Medtronic

Study Title	Evaluation of the Advanced Hybrid Closed Loop (AHCL) System in Type 1 Adult and Pediatric Subjects Utilizing Lyumjev® insulin lispro-aabc
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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Evaluation of the Advanced Hybrid Closed Loop (AHCL) System in Type 1 Adult and Pediatric Subjects Utilizing Lyumjev® insulin lispro-aabc
Clinical Investigation Plan Identifier	CIP335
Clinical Investigation Plan Version	E
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0, 28-JUN-2022	Not Applicable, New Document	[redacted]

2.0, 13-SEP-2022	Following sections updated per Protocol Version C:
	• 3.2 Purpose
	• 4. Study Objectives
	• 5. Investigation Plan
	  ○ Removed subjects 2-6 years of age throughout protocol
	• 6. Determination of Sample Size
	• 7. Statistical Methods
	  ○ Update endpoints for updated pediatric age group
	  ○ Update time window for analysis to reflect the newly added day 44 visit
		[redacted]

3.0, 20-DEC-2023	2. List of Abbreviations and Definitions of Terms
	• Add CSII
	7.4 Handling of Missing, Unused, and Spurious Data and Dropouts
	• Add data imputation when visit 13 missing
	7.9.4.2 Sensitivity Analysis 2: Site effect evaluation with ITT population
	• Clarify the description of "Pseudo-site"
	7.9.5 Descriptive Endpoints
	• Add Age subgroup
	7.9.6 Safety Data Summarized
	• Add analysis time window
	Following sections updated per Protocol Version D & E:
	• 5. Investigation Plan
	  ○ Updated "weeks" with associated study visit
	  ○ Removed the word "live" training
	  ○ subjects to avoid additional exercise and/or meals up to four hours after the start of the challenge
		[redacted]

Version	Summary of Changes	Author(s)/Title
	○ Details about regular sized meal challenge with missed meal bolus	

2. List of Abbreviations and Definitions of Terms

Abbreviations	
AHCL	Advanced Hybrid Closed Loop
AUC	Area Under Curve
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EOS	End of Study
FDA	Food and Drug Administration
HbA1c	Glycosylated hemoglobin
ICF	Informed Consent Form
ISO	International Organization for Standardization
ITT	Intention to Treat
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump
SAP	Statistical Analysis Plan
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TDD	Total Daily Dose
TIR	Time in Range
TLFs	Listings and Figures
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

3. Introduction

3.1 Background

In patients with insulin dependent diabetes mellitus, glycemic control is influenced by numerous factors such as insulin dosage, insulin absorption, timing, physiological/ lifestyle factors such as exercise, food intake, hormones and illness. These factors may contribute to significant variability in insulin requirements, which makes self-management of type 1 diabetes challenging.

Patients who are using continuous glucose monitoring (CGM), including sensor-augmented pump therapy, experience improvements in glycemic control. Advanced sensor-augmented insulin pumps are now being used in clinical practice including closed loop systems that automatically adjust the amount of insulin delivered to maintain glucose levels near the target value set by the user.[1]

The MiniMed 780G system is a closed loop insulin system. In addition to automatically adjusting the amount of insulin delivered based on sensor glucose (SG) readings while operating with SmartGuard feature activated, the MiniMed 780G insulin pump can also automatically deliver correction boluses when the system has been delivering at the maximum allowable basal rate and SG remains elevated. This pump is currently in commercial distribution in Europe and is under review by the United States Food and Drug Administration (FDA). Previous clinical investigations involved the 670G Version 4.0 pump (contains the 780G AHCL algorithm) used in combination with the Guardian Sensor (3) glucose sensor and Guardian Link 3 transmitter, Humalog and Novolog insulin. This investigation is intended to confirm safety of the 780G insulin pump used in combination with insulin lispro-aabc (Lyumjev).

3.2 Purpose

The purpose of this study is to evaluate the safety and effectiveness of Lyumjev insulin use in the MiniMed 780G System in type 1 diabetes adult and pediatric subjects in a home setting.

4. Study Objectives

The objective of this study is to evaluate the safety and effectiveness of utilizing Lyumjev insulin in the MiniMed 780G System to support product and system labeling.

5. Investigation Plan

This study is a multi-center, single arm study in insulin-requiring adult and pediatric subjects with type 1 diabetes on the MiniMed 780G system using Lyumjev insulin and Medtronic Extended infusion set and reservoir. The run-in period and study period will be approximately 120 days long.

The period from Visit 1 (consent and screening) through Visit 6 should be completed within 30 days.

Run-in Period (Visits 2-6):
The run-in period begins at Visit 2 and ends once Visit 7 occurs.

The intent of the run-in period will be to allow subjects to become familiar with new study devices while using their own insulin, either Humalog (insulin lispro injection) or NovoLog (insulin aspart solution for injection) or Admelog (insulin lispro injection). During the run-in period, study subjects will be using the study pump with only the Sensor Augmented Pump (SAP) function activated (i.e., SmartGuard feature is turned OFF) and Medtronic Extended infusion set and reservoir.

