Medtronic	
Study Title	Multi-center, Randomized, Parallel, Adaptive, Controlled Trial in Adult and Pediatric Patients with Type 1 Diabetes Using Hybrid Closed Loop System and Control (CSII, MDI and SAP) at Home
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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Multi-center, Randomized, Parallel, Adaptive, Controlled Trial in Adult and Pediatric Patients with Type 1 Diabetes Using Hybrid Closed Loop System and Control (CSII, MDI and SAP) at Home
Clinical Investigation Plan Identifier	CEP304
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Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	New Document	[redacted]
2.0	Updated the following sections to reflect changes from the version F protocol • Section 4.0 Study Objectives • Section 5.0 Investigation Plan • Section 7.0 Statistical Methods Updated sub-section 7.9 Evaluation of Objectives • Included additional analyses comparing the two firmware versions regarding the transmitter BG loop fix	[redacted]
3.0	Updated the following sections to reflect changes from the version G protocol • Section 3. Introduction • Section 5. Investigation Plan • Section 6. Determination of Sample Size • Section 7. Statistical Methods ○ Added an analysis for 2-6 Years of Age Population	[redacted]

2. List of Abbreviations and Definitions of Terms

Term	Definition
A1C	Glycosylated hemoglobin
AE	Adverse Event
BMI	Body Mass Index
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CL	Closed Loop
CSII	Continuous Subcutaneous Insulin Infusion

Term	Definition
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EMEA	Europe, Middle East and Africa
HCL	Hybrid Closed Loop
SAE	Serious Adverse Event
SADE	Serious Adverse Device Events
SAP	Sensor Augmented Pump
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TDD	Total Daily Dose
UADE	Unanticipated Adverse Device Effect

3. Introduction

Provisional studies employing closed loop technology have shown a reduction in both hypoglycemia and hyperglycemia, as well as glycemic variability. Previous studies have evaluated prototype versions of the Medtronic closed-loop insulin delivery systems in pediatric patients, as well as adolescents and young adults. Researchers at the Yale University School of Medicine studied the performance of both a hybrid closed-loop algorithm and a fully closed loop algorithm using the Medtronic MMT-715 insulin pump, the Medtronic Sof-sensor and MiniLink transmitter and a control algorithm running on a laptop computer [Weinzimer et al, 2008]. Seventeen subjects between the ages of 13 and 20 years participated in the study with eight subjects undergoing testing with a fully closed-loop algorithm, and the remaining nine subjects being evaluated using the hybrid closed-loop algorithm. This study demonstrated that a fully closed loop artificial pancreas using an external glucose sensor is feasible and effective in adolescents with type 1 diabetes.

The Type 1 Diabetes TrialNet Study Groups used this same system to evaluate inpatient hybrid closed-loop control (HCL) initiated shortly after the diagnosis of type 1 diabetes [Diabetes Research in Children Network Study Group, 2013]. Forty eight subjects between the ages of 7.8 and 37.7 years participated in the intensive treatment group and received inpatient HCL followed by outpatient sensor augmented pump therapy. Forty six of the 48 subjects were less than 18 years old. The study found that inpatient HCL safely initiated soon after the diagnosis of type 1 diabetes resulted in the rapid decrease in blood glucose levels within 24 hours of initiation and that while using HCL, about 80% of the glucose levels were in the target range of 71mg/dL -180 mg/dL, with minimal hypoglycemia.

Medtronic has completed 7 phases in the HCL Feasibility Study (CEP273) with a total of 71 subjects enrolled. In this Feasibility study, the closed loop system was stressed by artificially inducing sensor error as well as inducing physiologic stress such as exercise and administration of meals without bolus. The Feasibility study provided data which was used to develop the device algorithm that is being tested in this study.

A pivotal trial with 120 subjects completed in February 2016. This was a single arm study evaluating the safety of the MiniMed 670G HCL system in subjects 14-75 years of age, for 3 months in the home setting. The pediatric pivotal study for the HCL system was conducted as an at-home, multi-center study, which enrolled 162 participants ages 2-13 years of age. Patients were recruited at 11 centers (10 in the United States, 1 in Israel). The study was identical in design to the young adult/adult pivotal study.

