Medtronic

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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Evaluation of Meal Gesture Dosing in Adults with Type 1 Diabetes
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Sponsor/Local Sponsor	Medtronic MiniMed, Inc. (Global Sponsor) ("Medtronic") 18000 Devonshire St Northridge, CA 91325 Medtronic International Trading Sàrl (Local) ("Medtronic") Route du Molliau 31 1131 Tolochenaz, Switzerland

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AHCL	Advanced Hybrid Closed Loop
AUC	Area Under Curve
BG	Blood Glucose
CIP	Clinical Investigation Plan
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EOS	End of Study
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TDD	Total Daily Dose
USADE	Unanticipated Serious Adverse Device Effect

3. Introduction

In patients with insulin dependent diabetes mellitus, glycemic control is influenced by numerous factors, such as insulin dosage, insulin absorption, timing, and 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, including sensor-augmented pump therapy, experience improvements in glycemic control. Advanced features of sensor-augmented pump therapy are now being used in clinical practice; these include automatic suspension of insulin delivery when a pre-set glucose threshold is reached (low glucose suspend) or is predicted to be reached (predictive low glucose suspend). Both approaches have shown that a significant reduction in the risk and burden of hypoglycemia can be achieved, especially in patients who are prone to experiencing hypoglycemia.

Medtronic's latest system is the MiniMed 780G system, also referred to as the Advanced Hybrid Closed Loop (AHCL) system, a self-adjusting basal insulin pump with autocorrection dosing. Patients using the MiniMed 780G system are not required to confirm sensor glucose using a self-monitored blood glucose (SMBG) measurement before making therapy adjustments based on displayed sensor glucose values. Patients are still required to enter manual meal announcements (grams of carbs). With burden reduction in mind, the next generation of the AHCL system is focused on automated meal gesture dosing thereby eliminating the need for manual meal announcements.

Meal gesture dosing is a mode whereby meal announcements are not entered manually by the user. Instead, when meal gesture dosing is active, meal announcements are generated automatically by the system based on the detection of eating gestures. Eating gestures are derived from analyzing the motion sensor data from the user's Apple Watch (worn on the user's hand of eating). When eating is detected, the system translates the detected eating activity into an equivalent carb amount that is sent to the pump as a meal announcement. Sensor glucose based safety guardrails and rate control help ensure that automatic generation of meal announcements is safe.

The purpose of this study is to evaluate subject safety of using the Klue Health app utilizing meal gesture micro insulin dosing (meal gesture dosing) within the AHCL system in adult subjects with type 1 diabetes in a clinic setting.

4. Study Objectives

The objective of the study is to collect data for meal gesture dosing for unannounced meals within the AHCL system to be used for development of Medtronic Diabetes devices and products.

5. Investigation Plan

This study is a single-center, single arm study in adult subjects with type 1 diabetes utilizing AHCL System with meal gesture detection and micro dosing (meal gesture dosing). Meal gesture dosing is a mode whereby meal announcements are not entered manually by the user. Instead, when meal gesture dosing is active, meal announcements are generated automatically by the system based on the detection of eating gestures and micro doses of insulin are given.

Overall subject participation will be approximately 3 weeks to 4 months.

- A total of up to 40 subjects (aged 18-75) may be enrolled at one investigational center in Israel to have at least 16 subjects complete the study. Subjects may repeat participation at the request of the Sponsor and at the discretion of the investigator but will only be counted once toward the total number of subjects.

6. Determination of Sample Size

Given that this study is not statistically powered, no sample size calculation was performed. A total of up to 40 subjects will be enrolled at one investigational center in Israel to have at least 16 subjects complete the study. Subjects may repeat participation in the study at the request of the Sponsor and at the discretion of the investigator but will only be counted once toward the total number of subjects.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

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

7.1.2 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.3 Analysis Sets

All enrolled subjects who have participated in the study will be included in the efficacy analysis population. All enrolled subjects will be included in the safety analysis population.

7.2 General Methodology

All data collected 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.

7.3 Center Pooling

Not Applicable.

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

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.

All available data will be included in the data listings and tabulations. No imputation will be applied for the missing data.

7.5 Adjustments for Multiple Comparisons

No adjustments will be made.

7.6 Demographic and Other Baseline Characteristics

Subject demographics and baseline characteristics 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

The AHCL system with Meal Gesture Dosing evaluated in this study includes a commercial/CE-Marked insulin pump with investigational software and both CE-marked and investigational components, which will all be used as described in labelling and instructions for use for which CE mark has been obtained (as applicable). The AHCL system will also include the addition of the Klue Health mobile app with investigational software (installed on Apple Watch) for meal gesture detection and micro dosing. The AHCL system without meal gesture dosing is indicated for management of type 1 diabetes.

7.8 Interim Analyses

Not Applicable.

7.9 Evaluation of Objectives

Analysis will be performed by Klue Health App software release version, if applicable.

Given the exploratory nature of this feasibility study, in addition to endpoints described below, other outcomes may be assessed and/or analyses performed at any time during the study conduct, as needed.

7.9.1 Primary Endpoints

- Post-prandial Time in range (% of SG within 70-180 mg/dl) At-Home and In-Clinic Period will be summarized, respectively.

7.9.2 Safety Endpoints

- Number of (S)AEs, (S)ADEs, USADEs, Severe hypoglycemic events, DKA events, and Device Deficiencies

7.9.3 Other Endpoints

All measurements performed by Study Period (At-Home and In-Clinic period).

- Post-prandial Time in different ranges (% of SG): SG <54, 70 mg/dL, SG > 180, 250 mg/dL
- Change in post-prandial % of time in euglycemia (70-180 mg/dL) for meal challenges (intervention versus baseline)
- Change in post-prandial % of time in different ranges (% of SG): SG <54, 70 mg/dL, SG > 180, 250 mg/dL for meal challenges (intervention versus baseline)
- 24 hour Time in range (% of SG within 70-180 mg/dl)
- 24 hour Time in different ranges (% of SG): SG <54, 70 mg/dL, SG > 180, 250 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 180, 250 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54 and 70 mg/dL

- Time spent in Auto Mode versus time spent in Manual Mode
- Change of Total Daily Dose (TDD) of insulin from baseline to EOS Period
- Change in BG values during meal challenge (BG prior and BG 2 hours after meal)
- Insulin delivery at postprandial: Total unit of insulin in first 15 minutes, 60 minutes, 120 minutes, and 240 minutes postprandial
- Subgroup analysis by type of meals
- Between period analyses of all above (At-Home vs. In-Clinic)

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 Serious Adverse Device Effect (USADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA
- Device Deficiencies

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

Not Applicable.