During the run-in period, the use of SmartGuard, with the exception of Auto Correction, will be permitted for study subjects who were using the Auto Mode feature in a Medtronic pump prior to screening. In the MiniMed 780G pump, the term "Auto Mode" has been replaced with "SmartGuard". For those subjects, a 120 mg/dL Auto Basal target should be set. It is recommended that Active Insulin Time is set to 4 hours. All others are to use the system in Manual Mode during the run-in period.

Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.

Therapy at Screening	**Pump Setting During Run-in Period**
Continuous Subcutaneous Insulin Infusion (CSII)	Manual Mode
SAP (no closed loop)	Manual Mode
SAP (with closed loop) in non-Medtronic pump	Manual Mode
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard with Auto Correction OFF

All subjects, companions, and their parents/caregivers (if applicable) will be trained on diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. In addition, there will be training by the investigational center staff regarding the need to have access to and how to use glucose and glucagon in case of hypoglycemia.

Parents/caregivers (if applicable) and companions will be instructed that they should be with the subject in the same residence or building overnight.

If the MiniMed Clinical app and the CareLink Clinical app are being used, parents/caregivers (if applicable) will be instructed that subjects should be connected to CareLink via the appropriate Smartphone app for data uploading and push notifications for low or high blood sugar when they are apart, e.g., at school, other activities. Instructions on the appropriate operation of the apps will be provided.

For study purposes, subjects, parents/caregivers (if applicable) and companions will be trained and/or instructed to perform self-monitoring of blood glucose (SMBG) if subjects are experiencing a severe hypoglycemic event, severe hyperglycemic event or diabetic ketoacidosis (DKA). Subjects and their parents/caregivers (if applicable) as well as companions will also be instructed to check subject's blood ketones using a ketone meter if the Accu-Chek Guide Link study meter reading is greater than 300 mg/dL.

As a precaution, subjects and their parents/caregivers (if applicable) will be told that they should keep their own insulin pump supplies in a safe place and to have back up supplies on hand (such as insulin and syringe, or insulin pen) in the event they are asked to revert back to their own therapy during the study or experience study pump issues (i.e., infusion set occlusion with high glucose).

Subjects and their parents/caregivers (if applicable) will be instructed to insert the glucose sensors only in the locations that are specified in the User Guide. Reminders will be given to subjects and their parents/caregivers (if applicable), at each office visit. Information about sensor insertions will be collected on an electronic case report form (eCRF) in the study database (i.e. insertion location).

Subjects and their parents/caregivers (if applicable) will be trained on all parts of the device system. Companions should be trained on matters regarding responses to high or low glucose events. This will involve training conducted by the investigational center staff. A training checklist for each subject should be completed by investigational center-based trainers. Parents/caregivers (if applicable) and companions should be available for relevant parts or all of this training, either in person or virtually.

After completion oftraining on the study devices, subjects and their parents/caregivers (if applicable) may attend additional visits in the days immediately following the start of system use, as needed. They may also take advantage of having access to the digital learning content, provided it is available at study start.

The period from Visit 1 (consent and screening) through Visit 6 should be completed within 30 days.

Study Period (Visits 7-15):
The study period begins at Visit 7 and ends at the conclusion of Visit 15.

All subjects will use Lyumjev insulin for the remainder of the study. They will continue using the MiniMed 780G system, extended infusion set and extended reservoir. All SmartGuard features will be activated and should be used for the duration of the study period.

Subjects should use the system with SmartGuard turned on, while also using Lyumjev insulin at all times. When prompted by the pump, subjects should take appropriate measures and follow directions on the pump to remain in or return to SmartGuard. During times when subjects are not able to use SmartGuard, they should use the system in Manual Mode (e.g., with Suspend before low or Suspend on low activated).

Therapy at Screening	Pump Setting During Study Period
CSII	SmartGuard with Auto Correction ON
SAP (no closed loop)	SmartGuard with Auto Correction ON
SAP (with closed loop) in non-Medtronic pump	SmartGuard with Auto Correction ON
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard with Auto Correction ON

During the first 3 weeks (between Visits 7 and 11) of the study period, a 120 mg/dL Auto Basal Target should be set. It is recommended that Active Insulin Time is initially set to 4 hours and then titrated towards 2-3 hours at investigator's discretion.

During the next 3 weeks (between Visits 11 and 13) of the study period, the Auto Basal Target setting should be set to 100 mg/dL. Active Insulin time is recommended to be set to 2-3 hours or at investigator discretion.

During the remaining weeks of the study (any time after Visit 13) of the study period, the auto basal target as well as Active insulin time should be set to what is best for the individual subject, at investigator discretion.

Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above unless there is a documented safety reason that would not permit these settings to be used.