Study results in the pediatric study mirrored data from the pivotal trial of the system in adults and adolescents (14 and above), showing patients spent more time in euglycemic range, experienced less glycemic variability, had less exposure to hypoglycemia and hyperglycemia and significantly reduced HbA1c compared to baseline data where they used sensor-augmented pumps without SmartGuard™ automation activated. No episodes of severe hypoglycemia or diabetic ketoacidosis and no serious device-related adverse events were reported.

The MiniMed 770G Insulin Pump is equivalent in function to the MiniMed 670G insulin pump, with the exception of telemetry. While the MiniMed 670G insulin pump communicates on the basis of Tel-D (telemetry-diabetes) radio frequency (RF) technology, the MiniMed 770G pump contains BLE (Bluetooth Low Energy) RF communication, which allows for connectivity to patients' smartphones, CGM transmitter and an BLE RF enabled blood glucose meter.

4. Study Objectives

The purpose of this study is to evaluate the safety and effectiveness of the Hybrid Closed Loop system (HCL) in adult and pediatric patients with type 1 diabetes in the home setting. A diverse population of patients with type 1 diabetes will be studied. The study population will have a large range for duration

of diabetes and glycemic control, as measured by glycosylated hemoglobin (A1C). Different Cohorts will be enrolled in the study:

1) Cohort 1: Continuous Subcutaneous Insulin Infusion (CSII) or HCL;

2) Cohort 2: Multiple Daily Injections (MDI) or HCL;

3) Cohort 3: Sensor-Augmented Pump therapy (SAP) or HCL.

5. Investigation Plan

This is a 6 month, multi-center, randomized, parallel, adaptive study in type 1 diabetes with a 6 month continuation period. Up to 1500 subjects will be enrolled in order to have 1000 subjects who enter the study period. Up to 70 investigational Centers in the US, Europe, Canada, Australia and New Zealand will be enrolled. For additional information on investigational sites and investigators, refer to information listed on public databases (e.g., clinicaltrials.gov).

The study is anticipated to last no longer than 5 years from investigational center initiation to completion of all data entry and monitoring procedures. The study will target 36 months to complete subject enrollment. Subjects can expect to participate for approximately 7-8 months during the run-in period and study period, with a 6 month continuation period.

The study will have three periods per Cohort:

1. Run-in Period: The run-in period can be up to 60 days
   The run-in period will also be used for CGM data collection for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear (i.e. Monday Day 1 through next Sunday Day 14)

   For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7 days, a new sensor should then be inserted and worn for 3 days so that a total of 14 days of sensor wear is completed.

   All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day. Sponsor may request a repeat of blinded CGM. Repeat of blinded CGM may occur if the following are not met:

   - A minimum of 12 days of sensor wear have been self-reported to research staff

- A minimum of 2 blood glucose checks/day during the blinded CGM wear are confirmed on the subject's study BG meter.

If these requirements are not met then patient should repeat the entire 2 week blinded CGM data collection unless sponsor has approved that there was adequate data collection. An additional 21 days may be added to the run in visit window schedule if blinded CGM data collection needs to be repeated. Additional visits may also be allowed if needed.

2. Study Period: There will be a 6 month randomized study period with two arms: HCL system and Control. CSII and MDI control groups will undergo ***two*** blinded CGM collections during the study period.

   The first blinded CGM data collection during the study period will occur before the month three (see visit schedule) for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear. (i.e. Monday Day 1 through next Sunday Day 14)

   For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7 days, a new sensor should then be inserted and worn for 3 days so that a total of 14 days of sensor wear is completed.

   All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day. Sponsor may request a repeat of blinded CGM. The following should have occurred:

   - A minimum of 12 days of sensor wear have been self-reported to research staff
   - A minimum of 2 blood glucose checks/day during the blinded CGM wear are confirmed on the subject's study BG meter.

   If the above requirements are not met then patient should repeat the entire 2 week blinded CGM data collection unless the sponsor approves that there was adequate data collection. Additional visits may also be allowed if needed. No changes to the remaining visit schedule are needed.

   The second blinded CGM data collection during the study period will occur before the month six (see visit schedule) for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear. (i.e. Monday Day 1 through next Sunday Day 14)

   For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7 days, a new sensor should then be inserted and worn for 3 days so that a total of 14 days of sensor wear is completed.

All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day.

