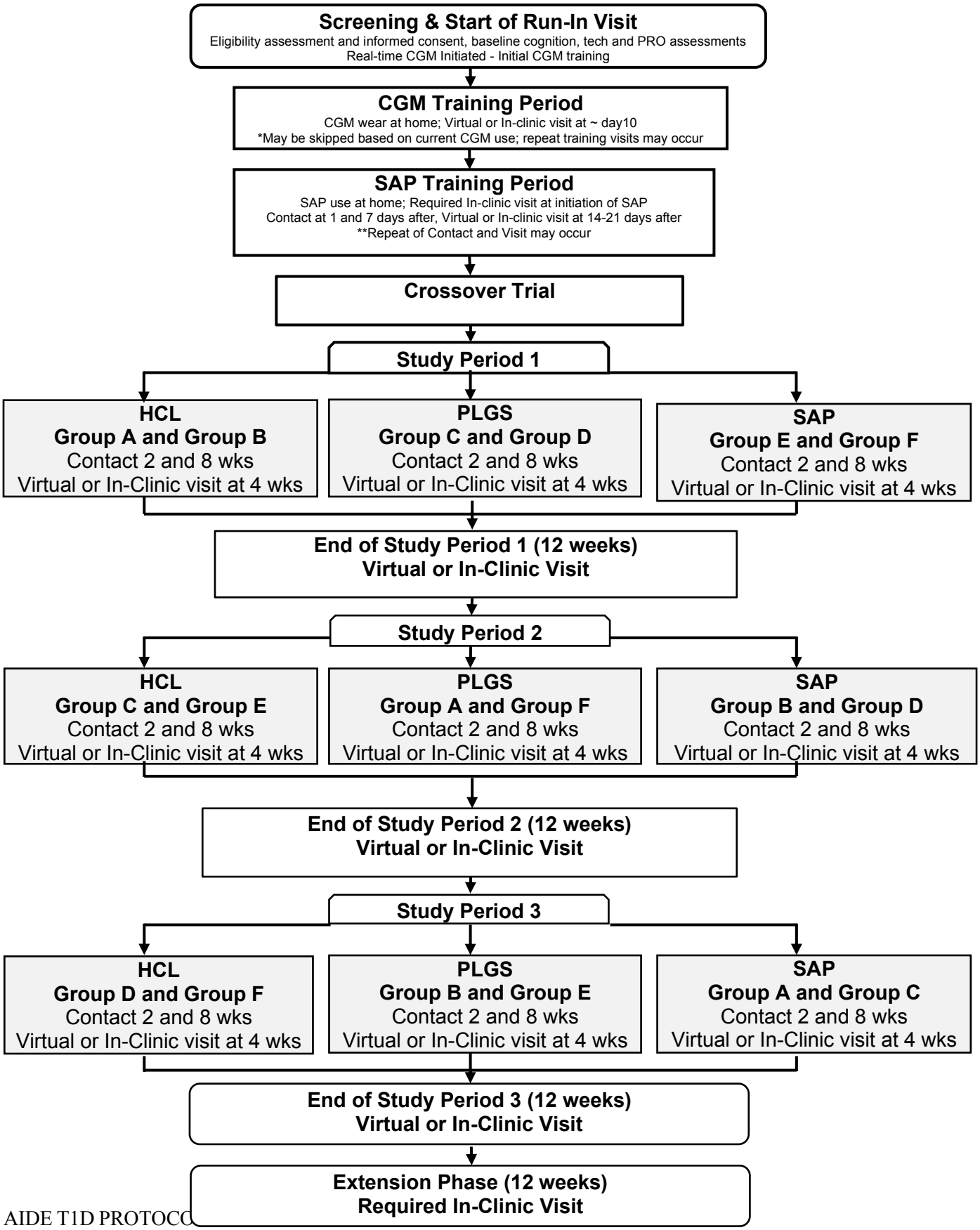
PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	A Randomized Cross-over Trial Evaluating Automated Insulin Delivery (AID) Technologies on Hypoglycemia and Quality of Life (QOL) in Elderly Adults with Type 1 Diabetes (T1D)
Précis	*The primary objective of this protocol is to assess the safety and effectiveness of both hybrid closed loop control (HCL) technology and predictive low-glucose insulin suspension (PLGS) on hypoglycemia and other glycemic outcomes, QOL and usability compared with sensor-augmented pump (SAP) therapy in older adults with T1D. A secondary objective is to identify patient characteristics associated with use of SAP, HCL or PLGS during a 12-week patient preference extension phase. The study aims will be completed via a multi-center, randomized, crossover trial consisting of three sequential 12-week periods, with the HCL feature used during one period, the PLGS feature used during one period and SAP therapy (control) during one period. The crossover trial will be preceded by a run-in phase in which participants will receive training using the study devices (Dexcom G6 and Tandem t:slim X2 pump). After the last crossover period, participants will be given the opportunity to use study devices for an additional 12 weeks to assess preference of system use (PLGS, HCL or SAP) and associated characteristics, durability and safety in a more real-world setting with less frequent study contact.*
Investigational Device	The HCL intervention arm will utilize the Tandem t:slim X2 with Control-IQ Technology and Dexcom G6 CGM. The PLGS intervention arm will utilize the Tandem t:slim X2 with Basal-IQ Technology and Dexcom G6 CGM. The control arm will utilize the Tandem t:slim X2 pump and Dexcom G6 CGM without HCL or PLGS features turned on.
Objectives	Primary RCT Objectives: 1) Determine the effect of HCL on hypoglycemia in adults with T1D ≥65 years old. 2) Determine the effect of PLGS on hypoglycemia in adults with T1D ≥65 years old. Extension Phase Objective: Determine user preferences of available CGM augmented pump technologies (PLGS, HCL or SAP) among elderly adults with T1D ≥65 years old in a more real-world setting during the twelve-week extension phase
Study Design	A multi-center, randomized, crossover trial consisting of three sequential 12-week periods, with the HCL feature used during one period, the PLGS feature used during one period and SAP therapy (control) during one period. The crossover trial will be preceded by a run-in phase in which participants will receive training using the study devices (Dexcom G6 and Tandem t:slim X2 pump). After the last crossover period, participants will be given the opportunity to use study devices for an additional 12 weeks to assess preference of system use (PLGS, HCL or SAP) and associated characteristics, durability and safety in a more real-world setting with less frequent study contact.
Number of Sites	3 to 5 in the United States
Endpoint	**Primary Efficacy Outcome:** CGM-measured time spent <70 mg/dL **Key Secondary Efficacy Outcomes:** *Hypoglycemia* • Percentage of values <54 mg/dL

PARTICIPANT AREA	DESCRIPTION
	• Incidence of CGM-measured hypoglycemic events *Glucose Control* • Mean glucose • Percentage of values 70 to 180 mg/dL • HbA1c *Hyperglycemia* • Percentage of values >250 mg/dL • Percentage of values >180 mg/dL *Glycemic Variability* • Coefficient of variation **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 active assistance from another person due to altered consciousness to actively administer carbohydrate, glucagon, or engage in other resuscitative actions; note severe hypoglycemia could be considered both an efficacy and safety outcome • Emergency room and hospitalizations related to SH and DKA • Severe adverse events • Unanticipated adverse device effects **Other Outcomes:** • Hypoglycemia unawareness • Participant reported outcomes: diabetes distress, hypoglycemic fear, hypoglycemia confidence and general quality of life • Usability and patient perspective of each system
Population	**Key Inclusion Criteria:** • Clinical diagnosis of T1D • Age ≥ 65 years old • T1D Duration of at least 1 year • HbA1c < 10.0% from point of care or local lab within 6 months • Insulin regimen involves basal/bolus insulin via insulin pump or multiple daily injections • Ability to download study devices at home or willing to come into clinic for devices to be downloaded at visits and when needed for safety **Key Exclusion Criteria:** • Use of PLGS technology or HCL insulin delivery in the past 1 month
Sample Size	At least 90 participants completing the crossover trial
Phase	N/A
Treatment Groups	Random assignment (1:1:1) to one of the following treatment orders: (A) HCL in period 1, PLGS in period 2, SAP in period 3 (B) HCL in period 1, SAP in period 2, PLGS in period 3 (C) PLGS in period 1, HCL in period 2, SAP in period 3 (D) PLGS in period 1, SAP in period 2, HCL in period 3 (E) SAP in period 1, HCL in period 2, PLGS in period 3 (F) SAP in period 1, PLGS in period 2, HCL in period 3
Participant Duration	*~ 54 weeks*

PARTICIPANT AREA	DESCRIPTION
Protocol Overview/Synopsis	**1) Screening and Enrollment** • Informed consent will be signed and eligibility will be assessed • Medical history obtained • HbA1c measurement if historical data within 6 months prior to enrollment not available (see eligibility criteria) • Evaluation of CGM experience and CGM use • CGM training and initiation of study CGM • Baseline patient reported outcomes • Brief cognitive assessment for eligibility (5 min MoCA) **2) CGM and SAP Run-In** a. CGM Training Period (~ 10 to 30 days): After ~10 days following the initial study CGM placement, participants who were not already CGM users at screening will have a visit for additional CGM training. b. SAP Training Period (~14 to 35 days): Participants will be provided the Tandem t:slim X2 pump which will be integrated with the Dexcom G6. Participants will be contacted 1 and 7 days following initiation of SAP and a SAP evaluation visit will occur 14 – 21 days following initiation of SAP. Basal and bolus insulin delivery will be adjusted as needed. Prior to initiating the cross-over trial the following will be done: • The clinician will confirm the participant's willingness to participate in the crossover trial • Study devices downloaded for baseline assessment and eligibility of device wear time • Baseline patient reported outcomes (at screening or prior to randomization) • Cognitive testing (In-person) • Frailty assessment • Physical Exam • Blood draw for central lab samples **3) Randomized Crossover Trial** Eligible participants will continue into randomized cross-over trial: • Random assignment to: (A) HCL in period 1, PLGS in period 2, SAP in period 3 (B) HCL in period 1, SAP in period 2, PLGS in period 3 (C) PLGS in period 1, HCL in period 2, SAP in period 3 (D) PLGS in period 1, SAP in period 2, HCL in period 3 (E) SAP in period 1, HCL in period 2 and PLGS in period 3 (F) SAP in period 1, PLGS in period 2, HCL in period 3 During each of the three 12-week intervention periods, a phone or virtual contact will occur at 2 and 8 weeks and a visit (in clinic or virtual) at 4 and 12 weeks. HbA1c will be measured at the end of each period either in clinic or using an at-home sample collection kit. **4) Extension phase** At the start of the extension phase participants will be given the opportunity to choose between SAP, PLGS or HCL and will be followed for an additional 12 weeks.