After completion of training on SmartGuard functions, subjects and their parents/caregivers (if applicable) may attend additional visits in the days immediately following the start of SmartGuard use, as needed. They may also take advantage of having access to the digital learning content, provided it is available at study start.

Staged Enrollment:

The enrollment of pediatric subjects 7-17 years of age into the study may not proceed until N=10 subjects 18 years of age or older have completed 30 days of the study period and the Data Monitoring Committee (DMC) has determined it is safe for subjects 7-17 years of age to be enrolled in the study.

SMBG recommendations for the MiniMed 780G system:
Calibration is not required with the MiniMed™ 780G system using Guardian 4 CGM. However, a calibration is optional and it will automatically occur any time a blood glucose (BG) is entered. Occasionally, subjects may receive a notification if the pump needs a BG to enter or stay in the SmartGuard™. Subjects will be instructed to perform SMBG if their symptoms do not match the sensor glucose (SG) value (i.e., they develop symptoms of hypoglycemia or hyperglycemia, but the SG value does not correlate with their symptoms).

Meal and Exercise Challenges:
Subjects will be asked to participate in meal and exercise challenges during the run-in and study period.

- All challenges are at least 4 hours in duration, beginning at the time when the challenge meals or exercise are started

- There should be no more than one meal challenge on a single day.
- Meal and exercise challenges should not be scheduled on the same day during the specified time periods.

For example: A study period regular sized or large sized meal challenge should not take place on the same day as an exercise challenge

Subjects will be asked to check BG at the start of the meal/exercise, as well as 2 hours and 4 hours after the start of the meal/exercise and provide insulin correction as necessary.

It is important for subjects to avoid additional meal/snack or exercise up to 4 hours after the start of each challenge. If additional meal/snack is consumed or exercise is done within 4 hours after the start of the challenge, the subject will acknowledge this on the challenge log. Content and timing of the meal and

exercise, along with answers to challenge questions, will be recorded on a log provided by the study team.

Meal Challenges for all Subjects (Run-in and Study Period):

The following meal challenges are required during the run-in and study periods:

- Two meal challenges during the run-in period with subjects using the system in **Manual Mode** (SmartGuard must be turned off at least 6 hours prior to the meal challenge for subjects using it during the run-in period) – between Visits 5 and 7
    - One Regular sized meal with ***missed meal bolus*** at lunch
    - One Large sized meal at breakfast, lunch or dinner
- Two meal challenges during the study period with subjects using the system in SmartGuard, Auto Basal target set at 120 mg/dL – between Visits 9 and 11 of study period
    - One Regular sized meal with ***missed meal bolus*** at lunch
    - One Large sized meal at breakfast, lunch or dinner
- Two meal challenges during the study period with subjects using the system in SmartGuard, Auto Basal target set at 100 mg/dL – between Visits 12 and 13 of study period
    - One Regular sized meal with ***missed meal bolus*** at lunch
    - One Large sized meal at breakfast, lunch or dinner
- One meal challenge during the study period with subjects using the system in SmartGuard, Auto Basal target set at investigator's discretion – at any time after Visit 13 of study period
    - One Large sized meal at breakfast, lunch or dinner

Meal challenges should only start if the following conditions are met:

- SMBG at start of meal is < 200 mg/dL
- Sensor glucose is available.

Timing	Settings/Conditions	Meal Size	Meal Type	Notes
Run-in Period between visits 5 and 7	Manual Mode only **Missed meal bolus**	Regular sized meal	Lunch	Meal content, meal size and time of meal consumption should be established so that regular sized meal challenges during the study period can be matched
Run-in Period between visits 5 and 7	Manual Mode only	Large sized meal	Breakfast Lunch or Dinner	Meal content, meal size and time of meal consumption should be established so that large sized meal challenges during the study period can be matched
Study Period, between Visits 9 and 11	SmartGuard (120 mg/dL setpoint) **Missed Meal bolus**	Regular sized meal	Lunch	Meal content, meal size and time of meal consumption should match regular meal taken during run-in and the

				regular meal taken at the 100 mg/dL setpoint
Study Period, between Visits 9 and 11	SmartGuard (120 mg/dL setpoint)	Large sized meal	Breakfast, Lunch or Dinner	Meal content, meal size and time of meal consumption should match meal at Setpoint of 100 mg/dL and run-in period meal
Study Period, between Visits 12 and 13	SmartGuard (100 mg/dL setpoint) **Missed meal bolus**	Regular sized meal	Lunch	Meal content, meal size and time of meal consumption should match regular meal taken during run-in and the regular meal taken at the 120 mg/dL.
Study Period, between Visits 12 and 13	SmartGuard (100 mg/dL setpoint)	Large sized meal	Breakfast Lunch or Dinner	Meal content, meal size and time of meal consumption should match meal at Setpoint of 120 mg/dL and run-in period large sized meal
Study Period Any time after Visit 13	SmartGuard (Auto Basal target at investigator's discretion)	Large sized meal	Breakfast Lunch or Dinner	Meal content, meal size and time of meal consumption should match large meal at Setpoint of 120 mg/dL /100mg/dL and run-in period large sized meals

Regular Sized Meal Challenge with Missed Meal Bolus:

Between visits 5 and 7 for the run-in period, while subjects are in Manual Mode with CGM, they will be asked to consume a meal without administration of a Meal Bolus at lunch. The size of the meal should be equivalent to what subjects would normally eat at this mealtime.