3. Continuation Period: There will be a 6 month continuation period during which time all subjects will use the HCL system

Enrollment Cohorts According to Treatment

At Enrollment, subjects will be identified according to the type of treatment regimen they are currently on. Treatment regimen is defined as follows and subjects will be enrolled in the following way:

- Cohort 1: CSII – subjects using pump (Medtronic or other pump systems) for at least 3 months at time of screening without concurrent use of real time CGM in the last 3 months. (Self-report acceptable.) Please note that alternatives to SMBG such as Freestyle Libre are not considered real time CGM and subjects who are using Freestyle Libre at time of Screening will be allowed to enroll in the study. During the study, however, subjects will not be allowed to use Freestyle Libre.
- Cohort 2: Multiple Daily Injections (MDI) - Subjects using MDI with or without concurrent use of CGM for at least 3 months prior to Screening. (Self report is acceptable.)
- Cohort 3: Sensor Augmented Pump (SAP) – subjects using pump for at least 3 months at time of screening with real time CGM use (Medtronic or other CGM systems) approximately 20% of the time (Self report acceptable). Subjects will use the Medtronic CGM starting at Visit 3, but they may use their own CGM until then. Sensor insertion placement will be according to User guide.

Staged enrollment in the post approval study for Subjects 2-6 Years of Age:

- Subjects 2-6 years of age will be allowed to enroll in the post approval study, once DMC has reviewed data from 10 subjects age 2-4 years who have completed participation in the study period of the CEP302 study and has given approval to enroll.

The Run-In Period: Following successful screening, all subjects (CSII, MDI or SAP) will enter the run-in period and collect blinded CGM data while using their own diabetes therapy. Blinded CGM consists of using a Guardian Sensor (3) connected to a Guardian Link (3) transmitter. A total period of 2 weeks of CGM data will be collected.

Cohort 1: CSII

The Study Period: After completion of the run-in period, subjects with CSII therapy (minimum N= 280) will be randomized and placed into one of 2 different arms during the study period:

1. The HCL Arm will use the MiniMed system (i.e., using Auto Mode) for 6 months during the study period. There will be N=140 for the HCL arm.

2. The Control Arm will use the MiniMed Pump without CGM

    a. Blinded CGM (Guardian Link (3) Transmitter and Guardian Sensor (3)) will only be worn at baseline, 3 months, and 6 months (two weeks of sensors use). There will be N=140.

Cohort 2: MDI

The Study Period: After completion of the run-in period, subjects with MDI therapy (minimum of N=280) will be randomized and placed into one of 2 different arms during the study period:

1. The HCL Arm will use the MiniMed system (i.e., using Auto Mode) for 6 months during the study period. There will be N=140 for the HCL arm.

2. The Control Arm will be using their current insulin therapy (MDI).

    The Multiple Daily Injection (MDI) subjects will remain on MDI therapy with subjects using their own insulin for 6 months during the study period. The Sponsor will not provide insulin. Blinded CGM (Guardian Link (3) Transmitter and Guardian Sensor (3)) will only be worn at baseline, 3 months and 6 months (two weeks of sensors use). There will be N=140.

    MDI subjects who are currently using CGM, i.e. Dexcom or Medtronic Guardian Connect or who are currently using a SMBG alternative, i.e. Libre, will be allowed to enroll in the study and continue using their own device. There will be N=100

Cohort 3: SAP

The Study Period: After completion of the run-in period, subjects with SAP therapy (minimum N=320) will be randomized and placed into one of 2 different arms during the study period. Sensor insertion placement will be according to User guide:

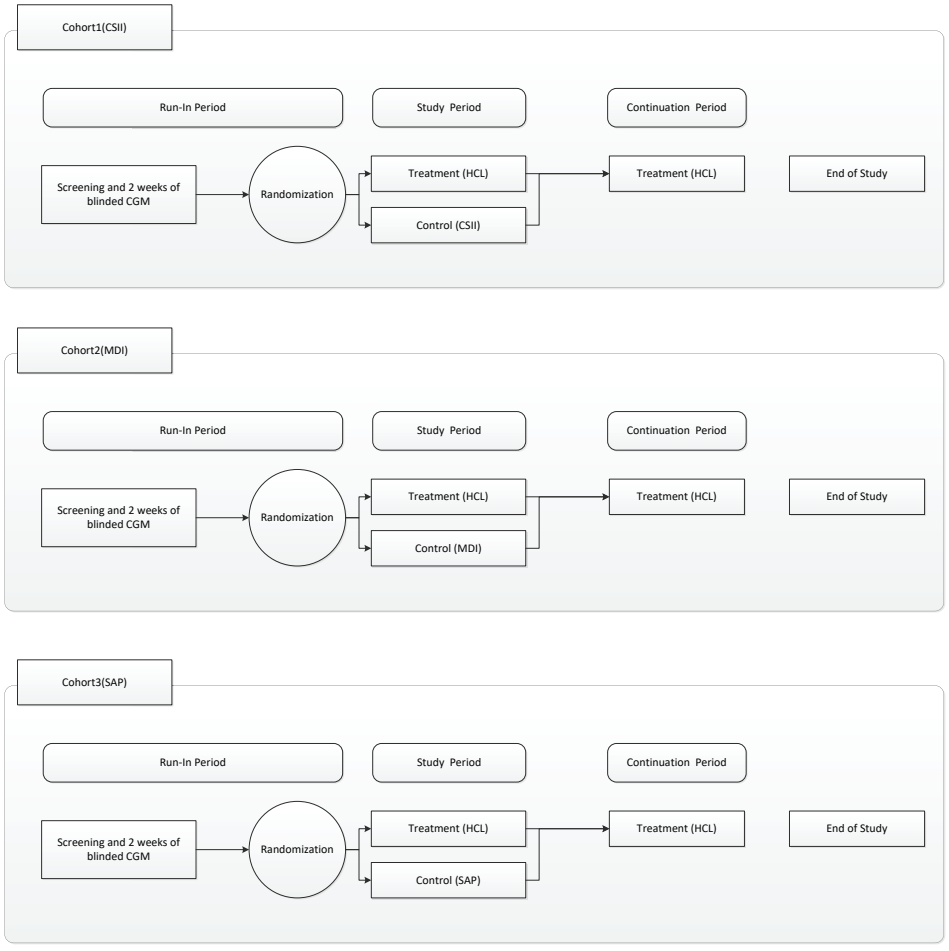
1. The HCL Arm will use the MiniMed system (i.e., using Auto Mode) for 6 months during the study period. There will be N=140 for the HCL arm.

2. The Control Arm will be using SAP therapy using the MiniMed System.

    a. The Sensor Augmented Pump (SAP) subjects will use the MiniMed System (SAP without Low Management Suspend on Low, Low Management Suspend before low or Auto Mode) with Real Time CGM for the 6 month study period. There will be N=140.

The Continuation Period: All subjects above will enter the continuation period for 6 months using the MiniMed system with Auto Mode on.

Figure 1. Study Design



Subjects may be re-tested as per sponsor discretion.

Per Cohort (CSII, MDI or SAP), here are the numbers of subjects expected to enroll:

- A1C at time of screening:
  - N = 70 A1C > 8% for HCL Arm
  - N = 70 A1C ≤ 8% for HCL Arm
  - N = 70 A1C > 8% for Control Arm
  - N = 70 A1C ≤ 8% for Control Arm

- Age at time of screening:

N=Minimum number of eligible subjects for each age group within each treatment cohort			N= Minimum number of eligible Subjects for each age group and cohort	N=Minimum number of eligible subjects for each age group for study
Age Group	Cohort	N	N	N
2-6 years	CSII SAP MDI	No Minimum	No Minimum	N=120
7 -13 years	CSII SAP MDI	No Minimum	No Minimum	N=180
14-21 years	CSII SAP MDI	N=45	N=45	N=135
22-64 years	CSII SAP MDI	N=120	N=120	N=360
65-80 years	CSII SAP MDI	No Minimum	No Minimum	N=150

[redacted]

[redacted]

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number of subjects enrolled in the study will be presented by Periods (run-in, study and continuation). The number of subjects discontinuing prior to study completion will be also summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.3 Analysis Sets

Intention to Treat (ITT) Population

The primary study population is the Intention to Treat (ITT) population, which consists of all randomized subjects.

