Official Title

Home Use of MD-Logic Automated Insulin Delivery System: Safety and Efficacy

Brief Title: Fuzzy Logic Automated Insulin Regulation (FLAIR)

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FLAIR- Fuzzy Logic Automated Insulin Regulation:
A Crossover Study Comparing Two Automated Insulin Delivery System Algorithms (PID vs. PID + Fuzzy Logic) in Individuals with Type 1 Diabetes

IDE Sponsor: Jaeb Center for Health Research

Version Number: v7.1

17 Mar 2020

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List of Abbreviations

ABBREVIATION	DEFINITION
AID	Automated Insulin Delivery
AHCL	Advanced Hybrid Closed-Loop
AP	Artificial Pancreas
ATTD	Advanced Technologies & Treatments for Diabetes
AUC	Area Under the Curve
BG	Blood Glucose
BGM	Blood Glucose Meter
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CLC	Closed-Loop Control
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
ID	Identification
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
NIH	National Institutes of Health
PID	Proportional, Integral, and Derivative
PLGS	Predictive Low Glucose Suspend
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
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
TDI	Total Daily Insulin
UADE	Unanticipated Adverse Device Effect
UI	User Interface

Site Principal Investigator Statement of Compliance

Protocol Title: *FLAIR- Fuzzy Logic Automated Insulin Regulation:* A Crossover Study Comparing Two Automated Insulin Delivery System Algorithms (PID vs. PID + Fuzzy Logic) in Individuals with Type 1 Diabetes

Protocol Version/Date: 7.1/ March 17, 2020

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

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following (use applicable regulations depending on study location and sponsor requirements; examples follow): United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

For the outside of US sites, the trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP), the Declaration of Helsinki, and specific regulations applicable to the countries in which the trial will be conducted.

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

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____ Date: _____ / _____ / _____
dd mon yyyy

Investigator's Name: _____

Site Name/Number: _____

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Protocol Summary

PARTICIPANT AREA	DESCRIPTION
Title	**A Crossover Study Comparing Two Automated Insulin Delivery System Algorithms (PID vs. PID + Fuzzy Logic) in Individuals with Type 1 Diabetes** ***(FLAIR- Fuzzy Logic Automated Insulin Regulation)***
Précis	*A randomized crossover trial will compare the efficacy and safety of an automated insulin delivery (AID) system with a proportional-integral-derivative (PID) algorithm versus an automatic insulin delivery (AID) system with a PID algorithm enhanced with a Fuzzy Logic algorithm.*
Investigational Device	The Minimed 670G 4.0 Advanced Hybrid Closed-Loop (AHCL) (PID + Fuzzy Logic) pump with the Guardian Sensor (3) continuous glucose monitoring sensor.
Objectives	The objective of the study is to compare the efficacy and safety of AID system with PID (Minimed 670G 3.0 HCL) to an AID system with combined PID + Fuzzy Logic algorithm (Minimed 670G 4.0 AHCL). In particular, the trial will test the hypothesis that the Minimed AHCL can reduce daytime hyperglycemia, currently the biggest challenge for AID systems, without increasing hypoglycemia.
Study Design	Randomized crossover trial with two 12-week crossover periods in auto mode preceded by a run-in phase.
Number of Sites	Approximately seven sites
Endpoint	**Primary Efficacy Outcome:** The co-primary outcomes are differences in CGM-measured metrics between periods: • Superiority for percent of time >180 mg/dL (10.0 mmol/L) from 6AM to 11:59PM and • Non-inferiority for percent of time <54 mg/dL (3.0 mmol/L) during the entire 24 hour period. **Key Secondary Efficacy Outcomes:** • CGM derived indices over the first 84 days of each treatment period for 24 hours (excluding time before auto mode is turned on), daytime (6AM-11:59PM), nighttime (12AM-5:59AM), and for each post-meal period (meal starts at the time the carbohydrate is entered), measured for up to three hours after a meal (or until another carbohydrate is entered): o Mean glucose o Coefficient of variation o Percentage of sensor glucose readings in the range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L) and 70 to 140 mg/dL (3.9 to 7.8 mmol/L) o Percentage of sensor glucose readings >180 mg/dL (daytime is a co-primary outcome) and >250 mg/dL (10.0 and 13.9 mmol/L, respectively) o Peak glucose and change in glucose from the start of the meal to the peak (only calculated for post-meal periods) • Amount of total, basal, and bolus daily insulin over the first 84 days of each treatment period (excluding time before auto mode is turned on) for 24 hours, daytime (6AM-11:59PM), nighttime (12AM-5:59AM), and for

PARTICIPANT AREA	DESCRIPTION
	each post-meal period (meal starts at the time the carbohydrate is entered), measured for up to three hours after a meal (or until another carbohydrate is entered) • HbA1c • BMI **Key Safety Outcomes** • Percentage of sensor glucose readings <54 mg/dL (overall is a co-primary outcome) and <70 mg/dL (3.0 and 3.9 mmol/L, respectively) • DKA events • Severe hypoglycemia events **Other Outcomes** • Amount of total basal and bolus insulin at daytime, nighttime, and post-meal analyzing both total units and units/kg • Human Factors and Diabetes Technology Attitude and Human Factors questionnaires
Population	**Major Eligibility Criteria** • Type 1 diabetes (T1D) for at least one year, using an insulin pump or multiple daily injections of insulin • Age 14-<30 years • HbA1c 7.0%-11.0% • For females, not currently known to be pregnant, be breast-feeding, or planning to become pregnant within the planned study duration. **Major Exclusion Criteria** • Concomitant disease that influences metabolic control or HbA1c interpretation • Use of antidiabetic agents other than insulin • One or more episodes of severe hypoglycemia (hypoglycemia requiring treatment by another person) within the previous 6 months • One or more episodes of ketoacidosis requiring hospitalization within 6 months prior to screening • Clinically significant nephropathy (eGFR <45 mL/min) or on dialysis
Sample Size	Enrollment will proceed with the goal of at least 100 participants completing the crossover trial. A maximum of 135 individuals may be enrolled and a total of approximately 112 are expected to enter the crossover trial.
Treatment Group	Random assignment (1:1) ratio to either begin with the PID (670G 3.0 HCL) AID system or the PID + Fuzzy Logic (670G 4.0 AHCL) AID system and then crossover to the other respective treatment.
Participant Duration	Approximately 28-36 weeks
Protocol Overview/Synopsis	**Screening and Enrollment** • Informed consent will be signed and eligibility will be assessed • Medical history and physical examination • HbA1c measurement • Urine pregnancy test (if applicable)

PARTICIPANT AREA	DESCRIPTION
	• Human Factors and Diabetes Technology Attitude Surveys **Run-In Period (2-8 weeks)** **Pump Run-In (670G 3.0 HCL)** Eligible participants will use the study 670G 3.0 HCL pump during the run-in. Participants who were pump users at screening may skip the Pump Run-In period (but must participate in the Pump+CGM Run-In period) per investigator discretion. 670G auto mode users may use the 670G pump in auto mode. Standardized pump training will be provided to study participants and their diabetes care partners (for participants <18 years old). The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. For current pump users, the study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed. Participants may continue to use their personal CGM if applicable. The pump will be used for at least two weeks during Pump Run-In, with the option of repeating Pump Run-In for an additional two weeks per investigator discretion. Contact will be made each week with additional contacts as needed. Prior to each contact, participants will be asked to upload device data for study staff to review. After completion of Pump Run-In, participants will proceed to use the study CGM along with the study 670G 3.0 HCL pump during the Pump+CGM Run-In period. **Pump+CGM Run-In (670G 3.0 HCL + Guardian Sensor (3))** All participants must complete a two-week run-in period with the use of the study pump and CGM before being randomized into the crossover trial. During Pump+CGM Run-In, the predictive low glucose suspend feature will be turned on and auto mode will be off (i.e. manual mode). Participants who were 670G auto mode users at screening may use the pump in auto mode. Standardized device training will be provided to study participants and their diabetes care partners (for participants <18 years old). Personal pumps and CGMs will be removed during the Pump+CGM Run-In period as applicable. Contact will be made each week with additional contacts as needed. Prior to each contact, participants will be asked to upload device data for study staff to review. **Run-In Assessment** Successful completion of Pump Run-In is per investigator discretion. Pump Run-In may be repeated once.

PARTICIPANT AREA	DESCRIPTION
	Successful completion of the Pump+CGM Run-In requires CGM data to be collected on at least 80% of the possible time in the prior 14 days of use. An average of at least three blood glucose meter (BGM) tests per day will also be required. If these are not achieved, the Pump+CGM Run-In period may be repeated once. **Randomization into the Crossover Trial** Eligible participants who successfully complete the Pump+CGM Run-In will be randomly assigned to begin with one Automated Insulin Delivery (AID) system during Period 1 and then crossover to the other AID system during Period 2. The two study AID systems (treatments) are: • 670G 3.0 Hybrid Closed-Loop (HCL) (PID) insulin pump + Guardian Sensor (3) CGM • 670G 4.0 Advanced Hybrid Closed-Loop (AHCL) (PID + Fuzzy Logic) insulin pump + Guardian Sensor (3) CGM **Home Use of AID System during the Crossover Trial** *Period 1 (~13 weeks)* Participants and their diabetes care partners (for participants <18 years old) will be trained by qualified personnel on the use of the assigned pump and on auto mode feature use including meal announcement, meal bolusing, and exercise. Training will also be provided in performing specific tasks including the following: • Confirming pump parameters • When not to use or rely on auto mode particularly during significant illness or acetaminophen use • CGM calibration instructions • Meal bolus procedures • What to do when exercising while using the system • How to react to safety/alert notifications • How to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device • When and how to contact study staff to ask questions during the study Study staff will discuss the visit and contact schedule with the participant and will make arrangements for follow-up appointments. Participants will be asked to upload data before each contact and at least every two weeks. After auto mode training has been completed, participants will proceed with home use of the AID system (meaning free-living use at work, home, etc.) during Period 1 with either the 670G 3.0 HCL or 670G 4.0 AHCL pump. The predictive low glucose suspend feature will be on. The system will initially be used with auto mode deactivated (except for 670G auto mode users at screening who may activate auto mode if using the 670G 3.0 HCL pump) until participants are contacted 6-10 days into Period 1 with

PARTICIPANT AREA	DESCRIPTION
	instructions to activate auto mode. Participants will then continue using the AID system for 12 weeks after auto mode is initialized. Participants will be expected to use auto mode at all times at home with some exceptions (e.g. times of illness, acetaminophen use). HbA1c, C-peptide, and glucose levels will be collected for central lab analysis at the beginning of Study Period 1. Human Factors and Diabetes Technology Attitude Surveys will be administered at the end of Study Period 1. *Period 2 (~13 weeks)* At the beginning of Period 2, a urine pregnancy test will be completed as applicable. Eligible participants will then use the other AID system during Period 2. The procedures in Period 1 will be repeated in Period 2. At the end of the 12-weeks of AID use in auto mode at home, the participant will complete a final study visit which may be conducted at home or remotely, if an in-clinic visit is not possible.

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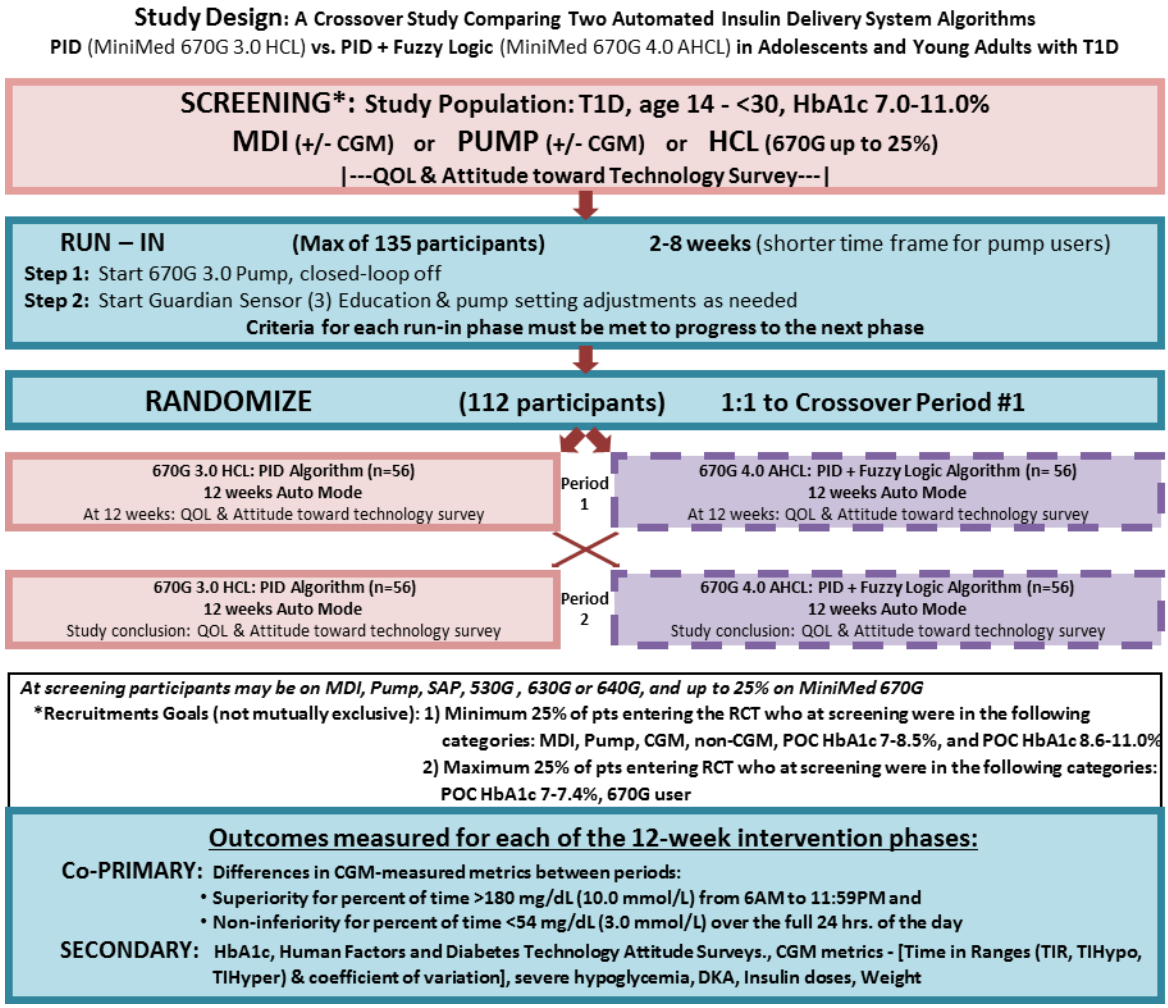
Schematic of Study Design

Figure 1. 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[5]	Pump Run-In[1]		Pump+CGM Run-In[1]	
		1 week after screening (±2d)	2 weeks after screening (+3d)	1 week after screening or end of pump run-in (±2d)	2 weeks after screening or end of pump run-in (+3d)
Visit (V) or Contact (C)	V	C	V	C	V (Same as Rand Visit)
Informed Consent	**X**				
Inclusion/Exclusion	**X**				
Medical history/physical exam	**X**				
Height, weight, blood pressure	**X**				
HbA1c – point-of-care or local lab	**X**				
Study pump training	**X[2]**				
Study CGM training	**X[3]**		**X**		
Questionnaires - Diabetes Tech Attitude + Human Factors	**X**				
AE Assessment		**X**	**X**	**X**	**X**
Upload device data from home		**X**		**X**	
Upload device data at clinic visit			**X**		**X**
Review blood sugars and make insulin adjustments as needed		**X**	**X**	**X**	**X**
Pregnancy test[4]	**X**				

[1]Run-in periods may be repeated once.
[2]Pump training will occur after participant is determined to be eligible.
[3]Current pump users at screening may skip Pump Run-In and proceed directly to Pump+CGM Run-In at investigator's discretion. CGM training will occur after participant is determined to be eligible.
[4]Additional pregnancy tests to be performed any time pregnancy is suspected.
[5]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.