During the study period, once at each Auto Basal setpoint (i.e. 120 mg/dL and 100 mg/dL), subjects will be asked to consume the same regular sized lunch meal that they had during the run-in period. For example, if the regular sized meal was consumed without an insulin bolus for the meal at 12 p.m. during the run-in period, that same regular sized meal should be consumed at approximately the same time of day at each setpoint during the study period. Subjects will be asked to check BG at the start of the meal, as well as 2 hours and 4 hours after the start of the meal and take bolus correction as necessary. Details should be recorded, on the log.

Large sized Meal Challenges:

On large sized meal challenge days, subjects will be instructed to eat one meal with at least 50% higher caloric intake, including 50% more carbohydrates and 50% higher in fat. It is recommended that subjects eat food at restaurants or consume prepared meals. The FoodPrint™ app (as well as questions that will be asked by investigational center staff during visits following meal challenges) will be used by subjects to collect information about the food that was eaten, the name of the restaurant (if applicable) and subject confirmation that meal size was at least 50% more in terms of calories, carbohydrates and fat.

The timing of the meal challenges will be at the investigator's discretion. The subject's parent/caregiver or companion should be physically present in the same building, home or location (if not at home) during the meal challenge (and for 4 hours following the start of the meal). They must be able to check SMBG (in case it is needed) and give glucose/administer glucagon if required.

Exercise Challenge for all Subjects (during Study Period only):

The following exercise challenges are required during the study period:

- 2 exercise challenges at setpoint of 120 mg/dL, between Visits 9 and 11 of the study period
- 2 exercise challenges at setpoint of 100 mg/dL, between Visits 12 and 13 of the study period
- 1 exercise challenge at setpoint investigator's discretion, at any time after Visit 13of the study period)

Conditions at start of the exercise challenges:

- SG should be present at the start of each exercise challenge
- The investigator or his/her staff will determine the minimum BG for each subject at the start of each exercise challenge. It will be noted on the subject's exercise log

Timing	Settings/Conditions	Exercise duration	Notes
Study Period, between Visits 9 and 11	SmartGuard (120 mg/dL setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period, between Visits 9 and 11	SmartGuard (120 mg/dL setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period, between Visits 12 and 13	SmartGuard (100 mg/dL setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period, between Visits 12 and 13	SmartGuard (100 mg/dL setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period Any time after Visit 13	SmartGuard (Auto Basal target at investigator's discretion)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge

Exercise Challenges Details:

To fulfill the exercise challenge requirement, subjects will be asked to engage in 0.5 up to 1.5 hours of physical exercise. During this time, subjects should use either the Auto Basal setpoint target of 100 mg/dL or 120 mg/dL, depending on what is required at that time of the study period, unless a subject prefers to use the 150 mg/dL temp target before, during and immediately after the exercise challenges. The FoodPrint™ app (as well as questions that will be asked by site staff during visits following exercise challenges) will be used by subjects to collect information about exercise type, date, time (start and finish of exercise) and duration. The timing of the exercise challenge will be at the investigator's discretion. A photograph should be taken on each day of the exercise challenges to indicate where the exercise took

place. The subject's parents/caregivers (if applicable) or companion must be physically present in the same building, home or location (if not at home) during the exercise challenge, must be able to check SMBG (in case it is needed) and give glucose/administer glucagon as needed. Examples of types of exercise include, but are not limited to:

- Running
- Cycling
- Swimming
- Hiking
- Walking
- Games (e.g. Wii interactive video games)
- Indoor/outdoor playground (Pediatric subjects)
- Yoga/stretching
- Any sport activity that involves ongoing physical movement (e.g., tennis, golf, basketball, volleyball, soccer)
- Dancing
- Zumba
- Aerobics
- Spinning

Companions:

Subjects will be required to have a companion who resides (or will live) in the same building (or home) during the study at night, and also to be physically present in the same building, home or location (if not at home) during the exercise and meal challenges. A companion should be present during meal challenges and for 4 hours following the start of the meal. Companions should be able to check SMBG, give glucose and/or administer glucagon.

Safety Considerations with the Use of Lyumjev insulin:

Sites will send out an email to each subject during weeks where no visit is scheduled to inquire about insulin infusion with Lyumjev insulin. The email will ask subjects whether or not they have experienced any insulin infusion reactions with the use of the Lyumjev insulin. The email will also remind subjects that sites should be called if any issues with Lyumjev insulin infusion occur. During such calls, photos and video should be used, if possible.