Per Protocol (PP) Population

The Per Protocol (PP) population will include all randomized subjects who complete the trial without any major deviations, have worn the sensor for both Arms (SAP and HCL) and have used Automode (HCL only) for $\geqslant$ 80% of the time, pump usage (HCL only) of at least 80% and sensor usage (HCL only) of at least 60% during the study period. CSII and MDI control arms need to have at least 60% sensor usage during the blinded sensor wear time. In addition, those subjects who take steroids after randomization will be excluded from PP population. Primary effectiveness endpoints and key secondary endpoints will be evaluated for PP Population.

Safety Population

The Safety Population will be all enrolled subjects.

2-6 Years of Age Population (670G and 770G only)

This analysis set will include subjects 2-6 years of age who used HCL therapy (670G or 770G). Descriptive summary statistics will be provided.

7.2 General Methodology

All data from the time of screening until the end of the study will be collected either on eCRFs or electronically by uploading the various devices. Data and analysis will be summarized in a Clinical Study Report.

All endpoints are hierarchically ordered and will be evaluated in the fixed sequence from primary endpoints to secondary endpoints. Unless the primary endpoints hypotheses are rejected, secondary endpoints will not be tested.

Effectiveness endpoints will be evaluated during the 6 month study period by individual Cohort (CSII, MDI or SAP), stratified by A1C;

Group 1: Baseline A1C > 8%

Group 2: Baseline A1C $\leqslant$ 8%

The comparison of HCL arm vs. Control arm will be performed. For SG-based comparison between HCL vs Control analyses, two weeks of CGM data collected at 3 month visit and 6 month visits will be used.

Please note: Only descriptive summary statistics will be provided for 2-6 years old who used HCL therapy (670G or 770G).

7.3 Center Pooling

To address the pooled investigative site factor in the statistical model, treatment by site interaction will be evaluated by the Gail-Simon test for the effectiveness endpoints. In the absence of significance for this test, the objectives will be evaluated using the overall treatment effect estimate. Sites with less than 6 subjects will be pooled into 'pseudo-sites' of at least 10 subjects per pseudo-site. Pseudo-site will be pooled by ranking those sites with less than 6 subjects by site number and pooling those sites in order of site number until the number of subjects reaches at least 10.

[redacted]

[redacted]

Dates of Adverse Events and Protocol Deviations

In determining the phase of adverse events and protocol deviations or in calculating the duration of diabetes, the first day of the month will be used for event dates with known year and month but unknown day, unless specified otherwise in the description; similarly, the first day of the year will be used for event dates with known year but unknown month and day, unless specified otherwise.

7.5 Adjustments for Multiple Comparisons

No adjustments will be made.

7.6 Demographic and Other Baseline Characteristics

Subject characteristics, including age, gender, ethnicity, diabetes History, height, weight, 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

For each Cohort (CSII, MDI or SAP) subjects will be randomized to HCL and Control Arm with a 1:1 ratio for greater than 6 years of age. 2-6 years of age subjects will automatically enter the HCL arm at the end of the run-in period.

The randomization will be stratified by the diabetes management therapies at time of enrollment and baseline A1c categories:

Diabetes Management Therapies(Cohort):

- CSII: Insulin pump therapy without CGM
- MDI: With and without CGM
- SAP: Insulin pump therapy with CGM

Baseline A1C categories(Group):

- Baseline A1C $\leqslant$ 8%
- Baseline A1C >8%

Randomization will be based on a total of four strata per Cohort. In each stratum, block randomization will be used to divide potential patients into 2m blocks of size of 2n (block size can be different for each stratum). The clinical team and investigators are blind to the block size. Equal amount of subjects will be enrolled for Baseline A1C $\leqslant$ 8% group and Baseline A1C > 8% group.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.9 Evaluation of Objectives

Primary Safety Endpoint:

The primary safety endpoint is the event rate of severe hypoglycemia and DKA from both Groups (1 & 2) during the first 6 months of study period and second 6 months of continuation period. The descriptive summary statistics will be presented by number of event and event rate (100 patient years) for severe hypoglycemia and DKA **separately**.

Descriptive summary (i.e. not statistically powered) for severe hypoglycemia and DKA events rates will be performed between the HCL and control arms for each age group (< 15 years, 15-25 years, and > 25 years), as well as the overall event rates.