SCHEMATIC OF STUDY DESIGN



SCHEDULE OF STUDY VISITS AND PROCEDURES

Table 1. Schedule of Visits and Procedures during Screening and Run-In

	Screening/Start of Run-In[1]	CGM Run-In	SAP Run-In		
		CGM Training Visit[3]	Initiation of SAP[4]	SAP Training Contacts[5]	SAP Evaluation[6]
Time from Randomization[2]	**At least 14 days prior**	**At least 14 days prior**	**At least 14 days prior**		**0 to 7 days prior**
In-clinic Visit or Virtual Visit (V) or Contact (C)	**V**	**V**	**In-clinic Visit**	**C**	**V**
Informed Consent	**X**				
Inclusion/Exclusion	**X**				
Medical history	**X**				
Physical exam, Height, weight, blood pressure			**X**		
HbA1c – point-of-care or local lab if historical value within 6 months not available	**X**				
Blood draw - central lab[8]			**X**		
10-foot timed walk			**X**		
5-min MoCA	**X**				
Cognitive Assessments			**X**		
Questionnaires[9]	**X**				
Study CGM training	**X**	**X**			
Study pump with integrated CGM training			**X**	**X**	**X**
Hypo Assessment[10]	**X**		**X**		
CGM Compliance					**X**
Skin Assessment[11]		**X**	**X**		**X**
Upload device data		**X**	**X**	**X**	**X**
Review blood sugars and make insulin adjustments as needed		**X**	**X**	**X**	**X**

	Screening/Start of Run-In[1]	CGM Run-In	SAP Run-In		
		CGM Training Visit[3]	Initiation of SAP[4]	SAP Training Contacts[5]	SAP Evaluation[6]

[1]The Screening and start of run-in training visits may occur on the same day or separate days but no more than 14 days apart.
[2]Visit timing will depend on experience with study devices.
[3]Participants using real-time CGM may skip CGM training period and proceed to SAP training period.
[4]**Required in-clinic visit.** Pump training will occur after participant is comfortable with use of CGM and meets minimum hypoglycemia requirement. Participants using both a Tandem t:slim X2 pump and Dexcom CGM may skip both the CGM training and SAP initiation visits but will need to use study devices for 14 days prior to randomization visit and have one in-person visit (screening or SAP evaluation) for completion of testing and assessments.
[5]Phone or video contacts to take place 1 day after SAP initiation and 7 days after SAP initiation and may be repeated as needed. Participants who are not able to upload device data from home may need to bring device to clinic to be downloaded and reviewed. Ability to upload device will be assessed during training on the device.
[6]Evaluate SAP use to determine eligibility and if ready to proceed with randomized trial. Participants who need additional training on pump may have a repeat visit.
[7]HbA1c obtained at screening only if not done as usual care in the prior 6 months from enrollment
[8]Blood draw for central lab HbA1c and C-peptide will take place on initiation of SAP for baseline assessment.
[9]Completed at screening or prior to randomization electronically or on paper if preferred.
[10]Assessment of amount of hypoglycemia for eligibility may be performed either at screening for those using CGM with available data or at the SAP initiation period.
[11]When possible via video for virtual visit.

Table 2. Schedule of Visits and Procedures During the Crossover Trial and Extension

	Randomization	Start of Period[1]	Crossover Period 1, 2 & 3			End of Period[1]	Extension Phase Start	End of Extension Phase
Time from Randomization or beginning of period	**0**	**0**	**2w ± 4d**	**4w ± 7d**	**8w ± 7d**	**12w ± 7d**	**End of Period 3 Visit ± 7d**	**48w±14d**
In-clinic Visit or Virtual Visit (V) or Contact (C)	**V**	**V**	**C[5]**	**V**	**C[5]**	**V**	**V**	**In-clinic Visit**
Re-review of eligibility	**X**							
Randomization of treatment order	**X**							
Height, weight, blood pressure[2]						**X**		**X**
HbA1c central lab[3]						**X**		**X**
Questionnaires[4]						**X**		**X**
Cognitive Assessments								**X**
AE Assessment			**X**	**X**	**X**	**X**		**X**
Upload device data			**X**	**X**	**X**	**X**		**X**
Review glucose patterns		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Training on PLGS or HCL user interface if starting next period		**X**				**X**		

[1]Start of period 1 will take place on same day as randomization. Start of period 2 and 3 will take place on same day at end of previous period or within 7 days. Start of extension phase should take place on same day of end of period 3.
[2]Completed for in-clinic visit but allowed to skip for virtual visit.
[3]Central lab HbA1c will be collected in-clinic or at home for virtual visits at the end of period 1, period 2, period 3. Collected in-clinic at the end of the extension phase.
[4] Completed electronically by participant or on paper if preferred.
[5] Device data review may take place during follow up contacts if participant can upload data from home. Clinic visit may be completed if participant cannot upload data from home. Ability to upload device will be assessed during training on the device.

Chapter 1: Background Information

1.1 Introduction

1.1.1 Background and Importance

Older adults with type 1 diabetes (T1D) are a growing but under-evaluated population (1-4). Older adults, particularly those with longstanding diabetes, are more prone to hypoglycemia and hypoglycemia unawareness. Hypoglycemia, which in addition to producing altered mental status and sometimes seizure or loss of consciousness, can be associated with falls leading to fractures, and cardiac arrhythmias resulting in sudden death (5-7). In Medicare beneficiaries with diabetes, hospitalizations related to hypoglycemia are now more frequent than those for hyperglycemia and are associated with high 1-year mortality (6; 8). Emergency room visits due to hypoglycemia also are common (5). These reports likely underestimate the risk of hypoglycemia in older adults with T1D since they include individuals with the more prevalent type 2 diabetes in whom severe hypoglycemic events are likely considerably less frequent than they are in individuals with T1D.

Current strategies for avoidance of hypoglycemia in older adults are insufficient. Unlike treatment guidelines in younger individuals with T1D, guidelines for older adults with T1D are focused on minimizing hypoglycemia rather than attempting to achieve low glycated hemoglobin (HbA1c) levels (9; 10). Despite these efforts, biochemical hypoglycemia occurs frequently and severe hypoglycemia (SH) occurs more often in older than younger adults with T1D. Data from the T1D Exchange registry has shown a remarkably high frequency of SH in older adults with longstanding T1D: 18% of registry participants ≥60 years old reported seizure or loss of consciousness due to hypoglycemia in the prior 12 months (11). In addition, T1D Exchange registry data indicate that SH is just as common with HbA1c levels >8.0% as it is for HbA1c levels <7.0% (11). A prior study we conducted within the T1D Exchange (12) of 201 adults ≥60 years old with T1D duration ≥20 years (101 with SH in the prior year and 100 without SH in the prior 3 years) found that glucose concentrations measured with blinded continuous glucose monitoring (CGM) were <70 mg/dL for a median of 91 minutes per day. Furthermore, mean HbA1c was similar in the individuals who had experienced SH in the prior year compared with those who had not experienced SH in the prior 3 years (7.8% versus 7.7%). These data in addition to the T1D exchange registry data do not support the strategy of "raising the HbA1c" as being a desirable or effective approach for hypoglycemia prevention in older adults with T1D.

Hypoglycemia impacts quality of life (QOL). Poor glycemic control, including frequent hypoglycemia, has adverse effects on QOL of both the individuals with T1D (13; 14) and their families (15). In fact, hypoglycemia has a stronger impact than diabetes complications on QOL in older adults (16). Hypoglycemic episodes and hypoglycemia fear limit participation in activities that are beneficial to emotional, cognitive and physical well-being (e.g., exercise, socializing, and travelling). Diabetes-related distress (i.e., the emotions, stresses and worries associated with diabetes) is also an important component of QOL for people with T1D and is associated with poor glycemic control, longer duration of diabetes, higher rates of depression, and SH (17). Automated insulin delivery (AID) systems hold promise for improving QOL via reductions in hypoglycemia. However, there are also possible adverse QOL impacts of advanced diabetes technologies that may limit uptake of these systems (18; 19).

Older adults with T1D have unique needs. The prevalence of hypoglycemia unawareness, or the loss of physiological symptoms associated with low blood glucose, is remarkably high in older adults with recent SH, with 58% of those with SH within the prior year having hypoglycemic unawareness compared with 25% in those with no SH in the prior 3 years (12). Furthermore, glycemic variability is greater for those having experienced SH within the prior year. Aging is associated with normative decline in cognitive functioning that may impact diabetes self-management and contribute to hypoglycemia risk. In addition, older adults with T1D have high rates of mild cognitive impairment (48% of those ≥60 years old (20), and cognitive impairment is associated with hypoglycemia unawareness and recent SH (20; 21). Further, we previously found that psychomotor processing speed, fine motor dexterity and executive functioning were poorer in older adults with SH in the past year (12) and was associated with simulated diabetes self-management skill (22). Thus, older adults with T1D may have more difficulty with the cognitive demands of diabetes self-management, coupled with high glycemic variability and hypoglycemia unawareness, that all contribute to hypoglycemia (21; 23). AID has the potential to reduce the cognitive burden of daily diabetes management decisions, thereby improving overall control in those with diminished cognitive resources. Conversely, learning and adopting new technologies and trouble-shooting component failures may be overwhelming for older adults with cognitive decline. Thus, it is imperative to assess whether automation of insulin delivery can be successfully implemented into diabetes management of older adults with and without cognitive impairment.

1.1.2 Predictive Low-Glucose Suspend Systems

Many episodes of SH occur during the night, specifically during sleep (24; 25). Even with the advent of real-time CGM, patients do not awaken to over 70% of nocturnal alarms (26). Studies have demonstrated that using a CGM device with a hypoglycemic prediction algorithm to suspend basal insulin delivery when hypoglycemia is predicted is both safe and effective (27-29). The suspension of insulin delivery when glucose is declining to prevent hypoglycemia was one of the first steps towards the development of an artificial pancreas. The first PLGS system was the Medtronic 640G which received approval outside of the US in 2015 after results showed the device to be safe and effective in reducing hypoglycemia (30). The first large RCT of the PLGS algorithm that was ultimately implemented in the Tandem Basal-IQ pump, published in 2013, showed a reduction in overnight hypoglycemia of about 50% (27). The Tandem Basal-IQ PLGS system, planned for this proposed study, received FDA approval in 2018 following results of a pivotal trial showing significant reduction in hypoglycemia with PLGS use (see Section 1.7 Preliminary Results).