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

	Randomization	Crossover Period 1 (P1)								Crossover Period 2 (P2)							
		Auto Mode Initiation	Time from Auto Mode Initiation							Auto Mode Initiation	Time from Auto Mode Initiation						
	-6-10d[1]	0d[1,4]	24[4] hours	5d[4] ± 2d	2w ± 4d	4w ± 4d	6w ± 4d	9w ± 4d	12w + 7d (and -6-10d from P2[1])	0d[1,4]	24[4] hours	5d[4] ± 2d	2w ± 4d	4w ± 4d	6w ± 4d	9w ± 4d	12w + 7d
Visit (V) or Contact (C)	V	C	C	C	V	C	V	C	V	C	C	C	V	C	V	C	V/C
Re-review of eligibility	X																
Assessment visit	X				X		X		X				X		X		X
Height, weight, blood pressure	X								X								X
Central lab – HbA1c	X								X								X
Central lab – random C-peptide and glucose	X																
Auto mode training	X																
Turn auto mode on		X								X							
Setpoint evaluation[2]					X	X	X	X					X	X	X	X	
Questionnaires - Diabetes Tech Attitude + Human Factors									X								X
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Upload device data from home		X	X	X		X		X		X	X	X		X		X	
Upload device data at clinic visit	X				X		X		X				X		X		X
Review glucose patterns	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[3]	X																

[1]Auto mode initiation will begin 6-10 days after Randomization and after end of Period 1. All follow-up visits are relative to the day auto mode is initialized.
[2]Setpoint evaluation will occur for 670G 4.0 AHCL users
[3]Additional pregnancy tests to be performed any time pregnancy is suspected
[4]Contacts must be completed by phone.

Chapter 1: Background Information

1.1 Introduction

Type I diabetes (T1D) causes autoimmune pancreatic beta cell destruction and lifelong dependency on exogenous insulin. Subsequently, patients with T1D are at risk for long-term life-threatening microvascular and macrovascular complications that can be abated by aiming to achieve near-normal blood glucose. However, this tight control is associated with a threefold increase in the risk of severe hypoglycemic events, one of the most feared and dangerous events for patients and their parents or caregivers.[1] Therefore, the ultimate goal in diabetes care is to keep blood glucose in a narrow desired range with minimal hypoglycemic events. Over the past decade, the use of insulin pumps and sensors and their combination (sensor-augmented pumps) have shown advances towards improving glucose control.[2-4] However, recent data from diabetes centers in Europe and the United States (US) indicate that the glycemic control achieved is still not satisfactory and is complicated by the risk of hypoglycemia,[5, 6] despite the use of the advanced technological tools now available.[7] Some progress is being made with the introduction of the threshold suspend or low glucose suspend (LGS) sensor and pump systems in the United States. We now need to combine predictive features with LGS features to minimize hyperglycemia as well,[8] without causing anxiety and burden for patients and caregivers due to the demand for continual attention to how well the systems cover meals, snacks and periods of illness. This is especially true in adolescents and some young adults whose compliance with treatment can be low, with 50% omitting or delaying insulin boluses needed for meals.[9] Automated decision support systems, and ultimately, full automated management solutions, are strongly desired by patients with T1D and their caregivers to improve metabolic control and relieve them of the stress and burden of daily treatment of this chronic disease.

1.1.1 Background: Studies descriptions below include data from PID, MD-Logic, and the combined algorithms:

Automated insulin-delivery systems have been a focus of diabetes research during the past two decades. Several prototypes of control algorithms have evolved and been tested over the world. Two commonly used algorithms have been the proportional-integral-derivative (PID) and model predictive controller (MPC).[10-13] These two systems of control use mathematical models that link insulin delivery with glucose excursions. A third approach to algorithms uses fuzzy logic algorithms (such as the MD-Logic) to modulate insulin delivery based on a set of rules that imitates the line of reasoning of diabetes practitioners, which in turn are based on common medical knowledge and the experience of traditional treatment.[14] The MD-Logic controller applies a basal-bolus approach of insulin delivery with event-driven treatment (i.e., meals and exercise) and a personalized system setting, learning capacity, and safety alerts and embedded insulin-safety layers.[15] The controller algorithms combine control to range and control to target and makes MD-Logic use intuitive for the patient and easy to transfer from pump therapy treatment to closed-loop. Over the past 8 years, the MD-Logic system has been tested in several clinical studies: in research centers, diabetes camps, and at patients' homes in Israel and Europe. In 2012 the system was the first to be studied for home use and, most importantly, was found to be safe in daily routine use.[16] Since then, the system has been evaluated in several home studies, in free-living conditions, and for longer durations: 4 nights, 6 weeks, and recently, 3 months overnight use. These extensive studies showed that MD-Logic is safe for home use and effective in reducing the occurrence, duration, and severity of hypoglycemia while improving metabolic

control by automating the delivery of insulin.[17] The MD-Logic closed-loop software received a CE Mark in Europe for the overnight algorithm, the first in the world to receive regulatory approval. The well tested enhanced bolus features of the MD-Logic algorithm was combined with the safe and effective Medtronic HCL PID platform and proven in in-silico testing to be safe and further reduce hyperglycemia compared to either system alone.

1.1.2 Pre-Clinical Testing of MD-Logic Algorithms

The MD-Logic algorithm was tested using an in-silico model, FDA-approved UVA simulator in 300 children, adolescents, and adults.[11, 19] The algorithm was effective in characterizing the patient profile from open-loop data. The simulations showed that the use of the MD-logic algorithm reduced the risk of hypoglycemia and improved glycemic control. In addition, the algorithm was useful in adjusting treatment to provide better glycemic control during closed-loop operation.[11, 15]

1.1.3 Clinical Studies using MD-Logic Systems

A stepwise approach to studies was used to test MD-Logic System in different settings. During these studies, described in greater detail below, the study duration also was gradually increased, with the final test of the system at home for day and night use: **The first feasibility clinical studies** using MD-Logic were conducted in 2009 in 7 adults with T1D, aged 19 to 30 years. All study participants underwent 14 full, closed-loop control sessions of 8 hours (fasting and meal challenge conditions) and 24 hours of full closed-loop control with three meals. During the 24-hour control, 73% of the sensor values ranged from 70 to 180 mg/dL (3.9-10.0 mmol/L), 27% were >180 mg/dL(10.0 mmol/L), and none were <70 mg/dL (3.9 mmol/L). There were no events of symptomatic hypoglycemia during any of the trials. During the overnight period, 91% of the time glucose concentrations were within 70-140mg/dL (3.9-7.8 mmol/L), and mean glucose was 112 ± 5 mg/dL (6.2 ± 0.3 mmol/L) with no episodes of hypoglycemia below 63 mg/dL (3.5 mmol/L).[20]

Next, the system was tested with and without evening exercise in three adolescents and four adults who underwent two sessions with the MD-Logic: one started at dinner alone and the other one at dinner time following exercise. These sessions were compared with data derived from nights spent at home with SAP in a similar scenario to this proposed study protocol. The mean percentage of time spent in the target range of 63-140 mg/dL (3.5-7.8 mmol/L) was 85% (78% to 92%) for the MD-Logic sessions compared with 27% (6% to 57%) using SAP, respectively [median (interquartile range -IQR)]. During the overnight closed-loop sessions at dinner alone, 92±9% of the sensor values ranged within target, compared with 73±19% for the sessions following exercise (P=0.03). No hypoglycemic events occurred during the closed-loop sessions. This study demonstrated the ability of the system to cope with evening exercise and to "support" meal insulin delivery (i.e., the system gave correction boluses or lowered basal insulin as needed to cope with the meal).[21]

Next was a multicenter, multinational study conducted in Slovenia, Israel, and Germany in an inpatient setting in 12 children, adolescents, and young adults randomly assigned to participate in two sequential overnight sessions: one using insulin pump treatment and the other MD-Logic closed-loop insulin delivery. Results showed that three events of nocturnal hypoglycemia occurred during control nights and none during MD-Logic nights (P=0.18).The

percentage of time spent in the target range of 63-140 mg/dL (3.5-7.8 mmol/L) was significantly higher during MD-Logic nights 76% (54% to 85%) compared with 29% (11% to 44%) during insulin pump nights, *P*=0.02 [median (IQR)].The mean glucose level overnight was reduced by 36 mg/dL (2 mmol/L) with the use of MD-Logic (*P*=0.02), with significantly less glucose variability than that of the pump therapy (*P*<0.001).[22]

The subsequent study transitioned use of the device to the outpatient setting in a multicenter, multinational, randomized, crossover trial in which the short-term safety and efficacy of the MD-Logic System was assessed for nocturnal glucose control in 56 children and adolescents with T1D at a diabetes camp who participated in two consecutive overnight sessions, one night with MD-Logic and the second night with SAP therapy, with the order of nights randomly assigned. The primary endpoints were overnight hypoglycemia (measured two ways, number of sensor readings below 63 mg/dL (3.5 mmol/L) and a more complex measure of episodes of hypoglycemia with several consecutive glucoses below 60 mg/dL(3.3 mmol/L) and mean overnight glucose concentrations. On MD-Logic system nights, compared with SAP nights, there were significantly fewer episodes of glucose concentrations below 63 mg /dL(3.5 mmo/l) (7 vs. 22) and significantly shorter periods or episodes when glucose levels were below 60 mg/dL (3.3 mmol/L) (*P*=0.003 and *P*=0.02, respectively). Median values for individual mean overnight glucose concentrations were 126.4 mg/dL (7.0 mmol/L) (IQR- 115.7 to 139.1 mg/dL) with MD-Logic and 140.4 mg/dL (7.8 mmol/L) (IQR- 105.7 to 167.4 mg/dL (5.9 to 9.3 mmol/L)) with SAP therapy. No serious adverse events were reported. This study demonstrated the safety and efficacy of short-term use of MD-Logic outside the hospital, during diabetes camp, with physical activities, and buffet-served meals. MD-Logic system therapy was found to be superior to SAP therapy, with a reduced risk of nocturnal hypoglycemia with tighter glucose control.[23]

Studies next focused on home use of the MD-Logic device for a 4-night duration using a single-blind, randomized, multicenter, multinational, crossover study designed to validate the feasibility, safety, and efficacy of MD-Logic in T1D at patients' homes.[16] Seventy-five participants (aged 10 to 54 years; average HbA1c 7.8±0.7%) were randomly assigned to participate in two overnight crossover periods, each including four consecutive nights: one under MD-Logic system and the second under SAP therapy at patients' homes in real-life conditions. Investigators were masked to treatment intervention. Primary endpoints were the time spent with glucose concentrations below 70 mg/dL (3.9 mmol/L), and the percentage of nights in which the mean overnight glucose concentrations were within 90-140 mg/dL (5.0 - 7.8mmol/L). The study results showed that on nights in which MD-Logic was used, time spent in hypoglycemia was significantly reduced (*P*=0.004) compared with nights in which SAP therapy was used. The percentage of individual nights in which mean overnight glucose concentration was within 90–140 mg/dL (5.0 – 7.8 mmol/L) was decreased for SAP, with a median (and IQR) of 75 mg/dL (4.2 mmo/l) (42, 75), and 50 mg/dL (2.8 mmol/L) (25, 75) for MD-Logic and SAP nights, respectively; *P*=0.008. [16] Exploratory comparisons of the intention-to-treat cohort demonstrate the safety and efficacy of MD-Logic in terms of significantly reducing the risk of nocturnal hypoglycemia parameters while improving overnight glycemic control and reducing the risk of nocturnal hyperglycemia. The same amount of total insulin doses were used during closed-loop and control nights. No serious adverse events were reported. Mean overnight glucose concentrations were more consistent and converging to a narrow range during closed-loop nights

compared with open-loop nights. In addition, worries about episodes of hypoglycemia were significantly reduced using the fear-of-hypoglycemia questionnaire when using the MD-Logic System compared with SAP therapy (*P*=0.017). Perceived ease of use significantly increased (*P*=0.002), and the overall satisfaction mean score after the intervention was 3.02±0.54 (range 0-4), demonstrating a high level of satisfaction with the system.[24]

The device was next tested in a randomized crossover study designed to evaluate the safety and efficacy of MD-Logic system for overnight use in T1D at patients' homes for 6 weeks.[25] Twenty-four participants (aged 12 to 43 years; average HbA1c 7.5±0.8%) were randomly assigned to participate in two overnight crossover periods, each six weeks of consecutive nights: one under MD-Logic and the second under SAP therapy. MD-Logic significantly reduced time spent in hypoglycemia at night (*P*=0.02) and increased the percentage of time spent in the target range of 70-140 mg/dL (3.9 – 7.8 mmol/L) (*P*=0.003) compared with SAP. The time spent in substantial hyperglycemia (>240 mg/dL) was reduced by a median of 52.2% (IQR, 4.8-72.9%) (*P*=0.001) under MD-Logic compared with SAP therapy. Total insulin doses were lower in the MD-Logic group than in the SAP night group (*P*=0.04). The average daytime glucose concentration after closed-loop operation were reduced by a median of 10.0 mg/dL (0.5 mmol/L) (IQR -2.7, 19.2, *P*=0.017) while lower total insulin doses were used (*P*=0.038). One severe hypoglycemia event was observed during a SAP night and none using MD-Logic. **[25]**

The MD-Logic HCL system was then tested over a weekend at home for 60 hours and glucose control was compared to that achieved on SAP therapy. The primary endpoint was the time within 70-180 mg/dL (3.9-10.0 mmol/L). Twenty-two patients were evaluated. Preliminary unpublished data from the intention-to-treat analysis showed that the time within the desired range was increased by a median of 19% during MD-Logic HCL control compared with SAP. The time spent in hypoglycemia and the amount of insulin use was the same during MD-Logic HCL as with SAP. Time spent in hyperglycemia above 180 mg/dL (10.0 mmol/L) was reduced by 32% during the MD-Logic HCL control compared with SAP.