In order to achieve safety success, the following study success criteria must be met for the HCL Arm by the end of the study:

Table 1. Safety Success Criteria

Adverse Event	Reference	Reference Rate > 25 years old	Reference Rate 15-25 years old	Reference Rate <15 years old	Study Success Criteria
DKA events per 100 patient years	STAR 3 Bergenstal et. al	SAP arm: 0.68 Control arm: 0	SAP arm: 2.7 Control arm: 3.6	SAP arm: 2.2 Control arm: 0	≤ 4 events per 100 patient years with HCL arm
	530 G Adult inhome study CEP 266 (MDT on file)	1.27	3.4	N/A	
	530 G Pediatric inhome study CEP 287 (MDT on file)	N/A	N/A	0	
	Type 1 exchange Weinstock et. al	4.8	N/A	N/A	
	Type 1 exchange Cengiz et. al	N/A	9.9	9.9	

Severe hypoglycemia per 100 patient years	STAR 3 Bergenstal et. al	SAP arm: 16.5 Control arm: 20.9	SAP arm: 5.4 Control arm: 3.9	SAP arm: 10.2 Control arm: 3.6	≤ 8 events per 100 patient years with HCL arm
	530 G Adult inhome study CEP 266 (MDT on file)	0.85	0	N/A	
	530 G Pediatric inhome study CEP 287 (MDT on file)	N/A	N/A	1.42	
	Type 1 exchange Weinstock et. al	11.8	N/A	N/A	
	Type 1 exchange Cengiz et. al	N/A	6.2	6.2	

Descriptive summary (i.e. not statistically powered) for severe hypoglycemia and DKA events rates will be performed between the HCL and control arms for each age group (< 15 years, 15-25 years, and > 25 years), as well as the overall event rates.

Severe hypoglycemia and DKA event rates were taken from the following

1. Richard Bergenstal et.al: Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1Diabetes.New England Journal of Medicine, 2010; 363:311-20
2. Weinstock et. al: Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013 Aug;98(8):3411-9.
3. Cengiz et. al: Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes. 2013 Sep;14(6):447-54.
4. MDT on file: Statistical Analysis Plan (SAP) for CEP304, 056-F286

Co-Primary Effectiveness Endpoints

The primary effectiveness endpoints consist of one-primary endpoint for each group.

Group 1 – Baseline A1C > 8%: Change in A1C (ΔA1C)

The primary effectiveness endpoints for the baseline A1C > 8% group is change in A1C from baseline to end of six-month treatment period, defined as A1C measured at the six-month treatment visit minus A1C measured at the randomization visit. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period.

The hypothesis is mathematically expressed as:

H_0: $\mu(HCL) \geqslant \mu(Control)$

Ha: $\mu(HCL) < \mu(Control)$

where μ(HCL) is the mean of change in A1C (%) with the HCL Arm, μ(Control) is the mean of change in A1C (%) with the Control Arm.

Group2 – Baseline A1C ⩽ 8%: Time in Hypoglycemic Range

The primary effectiveness endpoint for the baseline A1C ⩽ 8% group is the time with SG below 70 mg/dL (3.9mmol/L) during the six-month study period, defined as percentage of SG below 70 mg/dL (3.9mmol/L) out of total number of available SG readings. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing daily time in hypoglycemic range. The hypothesis is mathematically expressed as:

H_0: μ(HCL) ⩾ μ(Control)

Ha: μ(HCL) < μ(Control)

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in Control Arm.

Key Secondary Effectiveness Endpoints

Group 1 – Baseline A1C > 8%: Time in Hypoglycemic Range

The key secondary effectiveness endpoint for the baseline A1C > 8% group is the time with SG below 70 mg/dL (3.9mmol/L) during the six-month study period, defined as percentage of SG below 70 mg/dL (3.9mmol/L) out of total number of available SG readings. The goal is to show non-inferiority (with a non-inferiority margin of 2%) of the HCL Arm compared to the Control Arm. The hypothesis of non-inferiority is mathematically expressed as:

H_0: μ(HCL) ⩾ μ(Control) + 2%

Ha: μ(HCL) < μ(Control) + 2%

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the Control Arm.