1.1.3 Hybrid Closed Loop Systems

Hybrid closed loop (HCL) systems are a further step towards reducing the burden of diabetes management through the development of an artificial pancreas. These systems are classified as "hybrid" due to the fact that users still need to bolus for carbohydrate intake; however, basal insulin delivery is modulated without user input based on sensor glucose readings. Specifically, the various systems decrease insulin delivery when a patient's sensor glucose is predicted to be low and increase insulin delivery when a patient's sensor glucose is predicted to be high. Several years of HCL studies conducted for short durations with intense remote monitoring and study staff support for enrolled patients led to the first pivotal trial of the Medtronic 670 G system. This system was the first to be approved in the US in September 2016 following the single arm

clinical trial conducted in 2015/2016. This study enrolled 124 subjects with T1D of which 30 were age 14-21 years and the rest 22-75 years with mean 44 ± 12 years. There were ~ 10 subjects age ≥ 65 years in this study. Time spent < 70 mg/dL was reduced from 90 to 49 minutes in the adult cohort (p<.001) with A1c reduction from 7.3 % to 6.8 % (p<.001) (31). Currently, Medtronic is conducting a study randomizing subjects to 670 G HCL that includes older adults, but it is not focused on hypoglycemia. Subjects being enrolled are up to 80 years old. Another HCL algorithm was developed at Cambridge University and has been tested in a series of studies referred to as APCAM. Results of the at home study of APCAM HCL algorithm were published in Lancet in October 2018 and showed significant improvement in time in range in the HCL group compared with control as well as a reduction in hypoglycemia (% < 70 mg/dL) (32). In 2011, the Diabetes Assistant (DiAs) was developed – a smart-phone multi-use platform designed at the University of Virginia (UVA) to operate in several treatment modes ranging from CGM or insulin pump support to overnight and 24/7 HCL (33). Since its introduction in 2011, DiAs has earned regulatory approvals in the U.S., France, Italy, Netherlands, and Israel; 3 different control algorithms have been implemented on the DiAs platform and used in approximately 20 clinical trials, including long-term studies at home.

The Tandem X2 insulin pump with Control-IQ Technology is a third-generation HCL system retaining the same control algorithm that was initially tested by UVA's DiAs system and then implemented in the inControl system (33-36). The pivotal trial for the Tandem Control-IQ was published in the New England Journal of Medicine in October 2019 (37). This 6-month randomized trial included 168 patients age 14 to 71 years with 112 assigned to use HCL (Tandem Control-IQ) and 56 sensor augmented pump (SAP) therapy. Participants in the HCL group had significant improvements in time in target glucose range of 70 to 180 mg/dL as well as significant reductions in time spent in hypoglycemia (< 70mg/dL and <54mg/dL) and time spent in hyperglycemia (>180mg/dL). The Tandem X2 pump with Control-IQ technology received FDA approval on December 13, 2019.

1.1.4 Quality of Life Outcomes in Automated Insulin Delivery Trials

There is increasing recognition that positive glycemic outcomes with AID systems may not necessarily be indicative of positive user experiences. Thus, it is important to assess psychosocial and QOL impacts of AID systems (18; 19; 38; 39). Early systems were evaluated under artificial conditions (e.g., diabetes camp, inpatient or supervised hotel), in very small samples and for relatively short durations (typically under 1 week), making evaluation of QOL impacts difficult. Nonetheless, AID systems do appear to be associated with a generally positive user experience (40), including reduced diabetes management distress and improved attitudes towards diabetes technology (41). However, significant barriers have also been identified, including variable trust in the system, physical bulk, technical glitches and incorporation in daily life (40). As a result, it is possible that many patients may prefer a PLGS-only AID system compared with an HCL system. While our understanding of patient expectations of and experiences with AID systems is increasing, there continues to be very little data, especially with prolonged outpatient use (18). This is particularly true for the older adult population, as there is no available published data on the user experience and QOL impacts of AID in older adults.

1.2 Rationale

Automated insulin delivery (AID) technologies hold the promise of optimizing glycemic control and reducing the burden of diabetes care for patients with Type 1 Diabetes (T1D). However, clinical trials of lower burden AID technologies have not included older adults in sufficient numbers to allow for focused evaluation of efficacy and quality of life (QOL) impacts that may differ from those observed in younger age groups. Most notably, primary endpoints have focused on reducing hyperglycemia, while avoidance of hypoglycemia is of upmost concern for older adults with T1D. T1D Exchange clinic registry data have shown severe hypoglycemia (SH) occurs more commonly in older adults with longstanding T1D than in younger individuals with events occurring just as often with HbA1c levels >8.0% as with HbA1c levels <7.0%. These data do not support the strategy of "raising the HbA1c" as being an effective approach for hypoglycemia prevention in older adults with T1D. In addition to acutely altered mental status, hypoglycemia is associated with an increased risk for falls leading to fractures, car accidents, emergency room (ER) visits, hospitalizations, and mortality resulting in substantial societal costs. The occurrence of hypoglycemia, hypoglycemia unawareness and fear of hypoglycemia have adverse effects on overall QOL of both individuals with T1D and their families.

While continuous glucose monitoring (CGM) technology alone has been shown to be beneficial in reducing hypoglycemia in older patients, our data from the Wireless Innovations for Seniors with Diabetes Mellitus (WISDM) trial shows a majority of patients still have frequent hypoglycemia even when using CGM (42). Thus, knowledge of CGM alone may not be sufficient to avoid hypoglycemia in this population. Predictive low-glucose suspend algorithms have particular promise when the primary goal is hypoglycemia avoidance rather than glucose reduction. Whether the added complexity of closed loop systems provides additional glycemic benefit is not known. There is a *critical need* to determine whether automated insulin delivery can reduce hypoglycemia in the older adult population with T1D.

1.3 Potential Risks and Benefits

1.3.1 Known Potential Risks

Fingerstick Risks

A fingerstick will be performed for measuring HbA1c. This is a standard method used to obtain blood for routine blood glucose monitoring. Pain may occur at the time of lancing, but is less likely in patients with T1D who are used to frequent blood glucose monitoring. 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.

Venipuncture Risks

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.

Subcutaneous Catheter Risks (CGM and Insulin Pump)
There is a low risk for developing a local skin infection at the site of the sensor or infusion catheter placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies. Sensors may fracture in situ on rare occasions. In the rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation and allow the body to expel the foreign body on its own.

Risk of Hypoglycemia
As with any person having type 1 diabetes and using insulin, there is always a risk for experiencing low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery. Participants will be instructed to always check sensor readings with a self-monitored blood glucose measurement (fingerstick) if the sensor readings appear out of the expected range.

Risk of Hyperglycemia
Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery. Again, this risk is exceedingly low. As above, participants will be instructed to always check sensor readings with a self-monitored blood glucose measurement (fingerstick) if the sensor readings appear out of the expected range.

Risks of Questionnaires
As part of the study, participants will complete psychosocial questionnaires which include questions about their private attitudes, feelings and behavior related to diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon. Patients are reminded that they can refuse to answer questions that they do not wish to answer. Brief cognitive performance assessment will be completed at baseline and at the end of the extension phase. These measures may cause transient anxiety or distress, although the selected measures are commonly encountered in the context of routine medical care for older adults.

Other Risks
There is a possible risk of unsecured communication during the phone or telehealth contacts. In our experience with AP studies, this has not happened.

The study may include other risks that are unknown at this time.

1.3.2 Risk Assessment

Risk will be minimized by having participants be well informed about how to use the study devices and how to avoid hypoglycemia and hyperglycemia. A procedure manual including guidelines for risk management of hypoglycemia and hyperglycemia with each technology will be developed prior to the start of the trial.

The protocol risk assessment for this study has been categorized as minor increase over minimal risk. The Tandem t:slim X2 with Basal IQ technology and the Tandem t:slim X2 with Control IQ technology are FDA approved.

An investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is not required to conduct this study in the US. For these reasons, this study is being considered a non-significant risk device study.

1.3.3 Known Potential Benefits

It is expected that CGM has an important role in the management of diabetes in older adults with T1D. It is hoped that the HCL or PLGS technologies will reduce hypoglycemia more than just CGM alone. Therefore, the results of this study are likely to be beneficial for older patients with diabetes.

It is possible that participants will not directly benefit from being a part of this study. However, it is also possible that the glucose information from the CGM and automated suspension of insulin delivery will provide a direct benefit.

1.4 General Considerations

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

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

1.5 Virtual Visits

Due to the highly vulnerable nature of this patient population in relation to the COVID-19 virus, there is the option of virtual visit completion for certain visits. Virtual visits will take place using the institution's approved software for telehealth/telemedicine or via phone call when video is not possible. The procedures for virtual study visits that cannot be done virtually (such as height, weight and blood pressure) will be missing. Height, weight and blood pressure during follow-up is not considered to be key data but will be obtained when possible for exploratory analysis. Weight from baseline data collection may be used for calculation of total daily insulin.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of at least 90 participants completing the crossover trial. A maximum of 150 individuals may be enrolled in the study in order to achieve this goal. It is expected that about 40 participants may be excluded based on eligibility criteria during the screening/run-in period. Participants who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the randomization goal has been reached.

Study participants will be recruited from 3 to 5 clinical centers in the United States of America. All eligible participants will be included without regard to gender, race, or ethnicity.

The recruitment goal for each site is the same (approximately 30 participants per site); however, certain sites may recruit additional participants to meet the overall recruitment goal. Each site will aim to have at least 33% of their enrolled participants not currently using CGM, at least 33% using multiple daily injections and at least 33% using insulin pump at the time of enrollment. Across all sites the study will aim to enroll approximately 30% of participants with mild to moderate cognitive impairment.

2.1.1 Informed Consent and Authorization Procedures

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

The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. 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.

Participants who lack capacity, such that they would require the use of a legally authorized representative, shall not be enrolled in this study due to the level of self-management required by the participants including device set-up and use and questionnaire completion.