5.1 Duration

The study is anticipated to last approximately 18 months from first investigational center initiation to finalization of all data entry and monitoring procedures for data cleaning. Individual subject participation is expected to be approximately 120 days.

5.2 Rationale

Previous clinical investigations have confirmed the safety and clinical performance of the MiniMed 780G insulin pump when used to deliver Humalog or Novolog U100 insulin to patients 7-80 years of age. In-silico modeling indicates that the use of Lyumjev U100 insulin with the MiniMed780G pump will result in

similar outcomes. This investigation is intended to provide additional confirmation of the safety of the 780G insulin pump used in combination with Lyumjev U100 insulin in humans.

6. Determination of Sample Size

6.1 Sample Size and Investigational Centers

A total of up to 250 subjects with insulin-requiring type 1 diabetes age 7-80 will be enrolled at up to 25 investigational centers across the United States in order to have at least 200 subjects enter the study period. Up to 125 subjects will be enrolled in the pediatric age group (7-17 years of age) and up to 125 in the adult age group (18 years or older):

Subject Age Group	Sub-groups	Enrollment Goal (N)
Pediatric Age 7 – 17 years	All Pediatric	Minimum 100 Subjects
	Age 7 - 13 years	Minimum 20 Subjects
	Age 14 - 17 years	Minimum 20 Subjects
Adult Age 18 - 80 years	N/A	Minimum 100 Subjects

A minimum of 10 subjects and a maximum of 40 subjects is targeted for enrollment at each investigational center to ensure that the results from the individual investigational center may be pooled for analysis.

Investigational centers will be encouraged to enroll a study population that represents a wide variety of backgrounds.

6.2 Sample Size Considerations/Sample Size Justification

6.2.1 Age 18-80

- Sample size for the primary safety endpoint: the overall mean change in Glycosylated hemoglobin (HbA1c) from baseline to end of 3-month study period

  The overall mean change in HbA1c from baseline to end of 3-month study period from 670G (CEP294 HCL age 18 to 75, N = 101) study was -0.50%. Assuming the mean change in HbA1c from baseline to end of 3-month study period from 780G is the same as 670G, with a standard deviation of 0.7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power, to detect that mean HbA1c is less than -0.50% with a margin of 0.4% at a significance level of 0.025 (one-sided).

- Sample size for the primary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL)

  The mean % of time in target from 670G (CEP294 HCL age 18 to 75, N = 104) study was 73.7%. Assuming the mean time in target (%) from 780G is the same as 670G, with a standard deviation of 8.8%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power, to detect that mean % of time in target is greater than 73.7% with a margin of -7.5% at a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time below range (< 54 mg/dL)

  The mean % of time below range (< 54 mg/dL) from 670G (CEP294 HCL age 18 to 75, N = 104) study was 0.86%. Assuming the mean time below target (%) from 780G is the same as 670G, with a standard deviation of 0.79%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power, to detect that mean % of time below range is less than 0.86% with a margin of 2% at a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL)

  The mean % of time in target from 670G (CEP294 HCL age 18 to 75, N = 104) study was 73.7%. Assuming the mean time in target (%) from 780G is 76%, with a standard deviation of 7.2%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power, to detect that mean % of time in target is greater than 73.7% at a significance level of 0.025 (one-sided).

6.2.2 Age 7-17

- Sample size for the primary safety endpoint: the overall mean change in HbA1c from baseline to end of 3-month study period

  The overall mean change in HbA1c from baseline to end of 3-month study period from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was -0.38%. Assuming the mean change in HbA1c from baseline to end of 3-month study period from 780G is the same as 670G, with a standard deviation of 0.7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power, to detect that mean change of HbA1c is less than -0.38% with a margin of 0.4% at a significance level of 0.025 (one-sided).

- Sample size for the primary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL)

  The mean % of time in target from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 65.3%. Assuming the mean time in target (%) from 780G is the same as 670G, with a standard deviation of 8%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power, to detect that mean % of time in target is greater than 65.3% with a margin of -7.5% at a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time below range (< 54 mg/dL)

  The mean % of time below range (< 54 mg/dL) from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 0.71%. Assuming the mean time below target (%) from 780G is the same as 670G, with a standard deviation of 0.60%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power, to detect that mean % of time below range is less than 0.71% with a margin of 2% at a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL)

  The mean % of time in target from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 65.3%. Assuming the mean time in target (%) from 780G is 67.6%, with a standard deviation of 7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power, to detect that mean % of time in target is greater than 65.3% at a significance level of 0.025 (one-sided).

6.2.3 Expected Drop-out Rates

Incorporating the expected drop-out rates, a total of up to 250 subjects will be enrolled, in order to have 200 subjects enter the study period.

7. Statistical Methods

7.1 Study Subjects

7.1.1 General Aspects of Analysis

All data collected from the time of screening until the end of the study will be collected on eCRFs, subject questionnaires, and electronically by uploading the various devices. Data and analysis will be summarized in a Clinical Study Report. Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report.