The conclusion from this series of studies is that the MD-Logic (fuzzy logic algorithm) system was safe and effective in both inpatient and outpatient settings.

Next the studies using the Medtronic HCL (PID algorithm) system are outlined.

1.1.4 Medtronic HCL Studies

The feasibility of the Medtronic HCL algorithm has been proven in pediatric, adolescent, and young adult patients.[26-32] In a study of eight participants age 14-40 using the Medtronic HCL system with PID control algorithms on an android device compared to SAP with LGS, there was no significant difference in total time spent in target but hypoglycemia (< 2.8 mmol/L) was all but eliminated with HCL (1 vs. 9, p=.04) and no adverse effects were reported.[29] In response to promising data from these studies, Medtronic incorporated a more adaptive algorithm directly into the pump hardware (MiniMed 670G) and this Medtronic HCL platform has just been tested in 124 individuals (adolescents and adults at 9 centers in the US and one center in Israel) in a 3 month pivotal safety trial which concluded in March 2016 and was published in JAMA, September 15, 2016. Of the 124 participants (mean age, 37.8years [SD, 16.5]; men, 44.4%), mean diabetes duration was 21.7 years, mean total daily insulin dose was 47.5U/d (SD, 22.7),

and mean HbA1c was 7.4% (SD, 0.9). Over 12 389 patient-days, no episodes of severe hypoglycemia or ketoacidosis were observed. There were 28 device related adverse events all resolved at home (including skin irritation, infusion set malfunction, batteries needing replacement and damage to the pump screen). There were 4 SAE's but none related to the system. The system was in closed-loop 87.2% of the time and the MARD of the Guardian Sensor (3) was 10.3% (SD 9.0). Efficacy data showed is shown in the table below from Table 2 in the JAMA publication shown below:

Table 2. Glucose Control, Insulin Usage, and Weight Among Patients Using Hybrid Closed-Loop Systems

Parameter	Run-in Period	Study Period
Sensor glucose, mean (SD) [median], mg/dL	150.2 (22.7) [150.1]	150.8 (13.7) [149.9]
Percentage of time with glucose level in range, mean (SD); median (IQR)		
Sensor glucose values		
>300 mg/dL	2.3 (4.2); 1.3 (0.2-2.6)	1.7 (1.9); 0.9 (0.5-2.1)
>180 mg/dL	27.4 (13.7); 26.7 (16.0-37.2)	24.5 (9.2); 24.1 (17.3-29.8)
71-180 mg/dL	66.7 (12.2); 67.8 (59.0-75.1)	72.2 (8.8); 73.4 (67.7-78.4)
≤70 mg/dL	5.9 (4.1); 5.2 (3.0-7.6)	3.3 (2.0); 2.9 (1.7-4.3)
≤50 mg/dL	1.0 (1.1); 0.6 (0.2-1.3)	0.6 (0.6); 0.4 (0.2-0.8)
Sensor glucose values at night time only[a]		
>180 mg/dL	26.8 (15.2); 26.4 (15.3-35.8)	21.6 (9.9); 20.6 (13.6-28.5)
71-180 mg/dL	66.8 (14.0); 67.0 (57.6-75.2)	75.3 (9.8); 76.4 (69.0-83.1)
≤70 mg/dL	6.4 (5.3); 5.4 (2.3-8.5)	3.1 (2.2); 2.6 (1.7-4.2)
Within-day SD of glucose, mean (SD); median (IQR), mg/dL[b]	50.1 (9.9); 48.9 (43.7-56.2)	46.7 (7.3); 45.6 (41.7-50.4)
Within-day coefficient of variation of glucose, mean (SD); median (IQR), %[b]	33.5 (4.3); 33.1 (30.3-36.4)	30.8 (3.3); 30.7 (28.2-33.0)
Glycated hemoglobin, mean (SD) [median], %	7.4 (0.9) [7.3]	6.9 (0.6) [6.8]
Total daily dose of insulin, mean (SD) [median], U	47.5 (22.7) [43.9]	50.9 (26.7) [44.1]
Weight, mean (SD) [median], kg	76.9 (17.9) [73.5]	77.6 (16.1) [74.7]

Abbreviations: IQR, interquartile range.

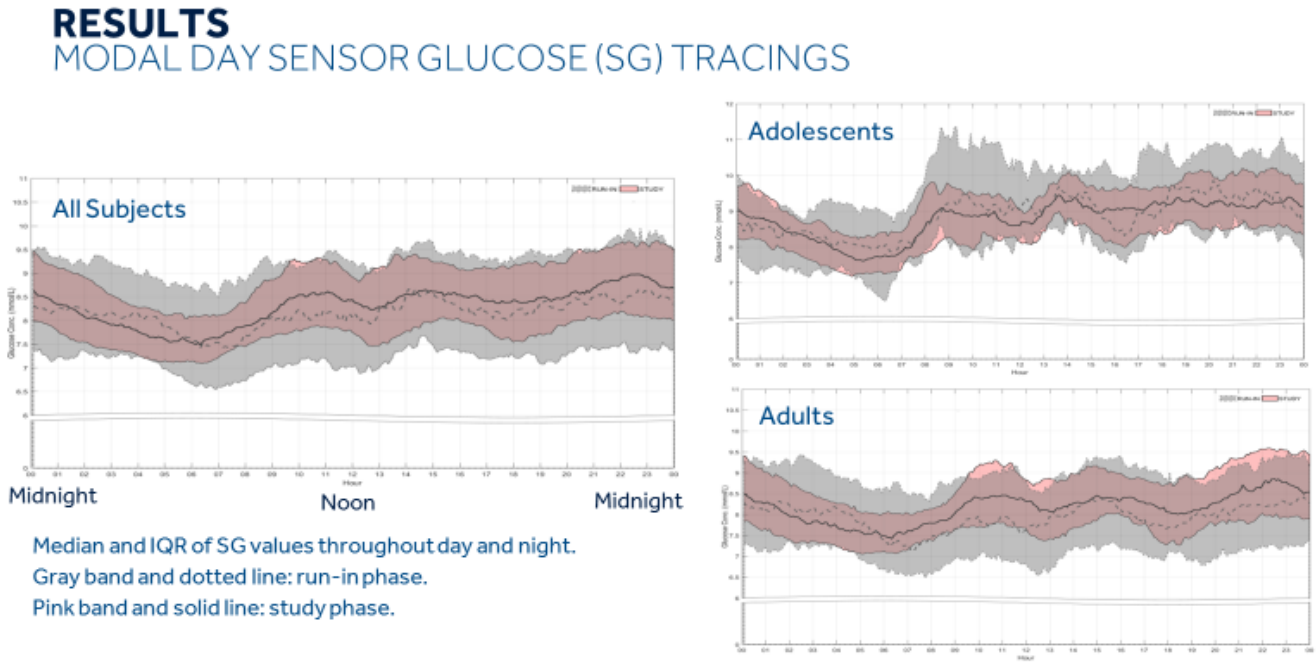
SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

[a] Night time was defined as 10:00 PM to 7:00 AM.

[b] Measures of glycemic variability.

The 670G hybrid closed loop system was approved by the FDA September 28, 2016 and has been marketed for clinical use since the Spring of 2017 in the United States. Eighty percent of the 670G pivotal study participants continued in an extension study that has been since completed.

Several of the PIs for this study are PIs on this Medtronic pivotal HCL study and are very familiar with the system safety and effectiveness, particularly the ability to control blood glucose overnight and between meals. However, as with other HCL systems being evaluated, there is still potential for improvement in mealtime glycemic control by incorporating the more sensitive bolus insulin delivery component of the fuzzy logic algorithm as described in this proposal (such as the PID + Fuzzy Logic / Advanced Hybrid Closed-Loop (AHCL) / 670G 4.0 System). The room for further glucose control can be appreciated from the 670G pivotal trial CGM profile figure below (2).



Particularly relevant to our proposal is that fact that in the 670G pivotal trial data shown below that the percent of time with sensor glucose reading >180 mg/dL (10.0 mmol/L) was higher in adolescents than adults and was higher in day time than the night time, **therefore confirming particular room for improvement in time spent >180 mg/dL (10.0 mmol/L) in adolescents during the day while using the 670G system, particularly in adolescents.**

RESULTS

PERCENT TIME IN SENSOR GLUCOSE RANGES, ADOLESCENTS

	Day		Night	
	Run-In	Study Phase	Run-In	Study Phase
SG Range (mmol/L)	Mean ± SD (95% CI)		Mean ± SD (95% CI)	
≤2.7	0.5±0.45 (0.28, 0.62)	0.4±0.41 (0.25, 0.56)	1.0±1.33 (0.54, 1.54)	0.6±0.58 (0.39, 0.82)
≤3.3	1.4±1.27 (0.93, 1.88)	1.1±0.82 (0.82, 1.43)	2.6±2.86 (1.50, 3.64)	1.4±1.00 (1.03, 1.78)
≤3.8	3.4±2.41 (2.48, 4.28)	2.7±1.30 (2.19, 3.17)	5.8±5.25 (3.80, 7.72)	2.9±1.64 (2.31, 3.54)
3.9 to 10	58.2±11.39 (53.93, 62.44)	64.5±8.97 (61.19, 67.89)	64.2±14.10 (58.94, 69.47)	**71.5±10.33** (67.64, 75.36)
>10 (180 mg/dL)	38.4±11.87 (34.01, 42.87)	**32.8±8.94** (29.44, 36.12)	30.0±15.64 (24.19, 35.87)	**25.6±9.78** (21.92, 29.23)
>13.8	11.8±7.99 (8.86, 14.83)	9.5±4.74 (7.68, 11.22)	8.2±8.11 (5.19, 11.25)	6.8±5.06 (4.87, 8.65)
>16.6	4.4±4.58 (2.70, 6.12)	3.1±2.12 (2.29, 3.87)	2.8±4.52 (1.10, 4.48)	2.3±2.64 (1.27, 3.24)

Night = 22:00 to 07:00

RESULTS

PERCENT TIME IN SENSOR GLUCOSE RANGES, ADULTS

	Day		Night	
	Run-In	Study Phase	Run-In	Study Phase
SG Range (mmol/L)	Mean ± SD (95% CI)		Mean ± SD (95% CI)	
≤2.7	1.0±1.19 (0.75, 1.24)	0.6±0.66 (0.49, 0.76)	1.1±1.55 (0.82, 1.46)	0.7±0.77 (0.50, 0.81)
≤3.3	2.8±2.54 (2.25, 3.29)	1.6±1.31 (1.37, 1.90)	3.1±3.14 (2.42, 3.71)	1.6±1.39 (1.29, 1.86)
≤3.8	6.2±4.39 (5.32, 7.11)	3.6±2.28 (3.08, 4.02)	6.6±5.34 (5.51, 7.70)	3.2±2.36 (2.70, 3.66)
3.9 to 10	69.5±12.01 (67.02, 71.94)	72.2±9.01 (70.37, 74.06)	67.6±13.88 (64.72, 70.41)	76.5±9.34 (74.55, 78.37)
>10 (180mg/dL)	24.3±13.74 (21.49, 27.12)	**24.2±9.60** (22.27, 26.20)	25.8±15.05 (22.74, 28.91)	**20.4±9.59** (18.40, 22.33)
>13.8	5.6±7.02 (4.20, 7.07)	5.0±4.46 (4.09, 5.92)	6.1±8.03 (4.42, 7.71)	4.3±4.06 (3.42, 5.08)
>16.6	1.8±3.90 (1.04, 2.64)	1.4±1.93 (1.00, 1.79)	1.8±4.71 (0.86, 2.79)	1.2±1.56 (0.86, 1.50)

Night = 22:00 to 07:00

1.1.5 Integrated Advanced HCL System In-Silico Testing

The Advanced HCL System has been evaluated with an in-silico (virtual) model and compared to the Medtronic HCL under carbohydrate (CARB) estimations that deviated from the actual CARB values by plus or minus 50%. Medtronic created the in-silico model of T1D pump users to test the effectiveness of insulin dosing algorithms prior to clinical study. A total of 218 virtual patients (112 female, median total daily insulin dose =40 units, age 43-55) were created using data from Medtronic's large pool of SAP uploads in Carelink. The model contains mathematical predictions of sensor glucose measurements validated using 51 days of Carelink uploads comparing model predictions to sensor glucose measurements of time >180 mg/dL (10.0

mmol/L) and < 70 mg/dL (3.9 mmol/L). The model had been used successfully in the development of Medtronic's HCL system.