A consent understanding assessment consisting of 5 true/false questions about content in the consent will be given to the participant to confirm understanding of the informed consent and study procedures. Patients who do not answer 4 out of 5 questions correctly will have the consent form reviewed with them again and will repeat the understanding assessment. Patients who are not able to successfully complete the understanding assessment after two attempts will not sign consent and not be enrolled in the study.

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

A participant is considered enrolled when the informed consent form has been signed. A copy of the informed consent form will be provided to the participant and another copy will be added to the participant's study record.

As an option, study staff can orally present the consent to potential participants over the phone rather in person due to the highly vulnerable nature of this patient population in relation to the COVID-19 virus. The procedures for administration are described in the study procedures manual.

2.2 Participant Inclusion Criteria

Individuals must meet all the following inclusion criteria in order to be eligible to participate in the study.

1) Clinical diagnosis of type 1 diabetes
2) Age ≥ 65 years old
3) T1D Duration of at least 1 year
4) HbA1c < 10.0% from point of care or local lab within the past 6 months
5) Insulin regimen involves basal/bolus insulin via insulin pump or multiple daily injections
6) Most recent GFR ≥ 30 ml/min/m^2 from local lab within the past 6 months
7) Willingness to use a rapid acting insulin compatible with the Tandem t:slim X2 pump (currently aspart and lispro; other rapid acting insulins likely to be approved for pump use prior to study initiation such as Fiasp)
8) Familiarity with and willingness to use a carbohydrate ratio for meal boluses
9) Willing to use study devices and automated insulin delivery features
10) Ability to download study devices at home or if not able to download at home willing to come into clinic to bring devices for download of data at visits and as needed for safety
11) Participant is independently managing his/her diabetes with respect to insulin administration and glucose monitoring *(may include assistance from spouse or other caregiver)*
12) Participant understands the study protocol, agrees to comply with it and is able to successfully pass the consent understanding assessment with no more than 2 attempts.
13) Participant comprehends written and spoken English
14) At least 240 hours of CGM readings available during the end of run-in assessment
15) At least 1.5% of time with CGM glucose levels < 70 mg/dL prior to SAP initiation
16) Activeprescription for glucagon and willing and able to have glucagon available

2.3 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1) Use of PLGS technology or HCL insulin delivery in the past 1 month
2) History of 1 or more Diabetic Ketoacidosis episodes in the previous 6 months

3) Clinical diagnosis by a primary care provider, neurologist or psychiatrist of dementia, in the investigator's opinion a suspected severe cognitive impairment such that it would preclude ability to understand the study or use devices, or a score of 6 or less out of 15 on the 5 min MoCA (5-min T MoCA Version 2.1) (mild cognitive impairment is not an exclusion)
4) A condition, which in the opinion of the investigator or designee, would put the participant or study at risk, including severe vision or hearing impairment and any contraindication to the use of any of the study devices per FDA labeling
5) Known adhesive allergy or skin reaction during the run-in pre-randomization phase or previous difficulty with pump and CGM insertions that would preclude participation in the randomized trial
6) Concurrent use of any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas)
7) Stage 4 or 5 renal disease
8) The presence of a significant medical or psychiatric condition or use of a medication that in the judgment of the investigator may affect completion of any aspect of the protocol, or is likely to be associated with life expectancy of <1 year

2.4 Screening Procedures

After the informed consent or short form has been fully signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel (when possible) and local laboratory testing if needed to screen for exclusionary medical conditions. The screening visit should take place within 30 days of obtaining informed consent. A local HbA1c measurement will be obtained if not already obtained as part of usual care within the prior 6 months of the screening visit. A serum creatinine for estimation for GFR will be obtained if one is not available within the previous 6-months. The 5-min MoCA should be completed prior to performing any other screening procedures to confirm eligibility.

2.4.1 Data Collection and Testing

The following procedures will be performed/data collected/eligibility criteria checked and documented:

- Inclusion and exclusion criteria assessed
- Demographics (socioeconomic status, date of birth, sex, race and ethnicity)
- Contact information (retained at the site and not entered into study database)
- Medical history
- Diabetes history
- Concomitant medications
- Fingerstick or blood draw for:

- HbA1c level measured using a point-of-care device or local lab will be used to assess eligibility unless a historical value is available within 6 months of enrollment
- GFR if not available in medical record in previous 6 months

- Testing and Assessments will include the following:
  - 5-min T MoCA – perform as first screening procedure
  - Hypoglycemic Awareness
  - Patient Reported Outcome Questionnaires completed online (or paper if online not possible); May be completed at time of screening visit or any time at home prior to randomization.
    - Functional Activities Questionnaire
    - Hypoglycemia Fear Survey (HFS-II)
    - Hypoglycemia Confidence Scale
    - T1D Diabetes Distress Scale (DDS)
    - Prospective Retrospective Memory
    - Barkley Deficits in Executive Function Scale (BDEFS)

Screening procedures will last approximately 1-2 hours.

2.5 Screen Failures

Participants determined to be ineligible during screening visit, with lab values out of range (HbA1c or GFR if done at screening visit) or who score a 6 or less on the 5-min T MoCA will be withdrawn from the study.
Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

2.6 Eligible Participants

Individuals who meet eligibility criteria will proceed to the Run-In Phase.

Chapter 3: Run-in Training Phase

3.1 Introduction

There are four parts of the run-in phase:

1) Start of Run-In – takes place on same day as screening or within 14 days
2) CGM Training Period – consists of a training visit and repeat training as needed
3) SAP Training Period – consists of SAP initiation visit and contacts with additional visits for training as needed
    a. If the participant is a CGM user the screening, start of run-in and SAP initiation visits can take place on the same day if able to be in clinic to complete all procedures
4) SAP Evaluation – use of devices will be evaluated prior to initiating cross-over trial. May be repeated if additional training needed.

The length of the run-in phases may vary depending on prior experience with devices. 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 below.

Table 3. CGM and SAP Training Periods Criteria

	CGM Use (Real-time CGM only, does not include flash monitoring)	**Use of Tandem t:slim X2 pump**	**CGM Training Period:10-30 days (Includes 10-day CGM training visit and re-training as needed)**	**SAP Training Period: 14-28 days (Includes SAP initiation visit and training phone calls with additional training as needed)**	**SAP Evaluation (Repeated if additional SAP training needed)**
Device Use	YES	YES	Skip per investigator's discretion	Required	Required
	YES	NO	Skip per investigator's discretion	Required	Required
	NO	YES	Required	Required	Required
	NO	NO	Required	Required	Required

3.2 Start of Run-In Visit (Same day as screening or within 14 days) (virtual or in-clinic)

3.2.1 Participants using CGM at Screening

- If the CGM device is able to be downloaded study personnel will assess whether the participant has at least 1.5% of sensor glucose values <70 mg/dL (average of ~30 minutes per day).
    - **Participants with < 1.5% of time spent with glucose levels < 70 mg/dL will be excluded in order to ensure all participants have the possibility to reduce hypoglycemia during the intervention periods.**
- The study Dexcom G6 CGM will be given to the participant and they will receive training on the study device similar to what is described below for those not using CGM.
- Participant will proceed to SAP initiation visit (see section 3.4) which may take place on same day if screening/start of run-in visit is in-clinic or within 14-days.

3.2.2 Participants not using CGM at screening/start of run-in

- Participants will initiate using the study CGM and will receive initial training on its use.
- Standardized CGM training will be provided using a training checklist and training materials will be provided to study participants. The study team will assist the participant with sensor insertion and calibration (as needed). Each participant will be asked to use a CGM sensor on a daily basis, inserting a new sensor as needed. Participants will be instructed to use the sensor according to FDA labeling. In addition, participants will be provided guidelines for when to confirm the CGM reading with a home BGM value including when hypo/hyperglycemia symptoms are discrepant from the CGM reading or if there are other reasons to doubt the CGM reading.
- A second CGM training visit will occur in approximately 10 days and may be repeated if additional training needed prior to proceeding with SAP initiation.

3.3 CGM Training Visit (virtual or in-clinic)

- Additional CGM training will take place using standardized materials.
- A skin assessment (via virtual video when possible) will be made where sensors were worn to be sure that the participant tolerates the sensor well enough to enter the randomized trial.
- The participant will be provided with additional sensors to wear at home for up to 20 days
- Next visit is the SAP Initiation Visit

3.4 SAP Initiation Visit (Required In-clinic Visit)

- Participants who haven't been evaluated for minimum hypoglycemia requirement (non-CGM users at start of run-in) will be evaluated at the beginning of this visit. Study personnel will assess whether the participant has at least 1.5% of sensor glucose values <70 mg/dL (average of ~30 minutes per day).

    - **Participants with < 1.5% of time spent with glucose levels < 70 mg/dL will be excluded in order to ensure all participants have the possibility to reduce hypoglycemia during the intervention periods.**
- Participants will be provided with the Tandem t:slim X2 Basal-IQ study pump integrated with the study Dexcom G6 CGM with Basal-IQ feature turned OFF
- Participants will be provided the Abbott Precision Xtra Meter and blood ketone strips to measure blood ketone levels as indicated.
    - Participants will be instructed on how to perform blood ketone testing per manufacturer guidelines.
    - Participants will be given a handout outlining when to check ketones and treatment action plan for elevated blood ketones.
- Standardized device training will be provided using a training checklist and training materials will be provided to study participants.
    - For participants currently on insulin pump therapy, the Tandem SAP will be programmed so that basal insulin delivery and other settings match the participant's personal pump settings. If appropriate, the pump settings will be optimized based on study investigator review of downloaded SAP data.
    - 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 procedure manual.
    - Further adjustments to total daily dose and intraday basal rate profile may be made during the course of the SAP Training Period.
    - Participants will be provided with a study account for t:connect and trained on how to upload the devices.
- A standard physical exam will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant).
    - Can be performed by clinic staff:
        - Weight, height
        - Vital signs including measurement of blood pressure and pulse
- A blood draw for measurement of central lab HbA1c and C-peptide will be performed.
- Frailty assessment using 10-foot timed walk
- Cognitive Assessment (See Chapter 8)
- Participants will be contacted 1 (±1 day) and 7 (±3 days) days following initiation of SAP.
- A SAP Evaluation Visit will occur 14 -21 days following initiation of SAP
    - The SAP training contacts and SAP evaluation visit may be repeated if needed for additional training on study devices prior to initiating cross-over trial

3.5 SAP Evaluation Visit (virtual or in-clinic)

- The CGM data will be downloaded to assess whether the participant has at least 240 hours of sensor data during the run-in.
    - Participants not meeting the CGM compliance requirement may be given a second opportunity to be evaluated.