7.1.2 Disposition of Subjects

The number of subjects enrolled, completed, and early terminated in the study will be presented. The reasons for discontinuing prior to study completion will be summarized.

7.1.3 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.4 Analysis Sets

- Intention to Treat (ITT) Population

  The ITT population will include all subjects who start the study period. Primary safety, primary effectiveness, secondary effectiveness and descriptive endpoints will be evaluated for ITT population.
- Per Protocol (PP) Population

  The PP population will include all subjects who complete the study period, are in Auto Mode ≥ 80% of the time and without any major deviations. Primary safety, primary effectiveness and secondary effectiveness endpoints will be evaluated for PP population as the sensitivity/supplementary analyses.
- Safety Population

  The Safety Population will include all enrolled subjects (subjects who signed Informed Consent Form (ICF)). Safety adverse events data summary will be evaluated for safety population.

7.2 General Methodology

Summary statistics for continuous variables will be represented by number of subjects (n), mean, median, standard deviation and categorical variables will be represented by counts and percentages. P-values for hypothesis testing will be evaluated based on one-sided testing using significance level of 0.025. Confidence intervals if needed will be reported as two-sided 95% confidence intervals. For primary safety, primary effectiveness and secondary effectiveness endpoints, normality will be verified for appropriate statistical methodology. Comparisons between the outcomes in study period and the threshold will be performed using one sample T-test for testing the statistical significance of the difference if normality assumption is met or Wilcoxon signed rank test if normality assumption is not met.

The templates for Tables, Listings and Figures (TLFs) will be available in the TLFs document.

7.3 Center Pooling

Data will be pooled for analysis. Additional sensitivity analysis will be performed for site effect in section 7.9.4.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

For the primary safety analysis (change of HbA1c), if HbA1c at end of study is not available in subjects, missing data in HbA1c measurements will be handled by the multiple imputation approach using imputation regression method. The independent variables in the regression model are age, gender, baseline HbA1c, diabetes duration, BMI. The imputation will be performed five times and the analysis results will be combined to form one inference in SAS.

For partial date stated in Medical history, the first day of the month or the first day of the year will be used.

For visit 13 date is missing and subjects exited after visit 7 + 44 days, the date of visit 7 + 44 days will be used for cut-off dates in analysis.No imputation for CGM related endpoints will be performed.

7.5 Adjustments for Multiple Comparisons

The following hierarchical test procedure reflects the relative importance of the endpoints and controls for multiplicity. Safety and effectiveness endpoints will be evaluated independently between age 18-80 and age 7-17.

Fixed sequential testing of primary safety, primary effectiveness and secondary effectiveness endpoints for age 18-80 and age 7-17.

7.5.1 Age 18-80

For the following endpoints from age 18-80, the procedure test hierarchically the ordered hypotheses in sequence at level α=0.025 until a first hypothesis is non-rejected.

Primary Safety Endpoint

- Age 18-80: The overall mean change in HbA1c from baseline to end of 3-month study period. The mean change will be estimated and compared to a threshold of -0.5% with a margin of 0.4%.

Primary Effectiveness Endpoint

- Age 18-80: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 73.7% with a margin of -7.5% and a significance level of 0.025 (one-sided).

Secondary Effectiveness Endpoints

- Age 18-80: The mean % of time in hypoglycemia (< 54 mg/dL) will be estimated and compared to a threshold of 0.86% with a margin of 2% and a significance level of 0.025 (one-sided).
- Age 18-80: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 73.7% and a significance level of 0.025 (one-sided).

7.5.2 Age 7-17

For the following endpoints from age 7-17, the procedure test hierarchically the ordered hypotheses in sequence at level α=0.025 until a first hypothesis is non-rejected.

Primary Safety Endpoint

- Age 7-17: The overall mean change in HbA1c from baseline to end of 3-month study period. The mean change will be estimated and compared to a threshold of -0.38% with a margin of 0.4%.

Primary Effectiveness Endpoint

- Age 7-17: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 65.3% with a margin of -7.5% and a significance level of 0.025 (one-sided).

Secondary Effectiveness Endpoints

- Age 7-17: The mean % of time in hypoglycemia (< 54 mg/dL) will be estimated and compared to a threshold of 0.71% with a margin of 2% and a significance level of 0.025 (one-sided).
- Age 7-17: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 65.3% and a significance level of 0.025 (one-sided).

7.6 Demographic and Other Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis, height, weight, Body Mass Index (BMI), and baseline HbA1c will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

7.7 Treatment Characteristics

Not applicable.

7.8 Interim Analyses

Not applicable.

7.9 Evaluation of Objectives

Safety and effectiveness endpoints will be evaluated independently between age 18-80 and age 7-17.

7.9.1 Pass/Fail Criteria

The study pass/fail criteria is based on statistical hypothesis of the primary endpoints. The study for each age cohort (age 18-80 and age 7-17) will be considered a success when the evaluation criteria of both primary safety and effective endpoints meets the predefined threshold per cohort.