Table 3. Comparing HCL and Advanced AID System with a constant CARB estimation error (a 50% underestimation)below summarizes the simulation results of the Advanced HCL system when CARB estimation was constantly underestimated by 50%. The simulation results indicate that, there is a significant improvement to the efficacy of glycemic control in the Advanced HCL system by incorporating the MD-Logic algorithms, especially in the presence of CARB estimation inaccuracies.

Table 3. Comparing HCL and Advanced AID System with a constant CARB estimation error (a 50% underestimation)

Parameter	HCL Mean ± SD (Median)	Adv HCL Mean ± SD (Median)
% Time > 250 mg/dL	15 ± 9 (14)	12 ± 8 (12)
% Time > 180 mg/dL	37 ± 11 (37)	33 ± 9 (33)
% Time < 70 mg/dL	0 ± 0 (0)	0 ± 1 (0)
% Time 70 – 180 mg/dL	63 ± 11 (63)	67 ± 9 (67)
Mean Senor Glucose	177 ± 19 (175)	169 ± 14 (168)
AUC < 70 mg/dL	0 ± 0 (0)	0 ± 0 (0)
AUC > 180 mg/dL	27 ± 15 (25)	22 ± 12 (20)

1.1.6 Further Studies and Updates to the Advanced HCL System:

Clinical testing to ensure safety of the integrated Advanced HCL (PID and fuzzy logic algorithms combined) was conducted in Israel as part of NIDDK bridge grant funding in anticipation of this proposal (NIDDK/UC4DK108611, Home Use of MD-Logic Automated Insulin Delivery System: Safety and Efficacy, PIs Bergenstal and Phillip) to compare the Advanced HCL system to the Medtronic 670G HCL system in a crossover RCT of 20-60 participants with T1D in a camp setting for 3-5 days. This study was completed successfully showing that the PID and fuzzy logic algorithms could be combined safely and effectively in this small pilot study.

Following the successful combination of the PID and fuzzy logic algorithms, Medtronic made a few additional adjustments to some software settings for the MiniMed 670G 4.0 AHCL system which FLAIR study will be comparing to the 670G 3.0 (commercial) system. These additional features that will be present in the 670G 4.0 AHCL system are compared to the current 670 3.0 system in Table 4 below. Note in Auto mode the 670G 4.0 AHCL system fine tunes some of the features to allow patients to spend more time in auto mode. In addition the glucose target setpoint can be set at 100 mg/dL (5.6 mmol/L) or 120 mg/dL (6.7 mmol/L) (the latter of which is like the 670G 3.0 HCL). The FLAIR protocol will start with a set point of 120 mg/dL (6.7 mmol/L) for all participants and move to 100 mg/dL (5.6 mmol/L) as long as there is no data indicating an undue risk of hypoglycemia after review of glucose/insulin data reports. An additional optional feature of auto correction boluses is present in the 670G 4.0 AHCL system (a function of the fuzzy logic algorithm component). Table 4 outlines a few other safety features that are added to the 670G 4.0 AHCL system including the ability for the software to reduce a meal bolus if based on the current glucose readings there would be an increased risk of

hypoglycemia and a correction bolus is allowed based on sensor glucose readings if a glucose meter BG is not available.

These updates to the 670G 4.0 AHCL system have been tested in an inpatient and outpatient setting (in Australia) then fine-tuned and tested again in an inpatient (stress testing: meals, exercise and testing glucose excursions) and outpatient setting in Israel. After final adjustments and reviewing the safety and efficacy parameters the configuration of the 670G 4.0 AHCL was determined to be ready for comparing to the 670G 3.0 HCL version in FLAIR.

Table 4. 670G 3.0 HCL vs 670G 4.0 AHCL

	MiniMed 670G 3.0 (MMT-1780, MMT-1781, MMT-1782)	**MiniMed 670G 4.0 (MMT-1741, MMT-1742)**
Manual Mode	Continuous delivery of basal insulin and delivery of user activated insulin boluses.	
	When used with Continuous glucose monitoring (CGM), the sensor signals are converted by the compatible transmitter to sensor glucose values (based on calibration values from a blood glucose meter) which are transmitted to the pump for display to the user.	
	MiniMed 670G 3.0 (MMT-1780, MMT-1781, and MMT-1782) allows the user to enable one of the following features to suspend delivery of insulin as follows: *"Suspend on Low"* will suspend when sensor glucose falls below the predefined threshold value *"Suspend Before Low"* will suspend delivery of insulin when the sensor glucose is predicted to the fall below predefined threshold values.	The MiniMed 670G 4.0 (MMT-1741, MMT-1741) allows the user to enable the following feature to suspend delivery of insulin as follows: *"Suspend on Low"* will suspend when sensor glucose falls below the predefined threshold value *"Suspend Before Low"* will suspend delivery of insulin when the sensor glucose is predicted to the fall below predefined threshold values.
Auto Mode	Automatically adjusts basal insulin using the control algorithm of PID-IFB (Proportional integral derivative controller with insulin feedback) to regulate the user's sensor glucose levels	
	Temporary target (user settable) remains unchanged with a setpoint of 150 mg/dL.	
	Target Setpoint of 120 mg/dL (6.7 mmol/L)	Target Setpoint of **100 mg/dL or 120 mg/dL (5.6 mmol/L or 6.7 mmol/L, respectively)**
	Correction bolus target is 150mg/dL (8.3 mmol/L)	Correction bolus target is **120 mg/dL (6.7 mmol/L)**
	Safeguards in Auto Mode include the following: • Min insulin delivery timeout 2.5 hours	Safeguards in Auto Mode are being fine-tuned to allow more time in Auto mode.

	• Max insulin delivery timeout 4 hours • Sensor integrity check logic to allow into Auto Mode • Safe basal will not exceed 90 min • Model Supervisor detects under read (30 min) • Missed Transmission switches to safe basal if there is a missed transmission • Low Glucose Alert will be a mandatory alert when the user is 50 mg/dL. • High Glucose Alert will alert and kick user out of Auto Mode when they are > 250 mg/dL for 3 hours and alert when the user is > 300 mg/dL for 1 hour.	• Min insulin delivery timeout **3-6 hours** *(dependent on the insulin on board)* • Max insulin delivery timeout **7 hours** • Sensor integrity check modified to **use sensor calibration logic** to allow into Auto mode • Safe basal will not exceed **4 hours** • Model Supervisor detects under-read **(2 hrs.)** • Missed Transmission switch to safe basal if there is a missed transmission • Low Glucose Alert will be a mandatory alert when the user is 50 mg/dL. • High Glucose Alert will **alert but not kick the user out of Auto Mode when they are > 250 mg/dL for 3 hours. The alert for > 300 mg/dL for 1 hour is being removed.**
	N/A	**Auto Correction Bolus** is an optional feature (user enabled) to deliver correction boluses automatically without any user input or acknowledgement.
	N/A	**Safe Meal Bolus** has the ability to further reduce the amount of a meal bolus if it is predicted to increase the risk of post-prandial hypoglycemia
	N/A	**Non-Adjunctive capabilities** permits correction boluses to use sensor glucose values if a meter BG is not available. All other correction bolus calculations, including the application of the Safe Correction Bolus logic, remain the same.

The updated 670G 4.0 system has features designed to address post-meal hyperglycemia, which is the biggest area where the initial 670G trials have shown there is room for improvement in glucose control. Next we selected the patient population previously shown to be have the most room for improvement in glucose control as defined by HbA1c levels.

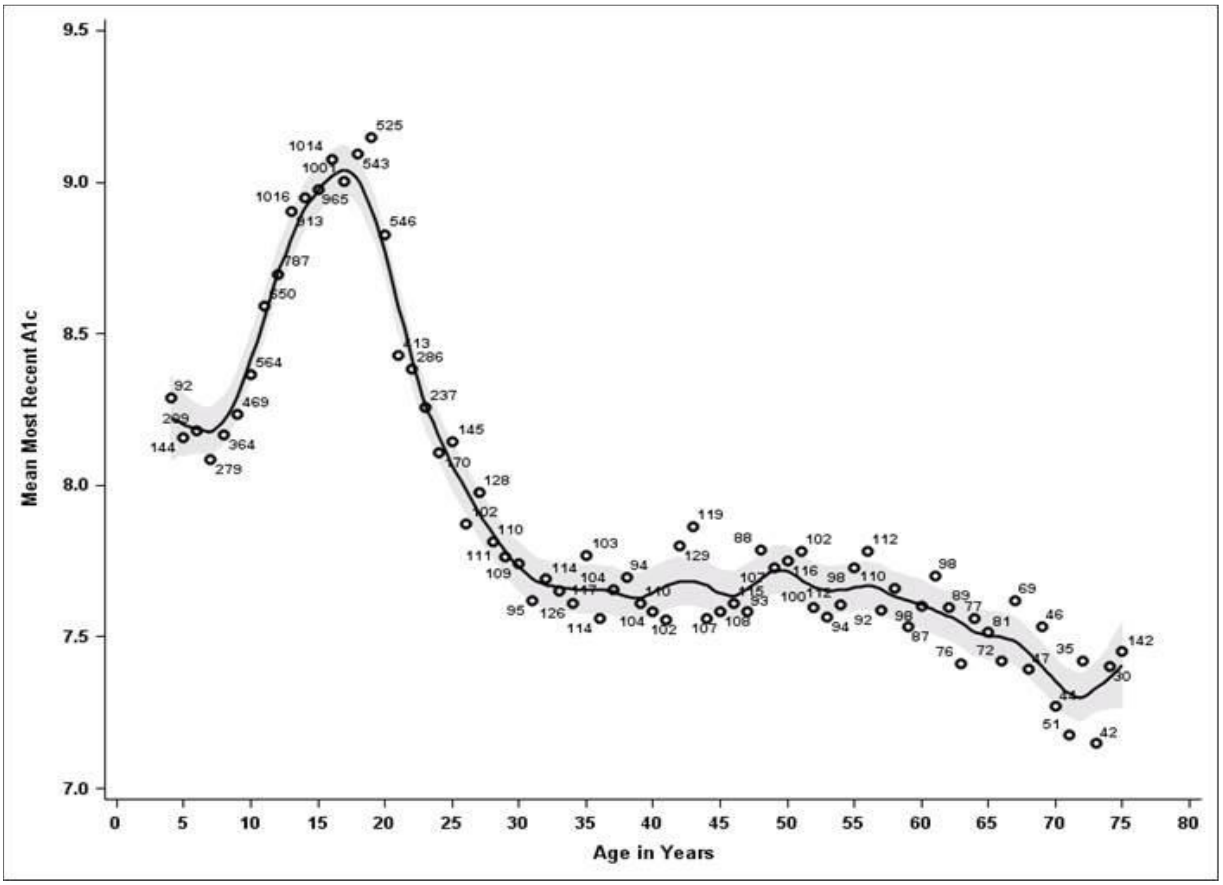
1.2 Rationale

While AP technology could potentially benefit many people with T1D, it could benefit young patients the most because this population has the greatest gap between desirable outcomes and those achieved, as shown in data from the T1D Exchange (Figure 2. T1D Exchange data showing relationship between age and glycemic control below).[5] This population has a higher risk of short- and long-term diabetes complications with evidence suggesting that metabolic memory of periods of suboptimal control can contribute to increased risk of complications later in life.[18] Avoidance of suboptimal control in this population could significantly reduce the treatment burden on healthcare facilities in years to come and reduce the number, severity, and duration of hypoglycemic and diabetic ketoacidosis events and related hospitalizations both now and in the future.

The investigators and research teams collaborating on this project have strong international expertise in diabetes research and closed-loop technology. The objective of this study is to combine and test the best of two AP approaches (PID and MD-Logic/fuzzy logic algorithms) in an integrated Advanced HCL System (670G 4.0 AHCL) in order to provide important data on the safety and efficacy of this promising AP system. If outcomes are positive, it will help promote the recognition of such systems as an effective and safe T1D management solution that

may address some of the gaps in glucose control (e.g., meals, snacks, illness) not adequately addressed by the HCL systems tested to date. In addition, this trial is one of first to screen patients for entry into the study who are managing their glucose control by a very wider variety of diabetes management strategies, with multiple daily injections or insulin pumps for insulin delivery and SMBG or CGM for glucose monitoring. This will help the findings of the trial have broad generalization.

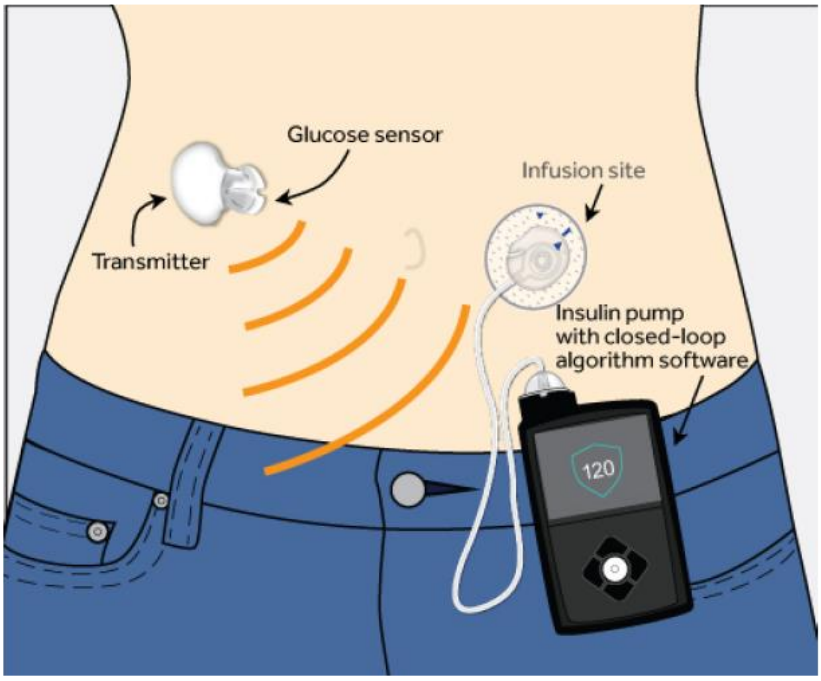
Figure 2. T1D Exchange data showing relationship between age and glycemic control



1.3 Automated Insulin Delivery System Description

The FLAIR study will compare two hybrid closed loop systems, the Minimed 670G 3.0 HCL (PID) and the Minimed 670G 4.0 Advanced Hybrid Closed-Loop AHCL (PID + Fuzzy Logic) pump. The sensor and infusion set will be the same in both systems. A schematic of the system hardware components of the closed loop system is depicted in Figure 3. Schematic of system hardware components below.