    - Participants who are unable to meet the CGM usage requirements after the second opportunity will be dropped from the study and not enter the randomized trial.
- Participants needing additional training should receive training at the SAP Evaluation visit and then repeat the SAP run-in period with a contact 7 days later and SAP Evaluation Repeat Visit in ~ 14 days

3.6 Device Data Uploads

Device data will be downloaded at each visit. Participants will be trained on how to upload devices from home. Participants who are unable to download devices from home will need to come to clinic to have device downloaded at study visits/contacts or as needed for safety reasons.

Chapter 4: Randomization & Start of Period 1 Visit

Once a study participant is randomized, that participant will be counted regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible and willing to follow the study period order and comply with each treatment arm.

4.1 Randomization

- Randomization on the study website will take place after the SAP Evaluation visit and may occur on the same day or within 7 days.
- Eligibility criteria from screening will be reviewed again and if the participant is no longer eligible based on these criteria, the participant will be dropped from the study prior to randomization.
- ***Investigators will be responsible for signing off on all CRFs and edits that occurred prior to randomization BEFORE the randomization form is submitted***.

The main phase of the study, a 36-week randomized crossover trial, will consist of three 12-week periods. The three treatment periods consist of HCL, PLGS and SAP.

Participant randomization assignment is determined after the Randomization Prompt is submitted on the study website. The data from this visit and where applicable, prior visits, are assessed to verify eligibility prior to the randomization process being completed.

Following confirmation of eligibility and successful completion of run-in participants will be randomly assigned with equal probability (stratified by clinical site) to one of the following treatment period orders:

(A) HCL in period 1, PLGS in period 2, SAP in period 3

(B) HCL in period 1, SAP in period 2, PLGS in period 3

(C) PLGS in period 1, HCL in period 2, SAP in period 3

(D) PLGS in period 1, SAP in period 2, HCL in period 3

(E) SAP in period 1, HCL in period 2, PLGS in period 3

(F) SAP in period 1, PLGS in period 2, HCL in period 3

The following devices will be used for each period:

- During the HCL period participants will use the Tandem t:slim X2 pump with Control IQ
- During the PLGS period participants will use the Tandem t:slim X2 pump with Basal IQ
- During the SAP period participants will use the Tandem t:slim X2 pump with Basal IQ feature turned OFF

4.2 Start of Period 1

The Start of Period 1 visit should take place on same day as randomization.

Chapter 5: Crossover Trial

5.1 Start of Period Visit

The Start of Period 1 visit should take place on same day as randomization. The Start of Period 2 and Period 3 visits should take place on same day as End of Period visit for previous period. See windows in 5.1.2.

5.1.1 HCL or PLGS System Training

Potential participants will be encouraged to involve a significant other in their care/training or invite anyone who is currently involved in their diabetes care. The participant and partner/caregiver (if warranted) will be trained by qualified staff on user interface, alarms, meal blousing, and exercise using standardize training materials and checklists. Training on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon also will be provided following standard clinic practices.

Participants will be provided with a handout summarizing tips and guidelines for use of the devices and safety measures.

Study team members will train the participant and care partner on specific tasks including the following:

- The study team will confirm the pump and sensor parameters entered in the system
- CGM calibration instructions (as needed)
- Meal bolus procedures
- What to do when exercising while using the system
- The participant and care partner will be assessed for understanding how to react to safety/alert notifications
- Device data upload instructions
- Participants will be reminded to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device
- Participants will be instructed when to contact study staff and provided with contact information to ask any questions they may have during the study

Study staff will discuss the visit schedule with the participant and will make arrangements with the participant for each visit. If the participant cannot be reached, the participant's other contact methods will be utilized. Participants will be trained on how to upload devices to be able to do this from home for study contacts and virtual visits. Participants who are not able to upload device data from home will need to come to the clinic for the device download for each visit and as needed for safety reasons.

5.1.2 Study Visits and Contacts for Periods 1, 2 and 3

During each period a virtual or in-clinic visit will occur at 4 weeks with an end of period/start of new period virtual or in-clinic visits occurring at 12 weeks. Study contacts (via phone or telehealth) will occur at 2 and 8 weeks. The study contacts and visits may be completed remotely (phone call or virtual visit) or in person at participant, investigator and study coordinator

discretion. Virtual visits will take place using the institution's approved software for telehealth/telemedicine when possible or by phone if video not feasible. Additional contacts or visits may occur as needed:

Visit	Target Day/Week	Target Window (around Target Day/Week)	Allowable Window (around Target Day/Week)
Start of Period (1, 2, 3)	Randomization or End of Previous Period	N/A	+ 7 days
2-week contact	Randomization Visit Date + 14 days or End of Previous Period Date + 14 days	±4 days	± 7 days
4-week visit	Randomization Visit Date + 28 days or End of Previous Period Date + 28 days	± 7 days	± 14 days
8-week contact	Randomization Visit Date + 56 days or End of Previous Period Date + 56 days	± 7 days	± 21 days
End of Period 1, 2, 3 12-week visit	Randomization Visit Date + 84 days or End of Previous Period Date + 84 days	± 7 days	± 21 days

The goal will be for all participants to complete all scheduled visits. However, participants who (because of unforeseen circumstances) are unable or unwilling to return for all follow-up visits will be permitted to return for key visits only as an alternative to withdrawal from the study. When a participant is placed into this status, missed visits will not be recorded as protocol deviations (since they would not be recorded as protocol deviations if the participant was dropped from the study).

5.1.3 Procedures during Study Periods

5.1.3.1 Procedures Performed during Each Contact and 4-week period visits

- The participant will be asked to upload device data for study staff review (participants not able to upload may be asked to come to the study clinic for a device download)
- Assessment of compliance with study device use
- Answer questions about using the system
- Assessment of adverse events, adverse device effects, and device issues
- Review of glycemic control

5.1.3.2 Procedures Performed during Each End of Study Period Follow-up Visit

Procedures listed below should be completed at the end of Periods 1, 2 and 3 (prior to start of next period):

- Assessment of compliance with study device use

- Retraining on system use as needed
- Assessment of adverse events, adverse device effects, and device issues
- Download of system data
- Capillary or venous collection of a blood sample to send to the central laboratory for HbA1c determination (completed in-clinic or at home for virtual visits)
    - Clinical site will provide at home HbA1c kits to participants
- Assessment of hypoglycemia unawareness
- Completion of Questionnaires -electronically or on paper if needed
    - Hypoglycemia Fear Survey (HFS-II)
    - Hypoglycemia Confidence Scale
    - T1D Diabetes Distress Scale (DDS)
    - System Usability Scale
    - AIDE Technology Acceptance

Following the completion of the end of period visit procedures, participants will be trained on the PLGS or HCL user interface if initiating during the next study period as part of the Start of Period visit.

5.1.3.3 Device Data Uploads During the Crossover Trial

Device data will be downloaded during each follow-up visit. Participants will upload devices from home for study contacts and virtual visits. Participants without access to a computer or who in the study staff opinion would struggle with the upload of the device may need to come to the clinic for the study contacts and virtual visits to have devices downloaded.

5.1.4 Early Termination Visit

If a participant discontinues the study early, an attempt will be made to have the participant complete an end of study visit to record any adverse events or device issues that have occurred, complete final questionnaires, and collect a final HbA1c. Study devices should be returned to the clinic.

Every effort will be made to keep all participants in the trial through each 12-week period. Participants who discontinue device use or initiate non-study treatment will be encouraged to remain in the study.

5.1.5 Unscheduled Visits

An Unscheduled Visit Form will be completed for any contact or visit the participant has with the site for significant protocol-related issues/questions outside the visit and contact schedule.

Chapter 6: Extension Study

6.1 Study Procedures During the Extension Study

Following the completion of the last study period, participants will enter a 3-month extension phase where they will be given the opportunity to choose to use either HCL, PLGS or SAP. Participants will be asked to choose their preferred technology at the start of the extension phase and will be permitted to change the technology being used at any time during the 3-month period.

6.1.1 End of Study Visit (Required In-clinic Visit)

At the end of the 3-month period, an end of study visit will occur.

Procedures listed below will be completed at the end of study visit:

- Venous or capillary collection of a blood sample to send to the central laboratory for HbA1c determination
- Download of system data
- Assessment of hypoglycemia unawareness
- Completion of Patient Reported Outcome Questionnaires
    - Hypoglycemia Fear Survey (HFS-II)
    - Hypoglycemia Confidence Scale
    - T1D Diabetes Distress Scale (DDS)
    - System Usability Scale
    - AIDE Technology Acceptance
    - Functional Activities Questionnaire
    - Prospective Retrospective Memory
    - Barkley Deficits in Executive Function Scale (BDEFS)
- Completion of cognitive assessments
- Assessment of adverse events, adverse device effects, and device issues

Additional unscheduled visits and contacts can be made.

Chapter 7: Study Devices and Safety

7.1 Description of the Study Devices

7.1.1 Insulin Pump

The system proposed for use in this study is comprised of a CGM sensor and transmitter along with an insulin pump with user interface (UI) for display of system information.

The insulin pump used in the study is the Tandem t:slim X2 pump, which is an FDA-approved device with no changes to its hardware or firmware components. The SAP/control arm will utilize the Tandem t:slim X2 pump without HCL or PLGS features activated.
The PLGS intervention arm will utilize the Tandem t:slim X2 pump with Basal-IQ Technology.
The HCL intervention arm will utilize the Tandem t:slim X2 with Control-IQ Technology. The tandem t:connect software will be used to obtain device data. Each participant will have a study specific t:connect account created.

7.1.1.1 Tandem t:slim X2 pump with Basal-IQ Technology

The Basal IQ System (PLGS) is able to stop and resume basal insulin delivery automatically in response to predicted or low sensor glucose values, thereby reducing the incidence and duration of hypoglycemic episodes. The pump includes the hypoglycemia minimization strategy that will issue insulin delivery commands. The algorithm looks ahead 30 minutes and suspends insulin when glucose is predicted to drop below 80 mg per dL or if glucose is currently below 70 mg per dL and falling. The system resumes basal insulin delivery once glucose values start to rise and are above 70 mg per dL or 2.5 hours have elapsed. Basal IQ works silently in the background and users can choose whether or not to receive alerts when insulin is suspended/resumed. Users can also choose to resume insulin delivery at any time when insulin is suspended.