Justification for Exclusion of Particular Information from the testing of the Hypothesis:
Not Applicable.

7.9.2 Primary Safety Endpoint

Age 18-80:

- The overall mean change in HbA1c, $\Delta\mu_{780G}$, from baseline to end of 3-month study period will be estimated and compared to the threshold of -0.50% with a margin of 0.4%. A significance level of 0.025 (one-sided) will be used. Analysis will be performed on the ITT and PP populations.

The hypothesis is mathematically expressed as:

H_0: $\Delta\mu_{780G} \geq -0.50\% + 0.4\%$

H_a: $\Delta\mu_{780G} < -0.50\% + 0.4\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. The mean change in HbA1c from baseline to end of 3-month study period is less than -0.50% with a margin of 0.4% for age 18-80 will be concluded if null hypothesis is rejected.

Age 7-17:

- The overall mean change in HbA1c, $\Delta\mu_{780G}$, from baseline to end of 3-month study period will be estimated and compared to the threshold of -0.38% with a margin of 0.4%. A significance level of 0.025 (one-sided) will be used. Analysis will be performed on the ITT and PP populations.

The hypothesis is mathematically expressed as:

H_0: $\Delta\mu_{780G} \geq -0.38\% + 0.4\%$

H_a: $\Delta\mu_{780G} < -0.38\% + 0.4\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. The mean change in HbA1c from baseline to end of 3-month study period is less than -0.38% with a margin of 0.4% for age 7-17 will be concluded if null hypothesis is rejected.

7.9.3 Analysis of Effectiveness Endpoint

All effectiveness endpoints will be analyzed using the data from the visit 13 to the end of the study (Auto Basal target set at investigator's discretion).

7.9.3.1 Primary Effectiveness Endpoint

Age 18-80:

- The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL) will be estimated and compared to the threshold of 73.7% with a margin of -7.5%. A significance level of 0.025 (one-sided) will be used. The 7.5%, which is approximately 100 minutes increase in TIR per day, was also observed from the HCL pivotal trials. Analysis will be performed on the ITT and PP populations.

  The hypothesis is mathematically expressed as:

  H_0: $\mu_{780G} \leq 73.7\% - 7.5\%$

  H_a: $\mu_{780G} > 73.7\% - 7.5\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Mean % of time in target from MiniMed 780G system utilizing Lyumjev insulin is greater than 73.7% with a margin of -7.5% for age 18-80 will be concluded if null hypothesis is rejected.

Age 7-17:

- The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL) will be estimated and compared to the threshold of 65.3% with a margin of -7.5%. A significance level of 0.025 (one-sided) will be used. The 7.5%, which is approximately 100 minutes increase in TIR per day, was also observed from the HCL pivotal trials. Analysis will be performed on the ITT and PP populations.

  The hypothesis is mathematically expressed as:

H_0: $\mu_{780G} \leq 65.3\% - 7.5\%$

H_a: $\mu_{780G} > 65.3\% - 7.5\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Mean % of time in target from MiniMed 780G system utilizing Lyumjev insulin is greater than 65.3% with a margin of -7.5% for age 7-17 will be concluded if null hypothesis is rejected.

7.9.3.2 Analysis of Secondary Effectiveness Endpoints

Age 18-80:

- Secondary Effectiveness Endpoint: The mean % time, μ_{780G}, in hypoglycemia (< 54 mg/dL) will be estimated and compared to the threshold of 0.86% with a margin of 2%. A significance level of 0.025 (one-sided) will be used. Analysis will be performed on the ITT and PP populations.

The hypothesis is mathematically expressed as:

H_0: $\mu_{780G} \geq 0.86\% + 2\%$

H_a: $\mu_{780G} < 0.86\% + 2\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Mean % of time below range from MiniMed 780G system utilizing Lyumjev insulin is less than 0.86% with a margin of 2% for age 18-80 will be concluded if null hypothesis is rejected.

- Secondary Effectiveness Endpoint: The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL) will be estimated and compared with a significance level of 0.025 (one-sided). Analysis will be performed on the ITT and PP populations.

The hypothesis is mathematically expressed as:

H_0: $\mu_{780G} \leq 73.7\%$

H_a: $\mu_{780G} > 73.7\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Mean % of time in target from MiniMed 780G system utilizing Lyumjev insulin is greater than 73.7% for age 18-80 will be concluded if null hypothesis is rejected.

Age 7-17:

- Secondary Effectiveness Endpoint: The mean % time, μ_{780G}, in hypoglycemia (< 54 mg/dL) will be estimated and compared to the threshold of 0.71% with a margin of 2%. A significance level of 0.025 (one-sided) will be used. Analysis will be performed on the ITT and PP populations.

  The hypothesis is mathematically expressed as:

  H_0: $\mu_{780G} \geq 0.71\% + 2\%$

  H_a: $\mu_{780G} < 0.71\% + 2\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Mean % of time below range from MiniMed 780G system utilizing Lyumjev insulin is less than 0.71% with a margin of 2% for age 7-17 will be concluded if null hypothesis is rejected.