Figure 3. Schematic of system hardware components



1.4 Potential Risks and Benefits of the Investigational Device

Study System

Even though the study system has been tested prior to this study, there is still a risk that parts of the system may not function properly. The following are possible reasons the system may deliver too much insulin or incorrectly stop insulin delivery:

- CGM sensor reads higher or lower than the actual glucose level which increases risk for hypoglycemia and hyperglycemia with automated insulin delivery system;
- Acetaminophen interference causing the CGM sensor to read high than actual glucose levels;
- Device malfunctions that could produce a suspension of insulin delivery or over delivery of insulin.

Potential risks associated with insulin pump therapy include:

- Slight discomfort at the time of insertion of the insulin delivery cannula (common)
- Slight bruising at the site of insertion (common)
- Infusion set and cannula occlusions (common) resulting in hyperglycemia or DKA
- Insulin pump malfunction and mechanical problems (common)
- Lipodystrophy/lypoatrophy (common)
- Bleeding at insertion site (rare)
- Infection at the site of insertion (rare)
- Allergy to the insulin delivery cannula or adhesive (rare)
- Allergy to insulin (very rare)

Continuous Glucose Monitoring

Potential risks associated with CGM:

- Slight discomfort at the time of insertion of CGM (common)
- Slight bruising at the site of insertion (unlikely)
- Bleeding at insertion site (common)
- Infection at the site of insertion (rare)
- Allergic reaction to the CGM sensor adhesive material (common)

If a skin reaction is classified as severe (the observation is noticeable and bothersome to participant and may indicate infection or risk of infection or potentially life-threatening allergic reaction), an adverse event form will be completed.

Risks with Infusion Sets	**Prevention and Mitigation**
Risks with infusion sets may include: • Localized infection • Skin irritation/redness • Bruising • Discomfort/pain • Bleeding • Irritation • Rash • Hyperglycemia secondary to infusion set occlusion or infusion site failure • Hyperglycemia secondary to site falling off • Anxiety associated with insertion	Prevention and mitigation include: • Follow the provided user guides for insertions and care of infusion sets. • If an infusion site becomes irritated or inflamed, the infusion set should be removed and another placed in a new location. • In case of hyperglycemia secondary to infusion set occlusion, remove current infusion set and replace with new infusion set and give correction insulin if directed with syringe. • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles and told to call with problems.
Risks with Insulin Administration and Pumps	**Prevention and Mitigation**
Risks with the use of an insulin infusion pump may include the risk of malfunction of the components of the system (pump, software, infusion set and reservoir) as well as the risk of use error during use of the system. Device deficiencies or use errors can result in administration of too much or too little insulin which can lead to the following clinical consequences: • Hypoglycemia • Hyperglycemia • Diabetic ketoacidosis (DKA)	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles and told to call with problems. • Check SMBG 4-6 times a day and also before driving (as applicable) or monitor the CGM. • Instructed to have glucose on hand for hypoglycemia

• Severe hypoglycemia with or without associated seizure, coma or death • Kinked cannula leading to hyperglycemia • Infusion set disconnection from pump leading to hyperglycemia • Dislodged cannula leading to hyperglycemia • A pump error may lead to under delivery or over-delivery of insulin • Battery failure – no insulin delivered leading to hyperglycemia • Insulin deterioration leading to hyperglycemia • Incomplete priming; fails to prime tubing and/or cannula, leading to hyperglycemia • Remove a reservoir, without suspending and reconnecting after a while resulting in hyperglycemia • Patient not filling pump reservoir when needed leading to hyperglycemia • Magnetic Resonance Imaging resulting in pump/Guardian Link 3 Transmitter malfunction • Inaccurate insulin delivery due to sudden altitude changes. • Hypoglycemia or hyperglycemia from manual bolus • Hypoglycemia or hyperglycemia from computer hacking	• Change infusion set if suspected catheter occlusion or administer insulin with syringe for persistent hyperglycemia especially if ketones develop. • Parent(s)/guardian(s) of participants <18 years old) will be present at night with participants and will be trained on study device and diabetes management principles.
Risks with hyperglycemia may include • DKA • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)for participants <18 years old will be present at night with participants and will be trained on study device and diabetes management principles and told to call with problems. • Training prior to study on device use and diabetes management principles. • Check SMBG 4-6 times a day or monitor the CGM.

	• Alternative method of managing glucose levels should be available (insulin and syringe for example)
Risks with hypoglycemia may include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Parent(s)/guardian(s) of participants <18 years old will be present at night with participants and will be trained on study device and diabetes management principles and told to call with problems. • Training prior to study on device use and diabetes management principles. • Check SMBG 4-6 times a day or monitor the CGM. • Instructed to have glucose on hand for hypoglycemia
Risk with Sensors	**Prevention and Mitigation**
Risks with Sensors may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Excessive bleeding due to anticoagulants • Bleeding • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Appearance of a small "freckle-like" dot where needle was inserted • Allergic reaction • Syncopal episode secondary to needle insertion • Soreness or tenderness • Swelling at insertion site • Sensor fracture, breakage or damage • Minimal blood splatter associated with sensor needle removal • Residual redness associated with adhesive	Prevention and mitigation include: • Follow the provided user guides for insertions and care of sensors. • If a sensor site becomes infected or inflamed, the sensor should be removed and another placed in a new location • Base diabetes management on fingerstick readings and not sensor glucose values.

and or tapes • Scarring • Scab • Blister • Itchiness • Inflammation • Anxiety • Incorrect sensor glucose reading results in incorrect diabetes management • Participant over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia • Anxiety associated with insertion	
Risks with Serter	**Prevention and Mitigation**
Risks with Serters may include: • Improper insertion may lead to device performance issue or hyperglycemia	Prevention and mitigation include: • Follow the provided user guides for insertions and care of Serters. • Training on proper use of the Serter and skin preparation prior to insertion.
Risks with Finger Sticks	**Prevention and Mitigation**
Risks with frequent finger stick testing may include: • Potential risks associated with frequent meter testing of blood glucose and blood ketones include discomfort and ecchymosis at tips of fingers Potential risks associated with drawing blood include discomfort and bruising	Prevention and mitigation include: • Follow the provided user guides for use of meter with fingerstick testing. • Training on proper use of the meter and fingerstick testing.
Risks with AHCL	**Prevention and Mitigation**
Risks with AHCL include:	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles and told to call with problems. • Check SMBG 4-6 times a day. • Instructed to have glucose on hand for hypoglycemia. • Subjects will be asked to avoid the use of products containing Acetaminophen • If Acetaminophen is taken, subjects will be instructed to use

• Hypoglycemia
• Severe hypoglycemia
• Hyperglycemia
• DKA
• User Entry Error
  ○ Patient administering boluses by entering false carb doses leading to hypoglycemia or hyperglycemia
  ○ Patient entering false glucose values for any reason leading to hypoglycemia and hyperglycemia
  ○ Patient entering false BG values for calibration leading to hypoglycemia or hyperglycemia
• Sensor failure resulting from patient failure to calibrate leading to hypoglycemia or hyperglycemia
• Sensor over-reading resulting in hypoglycemia
• Sensor under-reading resulting in hyperglycemia
• Sensor missed transmission, or any other fault resulting in no SG value, leading to hyperglycemia or hypoglycemia
• Voluntary insulin delivery (with the pump or with a syringe) immediately prior to entering Auto Mode may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm
• Patient takes insulin via injection while in Closed Loop
• Hypoglycemia or hyperglycemia related to entering or exiting Closed Loop
• Insulin over-delivery due to Acetaminophen
	additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels.
	• If Acetaminophen is taken, subjects should consider exiting Auto Mode.

Potential risks with acetaminophen may include: • False elevation of sensor glucose readings. The level of inaccuracy depends on the amount of acetaminophen active in subject's body and may be different for each subject.	Prevention and mitigation include: • Follow the user guide • Where possible, subjects should avoid the use of Acetaminophen • If Acetaminophen is taken, subjects should use additional BG

	meter readings (they are not to calibrate with those readings) to verify their glucose levels • Subjects should consider exiting AutoMode

1.5 Risk Assessment

Based on the facts that (1) adults and adolescents with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk.

1.6 Known Potential Benefits

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control the glucose level. This research is a definitive step on the path towards development of a fully closed-loop system. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the participants and general benefit to others with diabetes.

1.7 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).
Data will be collected in electronic or physical case report forms, either of which will be considered the source data when directly used.

The protocol is considered a significant risk device study, due to the fact that the PID +fuzzy logic algorithm is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study in the US. As the device is also investigational in Europe and Israel, approvals from the regulatory authorities in the countries where the study is being conducted will also be required as applicable.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of at least 100 participants completing the crossover trial. A maximum of 135 individuals may be enrolled and a total of approximately 112 are planned to enter the crossover trial. Participants who have signed consent and started the screening process will be permitted to continue into the crossover trial, if eligible, even if the crossover trial randomization goal has been reached.

Study participants will be recruited from approximately seven clinical centers. All eligible participants will be included without regard to sex, gender, race, or ethnicity. All sites are experienced in either adult or pediatric endocrinology, or both, and are established research centers with proven recruitment track records.

The recruitment goal for each site is the same (approximately 15-16 participants per site); however, certain sites may recruit additional participants if necessary for the study to meet the overall recruitment goal.

In order to have a broad representation of individuals, there will be the following recruitment goals:

- Minimum of 25% of participants entering RCT who at screening were on MDI therapy
- Minimum of 25% of participants entering RCT who at screening were on Pump therapy
- Minimum of 25% of participants entering RCT who at screening were on CGM therapy
- Minimum of 25% of participants entering RCT who at screening were not on CGM therapy
- Minimum of 25% of participants entering RCT who at screening had a POC HbA1c from 7.0 - 8.5%
- Minimum of 25% of participants entering RCT who at screening had a POC HbA1c from 8.6 - 11.0%
- Maximum of 25% of participants entering RCT who at screening had a POC HbA1c from 7.0 -7.4%
- Maximum of 25% of participants entering RCT who at screening were on the MiniMed 670G system

Potential eligibility may be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. For potential study participants ≥18 years old, the study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read and will be given the opportunity to ask questions. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

For potential participants under 18 years of age, a parent/legal guardian (referred to subsequently as “parent”) will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Potential participants meeting the minimum age of assent will be given a Child Assent Form to read and discuss with their parents and study personnel. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form will be

signed. A copy of consent forms will be provided to the participant and their parent and another copy will be added to the participant's study record.

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

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

2.2 Participant Inclusion Criteria

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

1. Type 1 diabetes mellitus (as diagnosed clinically) with a duration of at least one year
2. Age 14 - <30 years
3. For females, not currently known to be pregnant, be breast-feeding, or planning to become pregnant within the planned study duration.
   If female of child-bearing potential and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
4. Multiple daily injections (MDI) of insulin or an insulin pump user
   a. Participant must be able to obtain U-100 rapid acting insulin analogues, Aspart or Lispro, for use during the study (since these are the only insulins approved for the study pump and the study is not supplying insulin)
   b. MDI users must be on a basal/bolus regimen
   c. Participants must have a minimum total daily dose (TDD) of at least eight units
5. HbA1c from an approved local HbA1c point of care analyzer with an HbA1c value of 7.0-11.0%
6. Willingness or ability to do carbohydrate counting
7. In the investigator's judgment, participant is able to understand and likely to be adherent to the protocol
8. For participants <18 years old, living with one or more diabetes care partners (i.e. a parent/legal guardian) of whom at least one is committed to participating in study training for emergency procedures for severe hypoglycemia and able to contact the participant in case of an emergency
9. Have adequate internet access and computer system for uploading data
10. For participants currently using CGM or insulin pump, willingness to discontinue personal CGM and pump when using the study CGM and pumps (note: including implantable CGMs)

2.3 Participant Exclusion Criteria

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

1. Concomitant disease that influences metabolic control or HbA1c interpretation (e.g. anemia, significantly impaired hepatic function, confirmed gastroparesis, renal failure, history of adrenal insufficiency, sickle cell disease, haemoglobinopathy, or has received red blood cell transfusion or erythropoietin within three months prior to time of screening) or other medical condition which, in the Investigator's opinion, may compromise patient safety, affect outcome assessments, or affect the participant's ability to follow the protocol
2. Oral or parenteral glucocorticoids taken within 1 month prior to enrollment, or plans to take oral or parenteral glucocorticoids within the planned study duration. Exceptions: Short term oral or parenteral glucocorticoids up to seven days
3. Use of antidiabetic agents other than insulin
4. Use of other medications, which in the judgment of the investigator would be a contraindication to participation in the study
5. One or more episodes of severe hypoglycemia (hypoglycemia requiring treatment by another person) within the previous six months
6. Known allergy to medical grade adhesives
7. Participation in another study of a medical device or drug that could affect glucose measurements or glucose management or receipt of any investigational medical product within 1 month prior to enrollment
8. Current eating disorder such as anorexia or bulimia
9. Currently abusing illicit drugs, marijuana, prescription drugs, or alcohol
10. Visual impairment or hearing loss, which may compromise the participant's ability to perform all study procedures safely, as determined by the investigator
11. One or more episodes of diabetic ketoacidosis (DKA) requiring hospitalization within six months prior to screening
12. Working night shifts
13. Untreated celiac disease, hyperthyroidism, or hypothyroidism
14. Clinically significant nephropathy (eGFR <45 mL/min) or on dialysis
    - Creatinine to determine eGFR must have been obtained as part of usual care within 12 months prior to enrollment (if not available, at time of enrollment, screening can proceed but it must be available prior to randomization)

2.4 Screening Procedures

After informed consent has been 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, and local laboratory testing if needed to screen for exclusionary medical conditions.