7.1.1.2 Tandem t:slim X2 pump with Control-IQ Technology

The Control IQ uses advanced HCL algorithms that modulate insulin to keep CGM glucose within a targeted range, with meal time insulin boluses delivered by the user. The system components include the t:slim X2 with integrated Control-IQ Technology and the Dexcom CGM G6. During wakeful hours, Control-IQ modulates insulin to maintain CGM glucose within 112.5 to 160 mg/dL. While asleep, the targeted CGM glucose range is 112.5 to 120 mg/dL. During exercise, Control-IQ modulates insulin to maintain CGM glucose within 140 mg/dL to 160 mg/dL.

Control IQ uses the following algorithm:

- Insulin is decreased when a CGM reading of ≤ 112.5 mg/dL is predicted 30 minutes in the future. (≤ 140 mg/dL with exercise).
- Insulin is set to 0 units/hour when a CGM reading ≤ 70 mg/dL (≤ 80 mg/dL during exercise) is predicted 30 minutes in the future.
- Insulin is increased when a CGM reading of ≥ 160 mg/dL (awake), ≥ 120 mg/dL (asleep), or >160 mg/dL (exercise) is predicted 30 minutes in the future.
- Correction boluses (60% of the total correction bolus calculated based on correction factor and CGM reading) are delivered when a CGM reading > 180 mg/dL is predicted 30 minutes in the future.

7.1.2 Continuous Glucose Monitoring

The study CGM is the Dexcom G6. This is an FDA-approved device system with no changes to its hardware or firmware components. The sensor probe is inserted subcutaneously and transmits data every 5 minutes to the pump via the transmitter. The CGM sensor will be replaced in accordance with manufacturer labeling (e.g. at least once every ten days). A study specific Dexcom Clarity account will be created for each participant.

7.1.3 Ketone Meters and Strips

Blood ketone levels will be measured using the Abbott Precision Xtra meter and blood ketone strips as indicated. Blood glucose meter strips for the Precision Xtra device will not be provided.

7.1.4 Study Device Accountability Procedures

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any investigational device used in a research trial. It is expected that all investigational devices or approved devices used outside their approved intended use will be used in the manner intended during the study, that they will be stored under appropriately controlled conditions, and that they will be used by (on) participants who have consented to participate in the research study.

Any investigational device or approved devices used outside their approved intended use in clinical research must be strictly accounted for and will not be shipped to any site unless all of the necessary approvals (e.g. Regulatory, IRB/EC) have been received. This includes keeping records of:

1. Center receipt and inventory management
2. Storage
3. Participant Disbursement
4. Return (by Participants and Center) and/or disposal

During the conduct of the study the investigational center staff will account for and document the device accountability procedures as detailed in the site procedures manual.

7.2 Safety Measures

7.2.1 CGM Calibration

Throughout the study, participants will be instructed to calibrate the study CGM in accordance with manufacturer labelling. The Dexcom G6 does not require calibration with the exception of certain circumstances outlined in the user manual.

7.2.2 Pump System Failure

If the CGM signal becomes unavailable for more than 20 minutes consecutively, Control-IQ or Basal-IQ will not operate to automatically adjust or suspend insulin. If the CGM is not connected, the system will revert to usual function of the pump and deliver insulin with the insulin dosing parameters programmed in the system for that individual. Resumption of each algorithm will occur automatically once CGM signal is available again. Participants will be instructed to keep the alarms for CGM data loss turned on whenever possible.

If the study system is unable to activate Control-IQ for any reason, the pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the user.

If the t:slim X2 detects a system error that does not allow the pump to operate, the Malfunction Alarm will display and the participant will be instructed to contact the study team.

7.2.3 Hypoglycemia Threshold Alarm and Safety Protocol

During the course of the study, participants will be permitted to change the CGM low glucose threshold alert setting on their device or mobile app, but will be instructed to choose a value no less than 70 mg/dL. The severe low alert in the Dexcom software is set to < 55 mg/dl and cannot be turned off. If the participant receives a predictive Low Alert or low alert, a message appears on the user interface (UI) that is accompanied by vibration followed by vibrations and/or sound if not acknowledged by the user in 5 minutes. This alert remains on the screen until acknowledged by the user.

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 recommended and the participant will be instructed to treat hypoglycemia with ~16 grams of fast-acting oral glucose.

The t:slim X2 with Control-IQ will suspend insulin when the system predicts BG < 70mg/dL within 30 minutes or if in exercise mode < 80mg/dL within 30 minutes. The t:slim X2 with Basal-IQ will suspend insulin when the system predicts BG <80 mg/dL within the next 30 minutes or passes a threshold of < 70 mg/dL.

7.2.4 Hyperglycemia Threshold Alarm and Safety Protocol

During the course of the study, participants will be permitted to change the CGM high glucose threshold alert setting on their device or mobile app but will be instructed to choose a value no greater than 300 mg/dL. This feature is common for the SAP and PLGS treatment arms.
The t:slim X2 with Control-IQ system will issue a predictive hyperglycemia alert (Control-IQ High Alert) when the system has increased insulin delivery, but detects a CGM value above 200 mg/dL and does not predict the value will decrease in the next 30 minutes.

If the participant receives a Control-IQ High Alert, a message appears on the UI that is accompanied by vibration followed by vibrations and/or sound if not acknowledged by the user in 5 minutes. This alert remains on the screen until acknowledged by the user. The user is prompted to check the site for occlusion and test blood glucose.

If a participant's CGM reading is >300 mg/dL for over 2 hours or ≥400 mg/dL at any point, the participant will be instructed to take the following steps:

- Perform a blood glucose meter check.
- If the blood glucose is >300 mg/dL, participants will be encouraged to perform ketone testing using their study ketone meter
- If the ketone level is >0.6 mmol/L, take correction insulin, change insulin (pump) infusion site and contact study staff.
- During the Control-IQ period, if a participant administers correction insulin via insulin syringe, participants will be instructed to turn Control-IQ off for approximately four hours.

7.3 Participant Access to Study Device at Study Closure

Participants who complete the study will return the study pump and may be able to keep the other supplies assuming they are functioning at the end of the study.

7.4 Cognitive Assessment after SAE Occurrence

Following the occurrence of an SAE, participants will be administered the 5-min MoCA at the earliest reasonable opportunity following recovering of the event to ensure the participant is not cognitively impaired to a level that may impact the safety of using study devices. The same criteria for baseline eligibility of major cognitive impairment will be used to determine if continuing to use study device is a safety concern. Investigators may refer a study participant with evidence of major cognitive impairment for services in accordance with their practice standards.

Chapter 8: Testing Procedures and Questionnaires

8.1 Testing Procedures

- HbA1c:
  - Performed locally at the Screening visit. This may be done within 6 months prior to enrollment.
  - Collected via blood draw for central lab analysis at SAP Initiation, at the end of each period and at the end of extension phase. Final HbA1c may also be collected for participants who withdraw from the study.

- C-peptide:
  - Collected via blood draw at SAP Initiation and stored for central lab analysis.

- Frailty 10-foot walk:
  - Performed locally at the SAP Initiation visit.
  - This test will measure the time it takes for a participant to walk 10 feet, to obtain an estimate of frailty. Administration time is approximately 10 minutes (43).

- Brief Cognitive Screening
  - 5-min T Montreal Cognitive Assessment (MoCA)(44): Must be completed as the first screening visit procedure either over the phone or in person in order to exclude those with severe cognitive impairment and after an SAE occurrence to ensure the participant is not cognitively impaired to a level that may impact safety of using study devices. There are 15 total points: Verbal fluency (4), delayed recall (5) and orientation (6). Participants who obtain a total score of 6 or less will be withdrawn from the study. Investigators may refer a study participant for services in accordance with their practice standards.

- Cognitive Measures
  - Performed locally at the SAP Initiation visit and at the end of extension phase. Measured for cohort description, sub group analysis, and prediction of system preference during extension phase. Each measure is described briefly below. The procedures for administration are described in the study procedures manual.
    - Total score = 30. The Montreal Cognitive Assessment (MoCA); (45) – Performance-based assessment of general mental status consisting of several short tasks (executive function, visual spatial skills, naming, attention, language, verbal memory and orientation).
    - WAIS-IV Digit Symbol Coding Test (46)– Performance-based assessment of psychomotor processing speed. Using a key, participants copy symbols that are paired with numbers. Total score is the number correctly completed within a 120 second time limit.

- WAIS-IV Symbol Search Test (46)- Performance-based assessment of visual processing speed. Participants scan a search group and indicate whether one of the symbols in the target group matches. Total score is the number correctly completed, minus the number of errors, within a 120 second time limit.

Local laboratory testing will be performed if needed to screen for exclusionary medical conditions.

8.2 Questionnaires

Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

1. **Diabetes Distress Scale (DDS)(48)**

   The DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes. Completed at baseline, end of each period and end of extension phase.

2. **Hypoglycemia Fear Survey (HFS)(48)**

   The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 33 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that measures anxiety and fear surrounding hypoglycemia. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes. Completed at baseline, end of each period and end of extension phase.

3. **Hypoglycemia Confidence Scale (HCS)(49)**

   The HCS (20) is a 9-item self-report scale that examines the degree to which people with diabetes feel able, secure, and comfortable regarding their ability to stay safe from hypoglycemic-related problems. It has been validated for use in adults with type 1 diabetes and insulin-using type 2 diabetes. Administration time is approximately 5 minutes. Completed at baseline, end of each period and end of extension phase.

4. **System Usability Scale (50)**

   A 10-item questionnaire that measures the overall usability of a system. It is a valid and reliable measure of the perceived usability of a system and is technology-agnostic. Administered at the end of each period only.

5. **AIDE Technology Acceptance Questionnaire Post Device (51)**

This diabetes technology specific questionnaire based on the Technology Acceptance Model, assesses perceived system usefulness, ease of use and trust in the system. Administered at the end of each period only

6. **Prospective and Retrospective Memory Questionnaire (52)**

Self-report measure containing items asking participants how often they have difficulty remembering to do things in the future, as well as forgetting past events in their daily lives. Completed at baseline and end of extension phase.

7. **Barkley Deficits in Executive Function Scale (53)**

Self-report measure containing items asking participants how often they have difficulty with planning, problem solving, impulsivity, and inattention in their daily lives. Completed at baseline and end of extension phase.