- Secondary Effectiveness Endpoint: The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL) will be estimated and compared with a significance level of 0.025 (one-sided). Analysis will be performed on the ITT and PP populations.

  The hypothesis is mathematically expressed as:

  H_0: $\mu_{780G} \leq 65.3\%$

  H_a: $\mu_{780G} > 65.3\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Mean % of time in target from MiniMed 780G system utilizing Lyumjev insulin is greater than 65.3% for age 7-17 will be concluded if null hypothesis is rejected.

7.9.4 Sensitivity Analysis for Primary Safety, Primary Effectiveness and Secondary Effectiveness Endpoints

7.9.4.1 Sensitivity Analysis 1: PP population

Primary safety, primary effectiveness and secondary effectiveness endpoints will be evaluated for PP population as the sensitivity/supplementary analyses.

7.9.4.2 Sensitivity Analysis 2: Site effect evaluation with ITT population

To address the pooled sites in statistical analysis, sensitivity analysis 2 will be conducted if the site effect is significant (with a significance level of 0.1) in primary safety, primary effectiveness and secondary effectiveness endpoints.

The site effect will be evaluated by a linear mixed model. And the final estimate will be a weighted average of the estimate for each site, where the weight of each site is the inverse of the variance of each site estimate (which equals to the inverse of the square of the standard error of each site estimate).

Note: During the site effect test, all sites with less than 6 subjects per age group will be pooled into one 'Pseudo-site'. If the number of subjects in Pseudo-site is larger than 30, it will be split to two Pseudo-sites.

7.9.5 Descriptive Endpoints

Time windows for the following endpoints will be evaluated: visit 2 – visit 7 (Run-in period), visit 7- visit 11 (Auto Basal target set at 120 mg/dL), visit 11- visit 13 (Auto Basal target set at 100 mg/dL), and visit 13 to the end of study (EOS) (Auto Basal target set at investigator's discretion) or exit.

- Time spent in the SmartGuard feature versus time spent in Manual Mode
- Change in mean glucose value from baseline to EOS
- Time in different ranges (% of SG): SG < 54 mg/dL, SG < 70 mg/dL, 70 mg/dL ≤ SG ≤ 140 mg/dL, 70 mg/dL ≤ SG ≤ 180 mg/dL, SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54 and 70 mg/dL
- Meal/exercise challenge
    - Change in BG values during meal/exercise challenge (BG prior and BG 2 hours after meal/exercise)
    - Change in % of time in euglycemia 70-180 mg/dL during meal/exercise challenge, prior and 2 hours after meal/exercise
    - Difference in AUC during meal challenge prior and 2 hours after meal/exercise
- Change of Total Daily Dose (TDD) of insulin from baseline to EOS
- Change of weight from baseline to EOS
- Subgroup analysis will be performed for:
    - Setpoint
        - 100 mg/dL
        - 110 mg/dL
        - 120 mg/dL
        - 150 mg/dL (Temp Target Usage)
    - Age
        - Age 18-80
        - Age 7-17

- Age 7-13
- Age 14-17

7.9.6 Safety Data Summarized

Time windows for the safety data will be evaluated: visit1-visit2, visit 2 – visit 7, visit 7 to the end of study (EOS) or exit, and visit 13 to the end of study (EOS) or exit.

- Serious Adverse Events (SAE)
- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA

7.9.7 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.

7.9.8 Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. A total score, and the scores for each subscale of the Diabetes-39, Inspire and Treatment Related Impact Measure -Diabetes (TRIM-D) questionnaires will be calculated and reported. Refer to CIP335 Lyumjev - Questionnaire Guide for administration details.

7.10 Safety Evaluation

The safety of the study will be evaluated and summarized per all enrolled subjects, including but not limited to the following:

- Serious Adverse Events (SAE)
- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia

- Incidence of Severe Hyperglycemia
- Incidence of DKA

7.11 Health Outcomes Analyses

Descriptive summary will be used to characterize study questionnaire results. A total score, and the scores for each subscale of the Diabete-39, Inspire and and Treatment Related Impact Measure - Diabetes (TRIM-D) questionnaires will be calculated and reported. Refer to CIP335 Lyumjev - Questionnaire Guide for administration details.

7.12 Changes to Planned Analysis

Not applicable.

8. Validation Requirements

Level I or Level II validation are required for analysis output. Level I requires that the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer. Level II requires that the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9. References

1. Beato-Víbora PI, Gallego-Gamero F, Lázaro-Martín L, Romero-Pérez MDM, Arroyo-Díez FJ. Prospective Analysis of the Impact of Commercialized Hybrid Closed-Loop System on Glycemic Control, Glycemic Variability, and Patient-Related Outcomes in Children and Adults: A Focus on Superiority over Predictive Low-Glucose Suspend Technology. *Diabetes Technology and Therapeutics.* 2020;22(12):912-919.