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion. Individuals who do meet eligibility criteria will proceed to the Run-In period, which will be expected to start on the same day as screening, or up to 14 days thereafter.

2.4.1 Data Collection and Testing

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or qualified designee (e.g. a physician, fellow, nurse practitioner, or a physician assistant).

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
- Physical examination to include:
    - Weight, height
    - Vital signs including measurement of blood pressure and pulse
- Blood draw for:
    - HbA1c level measured using the DCA Vantage or similar point-of-care device or local lab (used to assess eligibility)
- Urine pregnancy test for all females of child-bearing potential

Screening procedures may last approximately 1-2 hours.

2.4.2 Questionnaires

The following questionnaires will be completed by adult and adolescent participants at Screening, End of Period 1, and End of Period 2:

- Diabetes Distress Scale
- Glucose Monitoring Satisfaction Survey
- Hypoglycemia Confidence
- Diabetes Technology Attitudes
- INSPIRE Survey (only collected at End of Periods 1 and 2)

Chapter 3: Run-in Phase

3.1 Introduction

There are two parts of the run-in phase:

1) Pump Run-In (670G 3.0 HCL)
2) Pump+CGM Run-In (670G 3.0 HCL + Guardian Sensor (3))

The length of the run-in phases may vary depending on prior experience with a 670G pump, the number of CGM hours collected during run-in, and how quickly participants become comfortable using the study pump and CGM according to Table 5. Pump and CGM Run-In Criteria below.

Table 5. Pump and CGM Run-In Criteria

	Pump Run-In: -670G 3.0 HCL -Two weeks, repeat if needed	**Pump+CGM Run-In:** -670G 3.0 HCL + Guardian Sensor (3) -Two weeks, repeat if needed -Auto mode off for non-670G auto mode users, PLGS on	
Pump Users	Optional (Complete per investigator discretion)	Required	Must have CGM data for at least 80% of the possible time during the prior 14 days and average BGM test 3x/day.
Non-Pump Users	Required	Required	Must have CGM data for at least 80% of the possible time during the prior 14 days and average BGM test 3x/day.

3.2 Pump Run-In – 670G 3.0 HCL

Eligible participants will use the study 670G 3.0 HCL pump during the Pump Run-In period. Participants who were current pump users at screening may skip the Pump Run-In period per investigator discretion. Participants using the 670G in auto mode at screening may use the 670G 3.0 HCL pump in auto mode.

Standardized pump training will be provided using a training checklist to study participants and their diabetes care partners (for participants <18 years old). Additional topics may include but are not limited to: infusion site initiation, cartridge/priming procedures, setting up the pump, changing batteries, and navigation through menus. The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. For current pump users, the study pump will be programmed with the participant's usual basal rates and pump parameters. Additionally, important differences between the study pump and personal pumps such as calculation of insulin on board and correction boluses will also be discussed. The participant's personal pump will be removed. Participants may continue to use their personal CGM if applicable.

The pump will be used for at least two weeks during the Pump Run-In, with the option of repeating the Pump Run-In for an additional two weeks per investigator discretion. A contact will be made each week with additional contacts as needed. Prior to each contact, participants

will be asked to upload device data for study staff to review. The visit and contact schedule during the run-in is summarized in Table 1. Schedule of Visits and Procedures during Screening and Run-In.

After completion of the Pump Run-In, participants will proceed to use the study CGM along with the study 670G 3.0 HCL pump during the Pump+CGM Run-In period on the same day.

3.3 Pump+CGM Run-In – 670G 3.0 HCL + Guardian Sensor (3)

All participants must complete a two-week run-in period with the use of the study pump and CGM before being randomized into the crossover trial. During the Pump+CGM Run-In, the predictive low glucose suspend feature will be turned on and auto mode will be turned off (i.e. manual mode). Participants who were 670G auto mode users at screening may use the pump in auto mode.

Standardized device training will be provided using a training checklist to study participants and their diabetes care partners (for participants <18 years old) if not already provided during pump run-in. Personal pumps and CGMs will be removed during the Pump+CGM Run-In period as applicable.

A contact will be made each week with additional contacts as needed. Prior to each contact, participants will be asked to upload device data for study staff to review.

3.4 Visit and Contact Schedule

All participants will be contacted by study staff at least once during the first seven days (7±2 days), followed by a clinic visit after 14 days (14+3 days) for each run-in period. If any run-in periods are repeated, the same contact schedule will be followed.

Table 2. Schedule of Visits and Procedures During the Crossover Trial lists the visit and contact schedule during run-in. Contacts may be substituted for a visit. Additional contacts or visits may be done as needed.

3.5 Run-In Assessments

Device data will be downloaded by study staff at each clinic visit during Run-In.

Successful completion of the Pump Run-In is per investigator assessment.

Successful completion of the Pump+CGM Run-In requires that CGM data be collected for at least 80% of the possible time during the prior 14 days in addition to having an average of at least three blood glucose meter tests per day. If this is not achieved the Pump+CGM Run-In may be repeated once. If the participant does not complete the Pump+CGM Run-In the second time, the participant will be dropped.

3.6 Device Data Uploads

In addition to device data downloads performed at each clinic visit, participants will be instructed to upload device data before each scheduled contact and at least every two weeks for study staff review.

Chapter 4: Randomization 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 they are convinced that the participant is eligible and will accept assignment to either of the two treatment orders.

4.1 Randomization Visit

The randomization visit is expected to begin on the same day the Pump+CGM Run-In period is completed. 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.

4.1.1 Randomization

Eligible participants will be randomly assigned to use the study pumps (along with the study CGM) in one of the following orders:

1. 670G 3.0 HCL during Period 1 then switch to the 670G 4.0 AHCL during Period 2; or
2. 670G 4.0 AHCL during Period 1 then switch to the 670G 3.0 HCL during Period 2

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

4.1.2 HbA1c, C-peptide, and Glucose

After the participant is randomized, a blood sample will be drawn to send to the central laboratory for baseline HbA1c determination to be used in outcome analyses and may be either venous or capillary. Blood samples will also be drawn to send to the central lab for random C-peptide and glucose levels.

Chapter 5: Crossover Trial

5.1 Study Procedures and Schedule during the Crossover Trial

5.1.1 AID System Training

Automated insulin delivery (AID) training can occur on the same day or extend up to one additional day if needed from randomization. AID training includes auto mode training and will be provided at the beginning of each crossover period.

The participant and care partner will be trained by qualified study staff regarding auto mode including meal announcement, meal bolusing, and exercise. For participants <18 years old, the diabetes care partner will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon, and on all other training procedures.

Participants will be provided with Hypoglycemia, Hyperglycemia, and Ketone Guidelines for when their glucose levels are ≥250 mg/dL (13.9 mmol/L) for more than two hours, or ≥300 mg/dL (16.7 mmol/L) for over 1 hour or >400 mg/dL (22.2 mmol/L) at any time or <70 mg/dL (3.9 mmol/L) or ketones ≥0.6 mmol/L.

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

- The study team will confirm the pump parameters entered in the system
- When not to use or rely on auto mode particularly during significant illness
- CGM calibration instructions
- 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
- 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 the contacts. If the participant cannot be reached, the participant's other contact methods will be utilized.

5.1.2 Home Use of AID System during Study Period 1

After AID training has been completed, participants will proceed with home use of the AID system (meaning free-living use at work, home, etc.) during Study Period 1 with either the 670G 3.0 HCL or 670G 4.0 AHCL pump as determined by the randomization order. The predictive low glucose suspend feature will be turned on. Participants starting with the 670G 4.0 AHCL pump will return the 670G 3.0 HCL pump used during Run-In.

The system will initially be used with auto mode deactivated (except for 670G auto mode users at screening who may activate auto mode if using the 670G 3.0 HCL pump) until participants are contacted 6-10 days into Study Period 1 with instructions to ensure auto mode is initialized.

Participants will also be instructed to ensure a new sensor is inserted 24 hours prior to initializing auto mode. Participants will then continue using the AID system for 12 weeks after auto mode is initialized. Participants will be expected to use auto mode at all times at home with some exceptions (e.g. times of illness, acetaminophen use).

5.1.3 Home Use of AID System during Study Period 2

There will be no washout period. Participants will proceed with home use of the AID system (meaning free-living use at work, home, etc.) during Study Period 2 with either the 670G 3.0 HCL or 670G 4.0 AHCL pump as determined by the randomization order. Week 12 of Crossover Period 1 will be the 1st day of Crossover Period 2.

The system will initially be used with auto mode deactivated (except for 670G auto mode users at screening who may activate auto mode if using the 670G 3.0 HCL pump) until participants are contacted 6-10 days into Study Period 2 with instructions to ensure auto mode is initialized. Participants will also be instructed to ensure a new sensor is inserted 24 hours prior to initializing auto mode. Participants will then continue using the AID system for 12 weeks after auto mode is initialized. Participants will be expected to use auto mode at all times at home with some exceptions (e.g. times of illness, acetaminophen use).

5.1.4 Visit and Phone Contact Schedule during Study Periods 1 and 2

During each of the two study periods, visits and contacts will be scheduled as outlined below. Additional contacts or visits may occur as needed:

- Study Period begins
  - 6-10 days – participants will be contacted by phone to ensure auto mode is initialized
- Auto mode is initialized (remaining visits and contacts are relative to the day auto mode is confirmed to be initialized by site staff)
  - 24-hour contact *(Contact must be completed by phone)*
  - 5-day contact (±2 days) = 3-7 days *(Contact must be completed by phone)*
  - 2-week visit (±4 days) = 10-18 days
  - 4-week contact (±4 days) = 24-32 days
  - 6-week visit (±4 days) = 38-46 days
  - 9-week contact (±4 days) = 59-67 days
  - 12-week visit/contact (+7 days) = 84-91 days (end of study period)

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).

5.1.5 Procedures During Study Periods

5.1.5.1 Procedures performed during each contact

- The participant will be asked to upload device data for study staff review
- Assessment of compliance with study device use

- Answer questions about using the AID system
- Assessment of adverse events, adverse device effects, and device issues
- Review of glycemic control

5.1.5.2 Procedures performed during each follow-up visit

- 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 AID system and study meter data (BG and ketone data)
- All study blood glucose and ketone meters will be quality control (QC) tested with the available concentration(s) of control solution if the meters are available during all office visits
- Venous or capillary collection of a blood sample to send to the central laboratory for HbA1c determination at the beginning and end of Periods 1 and 2
- Urine pregnancy test for females of child-bearing potential at the beginning of Period 2
- Participant weight, height, and blood pressure will be measured at the beginning and end of Periods 1 and 2.
- Completion of questionnaires at the end of Periods 1 and 2
- Review of glycemic control

At the Final Visit, participants will return study systems and be placed back on their pre-study insulin delivery method and glucose monitoring method. If the participant desires a change (e.g. prior MDI user who wants to use a pump, non-CGM user who wants to use CGM), this will be handled as part of usual care. The Final Visit may be completed in-person in clinic or in an alternate location such as the participant's home. If this is not possible, the study visit may occur remotely via phone or videoconferencing. Certain procedures such as the measurement of height, weight, vitals, and collection of the central HbA1c sample may be missed if the visit is not completed in-person. Participants requiring a remote final visit will be transitioned off of the study device during the remote contact and an arrangement will be made between site staff and the participant to return all required study devices either in-person or via mail.

5.1.5.3 Setpoint adjustments during 670G 4.0 AHCL use

All participants in the 670G 4.0 AHCL arm will start with an auto mode target glucose set point of 120 mg/dL (6.7 mmol/L). At the auto mode initiation contact, participants will be reminded to obtain an overnight fingerstick blood glucose measurement (between 2-3AM) for 2-3 nights following auto mode initiation and if SMBG is <70 mg/dL to treat with carbohydrate, discontinue closed loop mode, and notify the investigator or designee the next day for advice. Study staff will inquire about the fingersticks and reinforce the importance of these fingersticks at both the 24-hour and 3-7 day follow-up phone calls. At the 2-week assessment visit the target glucose set point should be lowered to 100 mg/dL (5.6 mmol/L) if the participant meets the criteria listed below since the previously scheduled visit or contact and the site investigators have no other clinical reason not to reduce the setpoint:

- No severe hypoglycemia; AND

- No more than 1% of sensor glucose readings <54 mg/dL (3.0 mmol/L) for the 24-hour time period based on review of CGM download AND no sensor glucose readings less than 54 mg/dL from Midnight to 6AM; OR
- No more than 3% of sensor glucose readings less than 70 mg/dL (3.9 mmol/L) for 24 hours

If the participant does not meet these criteria the setpoint should remain at 120 mg/dL (6.7 mmol/L) and the participant should be reevaluated at 4, 6, and 9 weeks to see if the setpoint can be reduced to 100 mg/dL (5.6 mmol/L) using the same criteria. When the setpoint is lowered, the same requirement as above will be provided regarding overnight fingersticks.

The setpoint may be adjusted at any time if clinically appropriate per investigator's opinion.

5.1.6 Device Data Uploads During the Crossover Trial

Device data will be collected by clinic staff during each follow-up visit. In between clinic visits, device data will be uploaded remotely by participants before each scheduled contact and at least every two weeks.

5.1.7 Early Termination Visit

If a participant discontinues the study early, an attempt will be made to have the participant come to the clinic for a visit to return study devices and supplies, to record any adverse events or device issues that have occurred, complete final questionnaires, and collect a final HbA1c.

5.1.8 Unscheduled Visits

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

Chapter 6: Study Devices and Safety

6.1 Description of the Study Devices

6.1.1 Insulin Pumps

One insulin pump used in the study is the Minimed 670G 3.0 HCL insulin pump, which is an FDA-approved and CE-marked device system with no changes to its hardware or firmware components (MMT-1780 in the United States, MMT-1781 and MMT-1782 outside the United States). The 670G 4.0 AHCL insulin pump will also be used and is an investigational product (MMT-1740 in the United States, MMT-1741 and MMT-1742 outside the United States). The 670G 4.0 AHCL pump is the same as the 670G 3.0 HCL pump except the AHCL pump includes the Fuzzy Logic algorithm software.