8. **Functional Activities Questionnaire (54)**

Self-report measure of instrumental activities of daily living. Completed at baseline and end of extension phase.

Chapter 9: Adverse Events, Device Issues and Stopping Rules

9.1 Adverse Events

9.1.1 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.

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, unless excluded from reporting as defined in section 8.2).

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.

9.1.2 Reportable Adverse Events

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

1. An SAE

2. An ADE as defined in section 9.1.1, unless excluded from reporting in section 9.2
3. An AE as defined in 9.1.1 occurring in association with a study procedure
4. An AE as defined in 9.1.1 not related to a device issue which leads to temporary or permanent discontinuation of a study device
5. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
6. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, hyperglycemia or ketosis event meeting the criteria defined below
7. Falls and fractures
8. Emergency room visits

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 adhesive placement are only reportable if severe and/or required treatment.

All reportable AEs—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 AE form online. Each AE form is reviewed by the Medical Monitor to assess safety and to verify the coding and the reporting that is required.

9.1.2.1 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 loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. If blood glucose measurements are not available during such an event, neurological recovery attributable to the restoration of blood glucose to normal is considered sufficient evidence that the event was induced by a low blood glucose concentration.

Severe hypoglycemia events should be considered to be serious adverse events with respect to reporting requirements. When a hypoglycemic event meets the criteria for severe hypoglycemia , a Hypoglycemia Form should be completed in addition to the Adverse Event Form.

9.1.2.2 Hyperglycemic/Ketosis Events

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, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis

- blood ketone level ≥1.0 mmol/L and communication occurred with a health care provider at the time of the event
- blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider

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

Events meeting DKA criteria should be considered to be serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA generally will not be considered as serious adverse events unless one of the SAE criterion in section 9.2.1 is met. When a hyperglycemia/ketosis event meets the criteria for an SAE, a Hyperglycemia/DKA Form should be completed in addition to the Adverse Event Form.

9.1.3 Relationship of Adverse Event to Study Investigational 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. Note that this assessment will be made for the Tandem t:slim X2 with Control-IQ Technology, the Tandem t:slim X2 pump with Basal-IQ Technology (with or without Basal-IQ feature), and the Dexcom CGM.

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

Unrelated: The AE is clearly not related to a study drug/device and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.

Unlikely Related: The AE does not follow a reasonable temporal sequence during or after use of study drug/device and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.

Possibly Related: The AE occurred in a reasonable time during or after use of study drug/device; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study drug/device.

Probably Related: The AE occurred in a reasonable time during or after use of study drug/device; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study drug/device.

Definitely Related: The AE occurred in a reasonable time during or after use of study drug/device; cannot be explained by another factor such as an underlying disease, environmental

or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study drug/device.

Not Assessable: Causality of an adverse event cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

9.1.4 Severity (Intensity) of Adverse Events

The severity (intensity) of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. 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, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.
- SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

9.1.5 Expectedness

For a serious adverse event that is considered possibly related to study device, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in approved labeling.

9.1.6 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor at the Coordinating Center will review all adverse events using a web-based procedure. When a serious adverse event is entered by the site, an email is triggered to prompt immediate review. All other adverse events are reviewed by the Medical Monitor within one week. 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.

9.1.7 Outcome of Adverse Events

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).

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified UADEs will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

9.2 Reportable Device Issues

All UADEs and ADEs as defined in section 9.1.1 will be reported on both a device issue form and AE form, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment.

Device complaints and device malfunctions will be reported except in the following circumstances. These occurrences are expected and will not be reported on a Device Issue Form assuming criteria for a UADE or ADE have not been met:

- Component disconnections
- CGM sensor lasting fewer than the number of expected days per CGM labeling
- CGM tape adherence issues
- Pump infusion set occlusion (including tubing and cartridge) not leading to ketosis ≥0.6 mmol/L or in the absence of checking for blood ketones, blood glucose >350 mg/dL (19.4 mmol/L); and not requiring an intervention other than replacing the tubing and/or cartridge
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.
- 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

9.3 Timing of Event Reporting

SAEs possibly related to a study device or study participation and UADEs must be reported to the Coordinating Center within 24 hours of the site becoming aware of the event. This can occur via phone or email, or by completion of the online serious adverse event form and device issue form if applicable. If the form is not initially completed, it should be competed as soon as possible after there is sufficient information to evaluate the event. All other reportable ADEs and other reportable AEs should be submitted by completion of the online form within 7 days of the site 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 10 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 Coordinating Center.

9.4 Stopping Criteria

9.4.1 Participant Discontinuation of Study Phase

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; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Two distinct episodes of DKA (as defined in section 9.1.2) unrelated to infusion set failure
- Greater than two distinct severe hypoglycemia events as defined in section 9.1.2.1
- Participants who obtain a total score of 6 or less on the 5-min MoCA administered after an SAE occurrence.

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

9.4.2 Criteria for Suspending or Stopping Overall Study

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in Section 9.1.1), 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 review all adverse events and adverse device events that are reported during the study typically on a weekly basis and will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB). 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.

9.5 Independent Safety Oversight

A Data and Safety Monitoring Board (DSMB) will be formed according to NIDDK requirements to review compiled safety data at periodic intervals (typically every 6 months). The DSMB may request to review certain serious adverse events (including UADEs) at the time of occurrence. 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 DSMB review will be documented in a separate DSMB document.

Chapter 10: Miscellaneous Considerations

10.1 Drugs Used as Part of the Protocol

Rapid acting insulins approved for the study pump will be used during the study. Insulins will not be provided by the study.

10.2 Collection of Medical Conditions and Medications

Pre-Existing Condition: Any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the course of the study (e.g., prior myocardial infarction or stroke).

Medical Conditions during the study: In addition to conditions meeting the reporting requirements for an adverse event or device issue as described in Section 9.1 and Section 9.2, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (i.e., not present at the time of enrollment), and (2) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment.

Medications: All medication for the treatment of chronic pre-existing conditions, medical conditions (including medical conditions that do not require recording), and/or adverse events that the participant is currently taking at screening and during the course of the study should be recorded. Nutraceuticals and preventative treatment also should be recorded. Medications only taken as needed either can be recorded when prescribed or only recorded if used during the study. Glucagon prescription will be confirmed as part of eligibility criteria but should only be recorded for treatment of severe hypoglycemia if used during the study.

10.3 Participant Compensation

Participant compensation will be specified in the informed consent form.

10.4 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. An early termination visit may be completed to collect final study data.

If participants wish to discontinue using the study device without withdrawing, participants will be encouraged to remain in the study through the end of study visit.

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

Chapter 11: Statistical Considerations

11.1 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.

11.2 Statistical Hypotheses

A. *Null hypothesis*: There will be no difference in percentage of CGM-measured glucose values <70 mg/dL between PLGS vs SAP.

   Alternate hypothesis: There is a non-zero difference in the percentage of CGM-measured glucose values <70 mg/dL between PLGS vs SAP.

B. *Null hypothesis*: There will be no difference in percentage of CGM-measured glucose values <70 mg/dL between HCL vs. SAP.

   Alternate hypothesis: There is a non-zero difference in the percentage of CGM-measured glucose values <70 mg/dL between HCL vs. SAP.

11.3 Sample Size

Data from the CGM group in the WISDM randomized clinical trial of older adults ≥ 60 years of age were used to estimate the standard deviation and frequency of time <70 mg/dL in the SAP control period. Data from the two weeks prior to the 4 week visit were used to mimic the run-in period in this study where the minimum hypoglycemia eligibility criteria will be assessed. Only WISDM CGM group participants who had ≥2% of time <70 mg/dL at the 4 week time point were included. Data from the two weeks prior to the 26-week visit for these participants were then used to estimate standard deviation and frequency of time <70 mg/dL. N=50 WISDM participants were included of which 28 were injection users and 22 were pump users.

The point estimate for the simple standard deviation was 2.24%. Percent time <70 mg/dL was skewed, so a robust estimate of the mean, 3.14%, was used to calculate the size of a 33% and 50% relative reduction in hypoglycemia.

Since the primary outcome of the study involves two comparisons, the sample size calculations assume an alpha of 0.025 in order to control the overall type 1 error rate at 0.05. In addition, a two-tailed test and 90% power are assumed. We assume the standard deviation is 2.24% in all three periods.

Table 1: Sample Size (Alpha=0.025, Power=90%, SD=2.24%)

Correlation between Periods	Relative Reduction in Hypoglycemia	
	33%	50%
0	119	54
0.3	84	38
0.5	61	28

The Tandem pivotal PLGS study, which was a 3 week period crossover of PLGS and SAP, observed a correlation of about 0.8 between the treatment arms (unpublished data). However,

since the periods in this study are longer, we assume a lower correlation of 0.3 to estimate sample size. A sample size of 84 will give us 90% power to detect a 33% reduction in % time <70 mg/dL. This is increased to 90 to account for 5% loss to follow-up. Loss to follow-up and missing data is expected to be minimal in this population as the retention rate in the WISDM study was 99% at 6 months.

11.4 Outcome Measures

Primary Efficacy Endpoint:

- CGM % time <70 mg/dL

Secondary Efficacy Endpoints:

Hypoglycemia

- CGM % time <54 mg/dL
- Frequency of CGM-measured hypoglycemic events (see definition below)

Glucose Control

- CGM mean glucose
- CGM % time in range 70 to 180 mg/dL
- Coefficient of variation (CV)

Hyperglycemia

- CGM % time >180 mg/dL
- CGM % time >250 mg/dL

HbA1c

- HbA1c

Hypoglycemia Unawareness

- Gold survey(55)

Patient-reported Outcomes

- Hypoglycemia Fear Survey (HFS-II)
  - Total score
  - Worry subscale
- Hypoglycemia confidence
- Diabetes Distress Scale (DDS)
- Technology acceptance
- System usability

Each of the CGM metrics listed will be calculated over 24 hours and separately for daytime and nighttime. Daytime and nighttime versions of CGM % time <70 mg/dL will be considered secondary. All sensor readings excluding the first 4 weeks will be pooled to calculate CGM metrics for that period.

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 15 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.HbA1c and patient-reported outcomes will be collected at baseline and following each 12 week period.