Group2 – Baseline A1C ⩽ 8%: Change in A1C (ΔA1C)

The key secondary effectiveness endpoint for the baseline A1C ⩽ 8% group is change in A1C from baseline to end of six-month treatment period, defined as A1C measured at the six-month treatment visit minus A1C measured at the randomization visit. The goal is to show non-inferiority (with a non-inferiority margin of 0.4%) of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period. The hypothesis of non-inferiority is mathematically expressed as:

H_0: μ(HCL) ⩾ μ(Control) + 0.4%

Ha: μ(HCL) < μ(Control) + 0.4%

where μ(HCL) is the mean of change in A1C (%) with the HCL Arm, μ(Control) is the mean of change in A1C (%) with the Control Arm.

Rest of Secondary Effectiveness Endpoints

Group1+Group 2: Time in Hypoglycemic Range during Night

The secondary effectiveness endpoint is the time with SG below 70 mg/dL (3.9mmol/L) during Night. The goal is to show superiority of the HCL Arm compared to the Control Arm reducing time in hypoglycemic range during night . The hypothesis is mathematically expressed as:

H_0: μ(HCL) $\geqslant$ μ(Control)

Ha: μ(HCL) < μ(Control)

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the HCL Arm during night, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the Control Arm during the night.

Group1+Group 2: Time in Hypoglycemic Range during Day and Night

The endpoint of time in hypoglycemic range below 70 mg/dL (3.9mmol/L) will be evaluated for superiority in the combined Groups during day and night. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing time in hypoglycemic range. The hypothesis is mathematically expressed as:

H0: μ(HCL) $\geqslant$ μ(Control)

Ha: μ(HCL) < μ(Control)

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the Control Arm.

Group1+Group 2: Time in Target Range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Night

The endpoint of time in target range measures the time with SG in target range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Night. The goal is to show superiority of the HCL Arm compared to the Control Arm in improving the time in target range. The hypothesis is mathematically expressed as:

H_0: μ(HCL) $\leq$ μ(Control)

Ha: μ(HCL) > μ(Control)

where μ(HCL) is the subject mean of time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the HCL Arm during Night, μ(Control) is the subject mean daily time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the Control Arm.

Group1+Group 2: Time in Target Range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Day and Night

The endpoint of time in target range measures the time with SG in target range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Day and Night. The goal is to show superiority of the HCL Arm compared to the Combined Control Arm in improving the time in target range. The hypothesis is mathematically expressed as:

H_0: μ(HCL) ≤ μ(Controls)

Ha: μ(HCL) > μ(Controls)

where μ(HCL) is the subject mean of time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the HCL Arm during Day and Night, μ(Control) is the subject mean daily time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the Control Arm.

Group1+Group 2: Change in A1C

The endpoint of change in A1C will be evaluated for superiority in the combined groups. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period. The hypothesis is mathematically expressed as:

H_0: μ(HCL) ≥ μ(Control)

Ha: μ(HCL) < μ(Control)

where μ(HCL) is the mean of change in A1C (%) with the HCL Arm, μ(Control) is the mean of change in A1C (%) with the Control Arm.

Note: Summary of all endpoints is presented with descriptive statistics with mean, SD, median, min and max values.

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7.10 Safety Evaluation

The primary safety endpoint is the event rate of severe hypoglycemia and DKA from both Groups (1 & 2) during the first 6 months of study phase and second 6 months of continuation phase. The descriptive summary statistics will be presented by number of event and event rate (100 patient years) for severe hypoglycemia and DKA **separately**.

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

- Diabetic ketoacidosis (DKA)

- Severe hypoglycemia
- Severe hyperglycemia
- Serious adverse events (SAEs)
- Unanticipated adverse device effects (UADEs)

7.11 Health Outcomes Analyses

Not Applicable

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

[redacted]

Diabetes Research in Children Network (DirecNet) Study Group; Type 1 Diabetes TrialNet Study Group, Buckingham BA, Beck RW, Ruedy KJ, Cheng P, Kollman C, Weinzimer SA, DiMeglio LA, Bremer AA, Slover R, Cantwell M. The effects of inpatient hybrid closed-loop therapy initiated within 1 week of type 1 diabetes diagnosis. Diabetes Technol Ther. 2013. May;15(5):401-8.

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Weinzimer et. al: Fully Automated Closed Loop Delivery versus Semi-Automated Hybrid Control in Pediatric Patients with Type 1 diabetes using the Artificial Pancreas. Diabetes Care, 2008, 31:934-939.