6.1.2 Continuous Glucose Monitoring

The study sensor is the Guardian Sensor (3) (MMT-7020). This is an FDA-approved and CE-marked device system with no changes to its hardware or firmware components. The CGM sensor will be connected to a Guardian Link (3) transmitter (MMT-7811) and the sensor will be replaced in accordance with manufacturer labeling (e.g. at least once every seven days). This device is not investigational.

6.1.3 Blood Glucose Meter and Strips

Blood glucose levels will be measured and the CGM device will be calibrated using the Contour Next Link 2.4 meter (MMT-1152 or MMT-1352) (or equivalent meter, such as the Contour plus Link) and test strips in accordance with manufacturer labeling.

6.1.4 Ketone Meter and Strips

Blood ketone levels will be measured using the Abbott Precision Xtra (or equivalent meter, such as the Optium Neo) meter and strips in accordance with manufacturer labeling. The blood glucose meter component of ketone meters will not be used.

6.2 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 only by (on) participants who have consented to participate in the research study.

Any investigational device or approved devices used outside their approved intended use being used 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

US: Investigational devices or approved devices used outside their approved intended use will be labeled “Investigational Device” in accordance with 21 CFR Part 812.140.
EMEA: In accordance with the MDD directive, the investigational devices for EMEA will be labeled “Exclusively for Clinical Investigations”

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.

6.2.1 Blood Glucose Meter Testing

- Participants will be provided with instructions to perform quality control (QC) testing per manufacturer guidelines. Participants will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
- A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.
- Participants will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device.

6.2.2 Blood Ketone Testing

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

6.3 Safety Measures

6.3.1 CGM Calibration

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

6.3.2 Pump Failure

In the event of a pump failure, the participant will be instructed to use their personal insulin regimen until the problem can be resolved. Reportable events are described in Chapter 8:.

6.3.3 Hypoglycemia Threshold Alarm and Safety Protocol

During the course of the study, participants will be permitted to change the low glucose threshold alarm setting, but it is recommend to set it to 70 mg/dL (3.9 mmol/L). Participants will be encouraged to be consistent with their use of any such features between the two periods of the crossover study.

If a participant receives a CGM hypoglycemia threshold alarm or notes that the CGM glucose is below the hypoglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labelling and the participant will be instructed to treat hypoglycemia with ~15 grams of fast-acting oral glucose.

6.3.4 Hyperglycemia Threshold Alarm and Safety Protocol

During the course of the study, participants will be permitted to change the high glucose threshold alarm setting, but it is recommend to set it to 300 mg/dL (16.7 mmol/L). Participants will be encouraged to be consistent with their use of any such features between the two periods of the crossover study.

If a participant receives a CGM hyperglycemia threshold alarm or notes that the CGM glucose is above the hyperglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labelling.

During the time period when auto mode is operational and active, if a participant's CGM reading is >300 mg/dL (16.7 mmol/L) for over one hour or ≥400 mg/dL (22.2 mmol/L) 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 (16.7 mmol/L), check for blood ketones with the study ketone meter.
        - If the ketone level is >0.6 mmol/L, contact study staff for further instructions, which may include replacing the insulin infusion set.

6.3.5 Safety Measures Specific to AID system use

6.3.5.1 Insulin Dosing

In auto mode, all dosing is supervised by the AID system. Insulin injection for meal boluses must be performed using the pump bolus calculator.

6.3.6 Safety Measures for Open-Loop (Manual Mode) CGM Use

These measures apply when the AID system (auto mode) is not being used or is not communicating with the CGM device.

6.3.6.1 Hypoglycemia Safety Protocol

If a participant receives a CGM hypoglycemia threshold or predictive alarm or notes that the CGM glucose is below the hypoglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labeling and the participant will be instructed to treat hypoglycemia with ~15 grams of fast-acting oral glucose.

6.3.6.2 Hyperglycemia Safety Protocol

If a participant receives a CGM hyperglycemia threshold alarm or notes that the CGM glucose is above the hyperglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labeling.

Chapter 7: Laboratory Testing and Questionnaires

7.1 Laboratory Testing

HbA1c:

- Performed locally at the Screening visit.
- Collected for central lab analysis at Randomization, and at the beginning and end of each study period during the crossover trial. Final HbA1c may also be collected for participants who withdraw from the study.

Random C-Peptide and Glucose:

- Collected at Randomization for central lab analysis

Urine Pregnancy:

- Performed locally for females of child-bearing potential at Screening and at the beginning of each study period during the crossover trial. This test may also be performed at any time pregnancy is suspected.

Local laboratory testing will be performed if needed to screen for exclusionary medical conditions. Normal creatinine levels must have been obtained within 12 months prior to enrollment (if not available, at time of enrollment, screening can proceed but it must be available prior to randomization).

7.2 Questionnaires

The following questionnaires will be completed at Screening and at the end of each period during the crossover trial (except that the INSPIRE survey will not be administered at Screening). Final questionnaires may also be collected for participants who withdraw from the study.

Each questionnaire is described briefly in Table 6. Questionnaires below. The procedures for administration are described in the study procedures manual.

Table 6. Questionnaires

Measure	Construct Measured / Relevant Points
Diabetes Distress Scale	Gold standard measure for understanding distress symptoms related to diabetes. A recently validated version for adults with T1D, but will also be administered to adolescents (17 items; 6 min)
Glucose Monitoring Satisfaction Survey	This recently validated survey is an outgrowth of DirecNet and JDRF CGM surveys; evaluates treatment satisfaction and burden. Administered to all participants (15 items; 4 min)
Hypoglycemia Confidence	Includes 8 different common situations where hypoglycemia occurs (e.g., physical activity, driving) and evaluates level of confidence in those situations (8 items; 3 min)
Diabetes Technology Attitudes	Subjective questions about attitudes related to diabetes technologies and devices (5 items; 3 min)
INSPIRE Survey	Measures the psychological side of automated insulin delivery. Adult survey has 22 items; adolescent version 17 items. (6-8 mins; only collected at end of periods 1 and 2)

Chapter 8: Adverse Events, Device Issues, and Stopping Rules

8.1 Adverse Events

8.1.1 Definitions

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

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

- Results in death.
- 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, an investigational 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). For reporting purposes, the ADE definition will be used to define reportable AEs for the commercially available system (670G 3.0) as well as the investigational system (AHCL).

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

8.1.2 Reportable Adverse Events

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

1. An SAE
2. An ADE as defined in Section 8.1.1, unless excluded from reporting in Section 8.2
3. An AE as defined in Section 8.1.1 occurring in association with a study procedure
4. An AE as defined in Section 8.1.1 which leads to discontinuation of a study device for two or more hours
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

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.

Pregnancy occurring during the study will be reported as an AE (see Section 8.3).

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.

8.1.2.1 Hypoglycemic Events

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

8.1.2.2 Hyperglycemic/Ketotic Events

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following four 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
- 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

8.1.3 Relationship of Adverse Event to Study Device

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device. Note that this assessment will be made for both the investigational device (AHCL system) and the commercially available system (670G 3.0).

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.

8.1.4 Intensity of Adverse Event

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

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

8.1.5 Coding of Adverse Events

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

8.1.6 Outcome of Adverse Event

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

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

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 subject 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.

8.2 Reportable Device Issues

All UADEs and ADEs as defined in Section 8.1.1 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 are not severe and/or require treatment.

Device complaints and device malfunctions for the investigational device 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:

- CGM sensor lasting fewer days than expected per manufacturer
- 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

8.3 Pregnancy Reporting

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

8.4 Timing of Event Reporting

SAEs possibly related to an investigational 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 seven 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 Coordinating Center will investigate the UADE and if indicated, report the results of the investigation to the sites' IRBs, and the FDA within ten working days of the Coordinating Center 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.

8.5 Stopping Criteria

8.5.1 Participant Discontinuation of Investigational Device

Rules for discontinuing investigational 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 8.1.2) unrelated to infusion set failure
- A single episode of severe hypoglycemia (as defined in section 8.1.2.1) or DKA (as defined in section 8.1.2.2) for which use of the investigational device (AHCL system) is considered by either the Medical Monitor or DSMB to be the cause of the event (ie, there is not another plausible assignable cause) in the absence of a device malfunction (e.g., software bug) for which the automated insulin delivery algorithm is temporarily or permanently discontinued for all subjects
- Two distinct severe hypoglycemia events (as defined in Section 8.1.2.1)

Even if the investigational device system is discontinued, the participant will be encouraged to remain in the study through the final study visit. If the investigational device (ie. AHCL system) is discontinued for safety reasons, the investigator with concurrence of the Medical Monitor can switch the participant to either use the 670G 3.0 HCL system in closed loop (if the participant entered the trial on 670G 3.0 HCL using closed loop) or to 670G 3.0 HCL system but in open loop only.

8.5.2 Criteria for Suspending or Stopping Overall Study

In the case of an unanticipated system malfunction of the investigational device resulting in a severe hypoglycemia or DKA event (both defined in Section 8.1), use of the investigational device system will be suspended while the problem is diagnosed.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

The study Medical Monitor will be informed of all adverse events and adverse device events that are reported during the study 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.

8.6 Independent Safety Oversight

A Data and Safety Monitoring Board (DSMB) will review compiled safety data at periodic intervals (typically every six months). In addition, the DSMB will review all DKA and severe hypoglycemia events irrespective of relatedness to study device use, and all serious events (including UADEs) related to the study device use 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 9: Miscellaneous Considerations

9.1 Drugs Used as Part of the Protocol

U-100 rapid acting insulin analogues, Aspart or Lispro, will be used during the study since these are the only insulins approved for the study pumps.

9.2 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 issues as described in Section 8.1 and Section 8.2, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (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, 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.

9.3 Prohibited Medications, Treatments, and Procedures

Acetaminophen/Paracetamol may cause unreliable glucose sensor readings. If possible, participants should avoid taking medications with acetaminophen while in Auto Mode. If acetaminophen is taken, participants will be instructed to turn off auto mode and use BG meter readings to follow glucose levels. Additional BG meter readings should not be used to calibrate the sensor. Auto mode should be restarted when BG meter and CGM readings are consistently in close agreement which may take up to 8-12 hours.

Exclusionary medications are:

- Oral or parenteral glucocorticoids taken within 1 month prior to enrollment, or plans to take oral or parenteral glucocorticoids within the planned study duration. Exceptions: Short term oral or parenteral glucocorticoids up to 7 days
- Any antidiabetic agents other than insulin

9.4 Participant Compensation

Participant compensation will be specified in the informed consent form.

9.5 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 final study visit.

9.6 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 10: Statistical Considerations

10.1 Statistical and Analytical Plans

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

10.2 Statistical Hypotheses

The co-primary outcomes are CGM-measured metrics over 12-week periods (excluding time before auto mode is turned on):

- Superiority in percent time >180 mg/dL (10.0 mmol/L) from 6AM to 11:59PM
- Non-inferiority in CGM-measured time <54 mg/dL (3.0 mmol/L) calculated over the full 24 hours of the day

The study hypotheses can be stated as follows:

Hyperglycemic Outcome:

- *Null Hypothesis:* There is no difference in the percentage of time spent with sensor glucose levels above 180 mg/dL between the two treatments during the daytime for the entire study population.
- *Alternative Hypothesis:* There is a nonzero difference in the percentage of time spent with sensor glucose levels above 180 mg/dL between the two treatments during the daytime for the entire study population.

Hypoglycemic Outcome:

- *Null Hypothesis:* There is a mean difference of at least 2% in the percentage of time spent with sensor glucose levels below 54 mg/dL between the AHCL system and the 670G 3.0 system over the full 24 hours of the day for the entire study population.
- *Alternative Hypothesis:* There is a mean difference of less than 2% in the percentage of time spent with sensor glucose levels below 54 mg/dL between the AHCL system and the 670G 3.0 system over the full 24 hours of the day for the entire study population.

10.3 Sample Size

The sample size calculation is detailed in a separate document and summarized below.
For computing sample size, estimates of the standard deviation (SD) for time spent in hypoglycemia and hyperglycemia were made based on data from previous studies, Medtronic 670G Pivotal Trial [1], DIAMOND[2], JDRF CGM RCT[3], and REPLACE-BG[4].

Analyses of both primary outcomes must have a significant result ($p < 0.05$) to declare benefit of the intervention. The two co-primary outcomes therefore do not inflate the type 1 error, but requiring both to be significant can inflate the type 2 error. A Bonferroni correction was therefore applied to the power calculations by adding the type 2 error rate (i.e., 100% minus power) for the two analyses. This represents a conservative estimate for composite power as the probability that both tests will reject the null hypothesis.

The total sample size was computed to be 65 for the following assumptions (1) 90% power, with adjustment to account for the two co-primary analyses, (2) a 5% absolute reduction in time >180 mg/dL (10.0 mmol/L) with a standard deviation of paired differences of 12%, and a 2-sided type 1 error rate of 5%, and (3) a non-inferiority limit of 2% for the treatment group comparison of time <54 mg/dL (3.0 mmol/L) with an SD of paired differences of 1.3% and 1-sided type 1 error of 2.5%.

A sample size of 100 completing the trial has been selected to provide increased precision for safety analyses and subgroup analyses. With a sample size of 100 participants completing the crossover trial, the primary analysis will have 98% power.

10.4 Outcome Measures

All CGM derived indices will be calculated over the first 84 days of each period. The beginning of the period is defined as the time that auto mode is first turned on, which per protocol is 6-10 days after the period starts. A post-meal period is defined as follows: meal starts at the time the carbohydrate is entered and post-meal period ends at three hours after a meal unless another carbohydrate is entered <3 hours, which is then considered the end of the post-meal period.

Hypoglycemia metrics are considered both safety and efficacy outcomes.