11.5 Analysis Datasets and Sensitivity Analysis

All analysis will follow the intention-to-treat principle with each period analyzed according to the treatment assigned by randomization regardless of actual system utilization. The Intention-to-Treat (ITT) Analysis Dataset will include all randomized participants for any period in which they meet the minimum data requirement (≥168 hours of CGM data after excluding the first 4 weeks for CGM metrics, non-missing for all other outcomes).

The Safety Analysis Dataset will include all enrolled participants, irrespective of whether the participant was randomized or the study was completed.

11.5.1 Per-protocol Analysis

The Per-Protocol Analysis Dataset will include participants for any period in which they meet the following criteria after excluding the first 4 weeks:

- ≥168 hours of CGM data
- CGM use ≥80%
- Control-IQ active ≥80% for the HCL period
- Basal-IQ active ≥80% for the PLGS period
- SAP active (Control-IQ and Basal-IQ not active) ≥80% for the SAP period

A per-protocol analysis will be performed for the primary outcome to provide additional information regarding the magnitude of treatment effect. The per-protocol analysis will only be performed if at least 10% of participants in any period would be excluded by these criteria.

The intent-to-treat analysis is considered primary and if the results of the per-protocol analysis and intent-to-treat analysis differ, the per-protocol analysis will be interpreted with caution.

11.5.2 Other Sensitivity Analysis

Missing Data

It is worth emphasizing that any statistical method for handling missing data makes a number of untestable assumptions. The goal will be to minimize the amount of missing data in this study so that results and conclusions will not be sensitive to which statistical method is used. To that end, sensitivity analyses will be performed to explore whether results are similar for the primary analysis when using different methods. The following methods will be applied:

- Direct likelihood (primary analysis described below)
- Rubin's multiple imputation
- Available cases only

Carryover

A period by treatment interaction will be added to the primary analysis model to assess for the presence of a carryover effect. We do not expect a carryover effect to be present because we

expect the effect of the treatment administered in the prior period to wear off during the first 4 weeks which are not included in the calculation of CGM metrics.

11.6 Analysis of the Primary Efficacy Endpoint

The primary analysis for CGM % time <70 mg/dL will involve two comparisons: PLGS vs. SAP and HCL vs. SAP. Each comparison will be allocated alpha 0.025 to control the family-wise type 1 error at 0.05.

Participants will be included for any period in which they have at least 168 hours of CGM data in the last 8 weeks.

Summary statistics appropriate to the distribution will be calculated for % time <70 mg/dL separately by treatment arm. A repeated measures regression model with an unstructured covariance will be fit including data from baseline and all three treatment periods. The model will adjust for period as a covariate. If residual values from the regression model have a skewed distribution then an appropriate transformation, truncation, or a nonparametric analysis based on ranks will be performed.

There will be no imputation of missing data in the primary analysis. Missing data will be handled by using a direct likelihood approach which will allow participants to be included even if they only have baseline and no follow-up data.

11.7 Analysis of the Secondary Endpoints

11.7.1 Secondary Hypoglycemia CGM Endpoints

Summary statistics appropriate to the distribution will be given by treatment group for the secondary hypoglycemia CGM endpoints (time <54 mg/dL and rate of hypoglycemic events). The primary hypoglycemia endpoint and the secondary hypoglycemia outcomes will be evaluated in a hierarchical approach to control the type 1 error (see the multiple comparisons section below for details). If the endpoint is to be formally compared between treatment groups, analysis will parallel that of the primary outcome.

Separate day and night versions of all three hypoglycemia CGM endpoints will be summarized by treatment group but will only be formally compared between groups in a secondary analysis if the overall version of the endpoint was formally compared and was statistically significant.

11.7.2 Additional CGM Endpoints

Summary statistics appropriate to the distribution will be given by treatment group for time in range 70-180 mg/dL, mean glucose, time >180mg/dL, and time >250 mg/dL. These metrics will be evaluated overall and separately for daytime and nighttime. Analysis will parallel the analysis of the primary endpoint above.

11.7.3 HbA1c

HbA1c will be measured by central lab at baseline and following each 12-week period. Summary statistics appropriate to the distribution for HbA1c will be reported by treatment group. A repeated measures regression model with an unstructured covariance will be fit including the data from baseline and all three treatment periods. The model will adjust for period as a

covariate. If residual values from the regression model have a skewed distribution then an appropriate transformation, truncation, or a nonparametric analysis based on ranks will be performed.

11.7.4 Questionnaires

Summary statistics appropriate to the distribution will be given by treatment group for each patient-reported outcome. Analysis outcomes will parallel the analysis of the primary endpoint described above.

11.8 Safety Analyses

Details of all reportable adverse events will be provided in a listing by treatment group. Pre-randomization adverse events will be listed separately and will not be included in any treatment group comparisons. Each period will inclusively consist of all days in between the treatment initiation visit and the end of treatment visit. If the subject drops out of the study in the middle of a period and the end of treatment visit for that particular period does not occur, then the dropout date will be used as the last day of the period.

For the following outcomes, summary statistics appropriate to the distribution will be tabulated by treatment arm.

- Number of adverse events
- Number of serious adverse events
- Number of unexpected device events
- Number of SH events and SH incidence rate per 100 person-years
- Number of hospitalizations related to a SH event
- Number of ER visits related to a SH event
- Number of fractures related to a SH event
- Number of falls related to a SH event
- Number of DKA events and DKA incidence rate per 100 person-years
- Number of hospitalizations related to a DKA event or severe hyperglycemia
- Number of ER visits related to a DKA event or severe hyperglycemia

If there are enough events for statistical analysis, the SH and DKA incidence rates will be compared between treatment arms using a repeated measures Poisson regression model adjusting for period and whether the subject had an event in the 12 months prior to the study as a covariate. If there are zero events in one treatment arm, Poisson regression will not converge and so the number of events will be compared pairwise using Barnard's test instead.

11.9 Protocol Adherence and Retention

The following will be performed according to treatment arm:

- A flow chart accounting for all participants for all visits
- Tabulation of visit completion rates for each follow-up visit
- Tabulation of protocol deviations

- Tabulation of number and reasons for unscheduled visits and phone calls
- Tabulation of device issues

11.10 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics will be summarized in a table. For continuous variables, summary statistics appropriate to the distribution will be given. For discrete variables, number and percentage will be reported for each category.

11.11 Planned Interim Analyses

No formal interim efficacy analysis is planned for this study. Safety data tabulations will be performed at least every 6 months for review by the Data and Safety Monitoring Board (DSMB).

11.12 Sub-Group Analyses

Subgroup analyses/assessments of effect modification (interaction) will be conducted for the primary outcome. These analyses will be considered exploratory. Additionally, interpretation of the analyses will depend on whether the overall analysis demonstrates a significant treatment group difference; in the absence of such an overall difference, subgroup analyses will be interpreted with caution. The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the models used for the primary analyses.

The baseline factors listed below will be assessed:

- Race/Ethnicity
- Gender
- Baseline % time <70 mg/dL
- Age
- Education
- Employment Status
- Duration of Diabetes
- Hypoglycemia Unawareness
- Cognition
- Functional activities questionnaire
- Frailty
- Prior CGM experience
- Prior Insulin Delivery Method
- Previous history of SH event in past 12 months
- C-peptide

11.13 Exploratory Analyses

All of the primary and secondary outcomes will be compared between PLGS and HCL in an exploratory analysis that parallels the analysis described above. A difference, if any, in the hypoglycemia outcomes between PLGS and HCL is expected to be small, so the power will be low.

11.14 Additional Tabulations and Analysis

Device Use

The percent of time in each system control mode and the percent of time using CGM will be tabulated by treatment arm overall and by 4-week intervals. These tabulations will be repeated separately over 24-hours, daytime, and nighttime. Overall 24-hour CGM use will be compared pairwise between all treatment arms using the same model described for the primary outcome.

In addition, we will tabulate the following for the HCL period overall between treatment initiation and the end of treatment visit and by 4-week intervals:

- Percent of time spent in sleep mode
- Percent of time spent in sleep mode outside of nighttime hours
- Percent of time spent in exercise modes

Insulin

Average total daily insulin per kg, basal insulin per kg, and bolus insulin per kg will be tabulated at baseline and by treatment arm using pump download data. Insulin metrics will be compared pairwise between all treatment arms using the same model described above for the primary outcome.

Pump Alert and Alarms

The number and rate per 24 hours of different alerts and alarms from the Tandem pump will be tabulated by treatment arm.

BMI

Height and weight will be measured at baseline and the end of each period when possible. BMI will be tabulated at baseline by treatment arm.

BG Checks

Average BG checks per day will be tabulated at baseline and by treatment arm.

11.15 Multiple Comparison/Multiplicity

For the primary comparisons of interest, PLGS vs. SAP and HCL vs. SAP, the three CGM-measured hypoglycemia metrics will be evaluated in a hierarchical approach to control the type 1 error at 0.05. Each comparison will be allocated alpha 0.025. The outcomes will be evaluated in the following order:

- % time <70 mg/dL
- % time <54 mg/dL
- Rate of hypoglycemic events

The process moves to the next variable down on the list until a non-significant result ($p \geq 0.025$) is observed, or all outcomes have been tested. If a non-significant result is encountered, then formal statistical hypothesis testing is terminated and any comparisons below on the list are not formally tested. If for either comparison of interest, PLGS vs. SAP or HCL vs. SAP, all three outcomes are rejected at the level of 0.025, the alpha can be recycled and the other comparison can be tested down the hierarchy at an alpha level of 0.05 rather than 0.025.

For all other secondary and exploratory outcomes the false discovery rate will be controlled using the Benjamini-Hochberg procedure adapted using the two-stage test. There will be no adjustment for safety outcomes.

11.16 Extension Phase

Exploratory analysis for the extension phase will be detailed in a separate document.

Chapter 12: Data Collection and Monitoring

12.1 Case Report Forms and Other Data Collection

The main study data are collected on 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. For any data points for which the eCRF is not considered source (e.g. lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.).

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.

12.2 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.

12.3 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, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. 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. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

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
- 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. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.4 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 13: Ethics/Protection of Human Participants

13.1 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.

13.2 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.

13.3 Informed Consent Process

13.3.1 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.

13.3.2 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 and genetic tests 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, regulatory agencies or 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 the reviewing IRB, institutional policies, or sponsor requirements.

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 (JCHR) in Tampa, FL. 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 the JCHR 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 JCHR in Tampa, FL.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

Chapter 14: References

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