The following co-primary outcomes will be compared between the two treatment arms in this crossover trial (PID algorithm vs. PID + Fuzzy logic algorithm):

- The percent time spent with sensor glucose >180 mg/dL (10.0 mmol/L) during the day (6AM – 11:59 PM)
- Non-inferiority for CGM time <54 mg/dL (3.0 mmol/L) over 24 hours

The secondary efficacy analyses will include treatment comparisons for the following outcomes:

- CGM derived indices for the full 24-hour day, during daytime (6AM-11:59PM), during nighttime (12AM-5:59AM), and for each post-meal period:
  - Mean glucose
  - Coefficient of variation
  - Percentage of sensor glucose from 70 to 180 mg/dL (3.9 to 10.0 mmol/L) and 70 to 140 mg/dL (3.9 to 7.8 mmol/L)
  - Percentage of sensor glucose > 180 (daytime is a co-primary outcome) and >250 mg/dL (10.0 and 13.9 mmol/L, respectively)
  - Peak glucose and change from the start of the meal to the peak (only calculated for post-meal periods)
- Amount of total, basal and bolus daily insulin for the full 24 hour, daytime (6AM-11:59PM), nighttime (12AM-5:59AM), and for each post-meal period (both total units and units/kg).
- HbA1c
- BMI

Additionally, summary statistics will be reported (but treatment arm comparisons will not be done) for the following outcomes:

- CGM-derived indices over the first 84 days of each treatment period for 24 hours (excluding time before auto mode is turned on), daytime (6AM-11:59PM), nighttime (12AM-5:59AM), and for each post-meal period (meal starts at the time the carbohydrate is entered), measured for up to three hours after a meal (or until another carbohydrate is entered):
    - Percentage of sensor glucose <50 and <60 mg/dL (2.8 and 3.3 mmol/L respectively)
    - Glucose area under the curve >180 mg/dL (10.0 mmol/L)
    - Glucose area over the curve <70 mg/dL (3.9 mmol/L)
    - Percentage of sensor glucose >300 mg/dL (16.7 mmol/L)
    - Glucose standard deviation
- Three level variables denoting change in total insulin, basal insulin, and bolus insulin (increase by >10%, decrease by >10%, or in between)
- Binary HbA1c variables:
    - Improvement ≥0.5% and ≥1.0%
    - Relative reduction ≥10%
    - Proportion of participants achieving HbA1c <7.0%

10.5 Analysis Cohorts

Intent to treat

The co-primary analyses will follow the intention-to-treat principle. They will include all randomized participants, and data will be analyzed based on the treatment sequence assigned from randomization regardless of the actual treatment received. Data will not be truncated due to protocol deviations. No imputation will be made for missing data.

Per-protocol

A per-protocol analysis for the co-primary outcomes also will be conducted by limiting to those participants who used the CGM at least 80% of the time in both periods and who used the auto mode feature for at least 80% of the time in both treatment periods, unless the N for the analysis is ≥95% of the N in the primary intent-to-treat analysis.

Safety

All participants will be included in safety analyses.

10.6 Analysis of the Primary Efficacy Endpoints

For each co-primary outcome, a single value will be calculated for each participant during each period. Details regarding the primary analysis cohorts, handling of missing data, and protocol deviations are discussed in Section 10.5. Mean ± SD or percentiles appropriate to the distribution will be reported for each co-primary outcome by treatment period. A repeated measures least squares regression model with an unstructured covariance structure will be fit for the two co-primary outcomes to compare the two treatments adjusting for period, pre-study 670G system use, and HbA1c at randomization as fixed effects. In order to declare benefit of the intervention, both outcomes must be significant based on these models.

Time >180 mg/dL (10.0 mmol/L) (superiority)

A 95% confidence interval will be reported for the difference between the two treatment arms based on the least squares model. Residual values will be examined for an approximate normal distribution. If values are highly skewed, then a transformation or nonparametric method will be used instead. Based on previous data, we do not expect that a transformation will be necessary. A two-sided p-value will be reported, and a 5% significance level will be used to declare statistical significance.

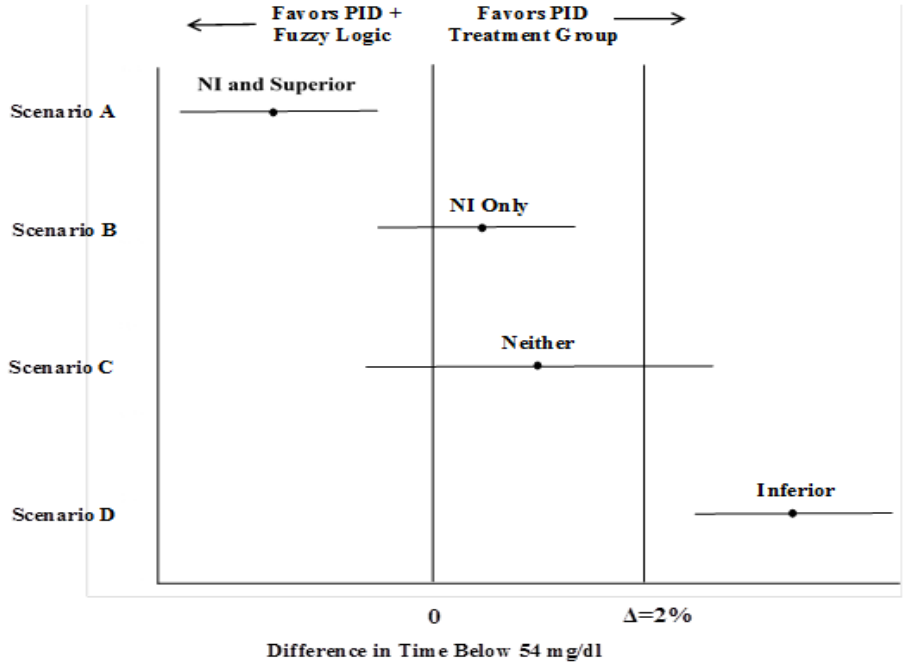
Time <54 mg/dL (3.0 mmol/L) (non-inferiority)

A two-sided 95% confidence interval will be reported for the difference between the two treatment arms based on the least squares model. Non-inferiority will be assessed by comparing the upper limit of this confidence interval to a non-inferiority limit of 2% (approximately 30 minutes per day). This limit was selected solely based on clinical judgment. The non-inferiority limit corresponds to the difference between the 670G 4.0 AHCL system (which is the experimental treatment) and the 670G 3.0 HCL system (which is the active control). Residual values will be examined for an approximate normal distribution. If values are highly skewed, then a transformation or nonparametric method will be used instead. A two-sided p-value will be reported, and a 5% significance level will be used to declare statistical significance.

Since non-inferiority is typically framed in terms of a one-sided test, it is worth noting that the left half of a two-sided test at alpha = 0.05 gives the same rejection region as a one-sided test at alpha = 0.025. Therefore, reporting a two-sided 95% confidence interval will provide flexibility to test for inferiority if non-inferiority cannot be declared while maintaining the overall type 1 error rate at 5%. Figure 4 below shows the inference to be drawn for various scenarios of the two-sided 95% confidence interval:

Figure 4. Non-Inferiority and Superiority

Interpretation of Various Scenarios of Non-inferiority (NI) and Superiority for Treatment Group Comparison of Time Below 54 mg/dl



* NI refers to non-inferiority of PID + Fuzzy Logic compared with PID with a non-inferiority limit of Δ=2% time below 54 mg/dl.

Monthly trends for the co-primary outcomes will also be evaluated using boxplots. Summary statistics also will be displayed by treatment arm for each hour of the day.

The co-primary analyses will also be performed after omitting the first 4 weeks of each of the crossover periods.

10.7 Analysis of the Secondary Endpoints

Secondary CGM-measured glycemic metrics will be calculated in the same way as the co-primary outcomes.

Mean ± SD or percentiles appropriate to the distribution for above secondary outcomes will be reported by treatment period. For each secondary CGM metric, a repeated measures least squares regression model with an unstructured covariance structure will be fit to compare the two treatments by adjusting for period, pre-study 670G system use, and HbA1c at randomization as fixed effects. For those metrics which have highly skewed distribution, a ranked normal score transformation of outcome data will be applied in the regression model.

For comparing changes in HbA1c and BMI over each treatment period, the least squares regression models will adjust for period, pre-study 670G system use, and HbA1c at randomization. The model for BMI will additionally adjust for baseline value, age, and sex.

Monthly trends for selected secondary outcomes will be evaluated using boxplots.

10.8 Safety Analyses

All reportable adverse events will be tabulated by treatment group from the time of enrollment through the last study visit. Events will be separately listed in detail and tabulated for the pre-randomization period and each study period. Coding will use the Medical Dictionary for Regulatory Activities (MedDRA).

In addition, the following will be tabulated by treatment arm:

- Number of adverse events/ participants with at least one event
  - Number of events meeting definition of ADE
- Number of serious adverse events/participants with at least one event
  - Number of SAEs meeting definition of UADE
- Listing of hospitalizations and reasons for the hospitalization
- Severe Hypoglycemic Events
  - Number of severe hypoglycemic events as defined in the protocol/number of participants with an event
  - Number of severe hypoglycemic events associated with seizure or loss of consciousness/number of participants with at least one event
- Diabetic Ketoacidosis
  - Number of diabetic ketoacidosis events, as defined in the protocol/number of participants with an event

If there are enough observed events to allow formal statistical modelling the following analyses will be conducted for severe hypoglycemia and diabetic ketoacidosis events outcomes. For binary variables, repeated measures logistic regression which adjust for period, pre-study 670G system use, HbA1c at randomization, and whether the participant experienced any events in the 12 months prior to enrollment as fixed effects will be used to compare treatment groups. For counts, such as the number of severe hypoglycemic or diabetic ketoacidosis events per participant, data will be compared using repeated measures Poisson regression with period, pre-study 670G system use, HbA1c at randomization, and whether the subject experienced any events in the 12 months prior to enrollment as fixed effects adjusted in the model. All participants will be included in these analyses.

10.9 Adherence and Retention Analyses

Tabulations and figures by treatment period to assess protocol adherence will include:

- Flowchart showing any dropouts prior to and post randomization and treatment arm completion
- Visit completion rates for each follow up visit
- Protocol deviations
- Numbers and reasons for unscheduled visits and phone calls

10.10 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics will be tabulated by randomization group.

10.11 Planned Interim Analyses

No formal interim analyses or stopping guidelines are planned for this study.

The DSMB will review data for safety per the DSMB Standard Operating Procedures approximately every six months. The data to be reviewed will include information regarding adverse events, device issues, and protocol adherence/deviations as they may relate to participant safety.

10.12 Sub-Group Analyses

Exploratory subgroup analyses/assessments of effect modification (interaction) will be conducted for each of the two primary outcomes. Interpretation of the analyses will be made with caution, particularly in the absence of an overall difference. The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the model used for the primary analysis.

The following baseline factors will be assessed:

- Age: as a continuous variable and in two age groups: 14-<21 and 21-<30 years old
- Baseline HbA1c: as a continuous variable and in two groups: HbA1c ≤8.5% and ≥8.6%
- Insulin method/CGM: 670G user, injection user with CGM, injection user without CGM, pump user with CGM, pump user without CGM
- T1D duration as a continuous variable
- Sex
- Race/ethnicity
- Random C-peptide level

Beyond above assessment for interactions, the primary and secondary analyses also will also be conducted separately in the two age groups and the two HbA1c groups, in addition to the CGM metrics considered as safety outcomes. Analyses will only be replicated within these subgroups for efficacy outcomes where p-values are being computed.

10.13 Multiple Comparison/Multiplicity

For the primary analyses, the intervention will be deemed effective only if the null hypotheses for both co-primary outcomes are rejected. The type 1 error is therefore not inflated and there will be no correction for multiple comparisons.

For the secondary analyses, the false discovery rate will be controlled using the adaptive Two Stage Benjamini-Hochberg procedure with <0.05 as the threshold for statistical significance.

10.14 Additional Tabulations and Analyses

10.14.1 Device Issues and Tabulations

All reported device issues will be tabulated regardless of whether they were associated with adverse events.

Detailed tabulations will include frequency of use of the system, discontinuation rate, and reasons for discontinuation.

The amount of auto mode system use and CGM use will be calculated over each treatment period. Similar repeated measures least squares regression models as described for the co-primary outcomes will be used to compare the percentage of time of CGM use and auto mode

use between the two periods. Monthly values for auto mode use and CGM use also will be reported.

10.14.2 Analysis of Quality of Life Data

Quality of life data collected during study assessments will be scored based on established procedures and descriptive statistics (e.g., mean, range) will be calculated for each questionnaire at each time point and across treatment groups. Similar models as described above for the primary analysis will be used to compare the questionnaire scores between the two treatments.

Chapter 11: Data Collection and Monitoring

11.1 Case Report Forms and Device Data

The main study data are collected through a combination of electronic case report forms (eCRFs) 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. If paper source documentation is used to initially collect data, this will be considered the source.

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

11.2 Study Records Retention

Study documents should be retained for a minimum of two 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 two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

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

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

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

- Device accountability
- Communications with site staff
- Participant retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

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

11.4 Protocol Deviations

A protocol deviation is any action that departs from the established policies and procedures, formal documents or processes, Good Clinical Practice, federal or state laws, or regulations applicable to the conduct of the research.

A significant protocol deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to the participant, adversely affects the welfare, rights, or safety of the research subjects, or negatively influences the scientific study integrity.

Noncompliance with the clinical trial protocol, GCP, or procedure requirements may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB/EC requirements for reporting. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 12: Ethics/Protection of Human Participants

12.1 Ethical Standard

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

12.2 Institutional Review Board (IRB) (or Ethics Committee (EC))

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/EC 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/EC before the changes are implemented to the study. All changes to the consent form will be IRB/EC approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1 Consent Procedures and Documentation

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

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.3.2 Participant and Data Confidentiality

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

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

records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research (JCHR) in Tampa, FL, USA. 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.

12.4 CareLink Clinical System

The CareLink Clinical system uses standard Transport Layer Security (TLS) technology. TLS transmission invokes encryption on both ends of the transmissions and is the standard for all security-based systems. The encryption remains in effect whether the data are moving to and from the client and server in the United States, or to and from a client in another country to the United States. The data are secure behind a three-tier industry standard architecture, which places the database behind three different firewalls, where each firewall separates a tier:

- The internet to the web server;
- Web server to the application server;
- Application server to the database server.

Chapter 13: References

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