Medtronic

Study Title	Feasibility Study of New Subcutaneous Glucose Sensor with Recording Devices- Phase 3 Group
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ATTACHMENT A

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Feasibility Study of New Subcutaneous Glucose Sensor with Recording Devices- Phase 3 Group
Clinical Investigation Plan Identifier	CIP318
Sponsor/Local Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
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1. List of Abbreviations and Definitions of Terms

Term	Definition
AE	Adverse Event
ADE	Adverse Device Effect
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CIP	Clinical Investigation Plan
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EOS	End of Study
ER	Engineering Report
FDA	United States Food and Drug Administration
FST	Frequent Sample Testing
GST	Glucose Sensor Transmitter
ID	Identification
MARD	Mean Absolute Relative Difference
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
R&D	Research and Development
RF	Radio Frequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
UADE	Unanticipated Adverse Device Effect

Term	Definition
USA	United States of America

2. Introduction

The intent of this study is to gather data from both commercially available devices and FDA approved devices used in an investigational manner used independently or in combination with each other.

Frequent self-monitoring of blood glucose (SMBG) is an important part of diabetes management. Careful attention to blood glucose (BG) values throughout the day allows patients to more precisely adjust insulin dosages and to adjust their food intake and activity levels accordingly. However, because SMBG values are taken only at specific time points and measure brief instances of time within a 24-hour period, there are limits to the usefulness of this information. The addition of continuous interstitial glucose values allows identification (ID), assessment, and monitoring of BG trends.

Current methods of continuous glucose monitoring (CGM) include the use of subcutaneous glucose sensors worn by the user which convert glucose from the subject's interstitial fluid into an electronic signal, the strength of which is proportional to the amount of glucose present in the fluid. (Note that throughout the protocol, a reference of "sensor" is meant to imply glucose sensor unless noted otherwise). A CGM sensor is typically attached to a transmitter which sends interstitial glucose information to a monitor (e.g. Guardian® Glucose Monitor) as radio frequency (RF) or Bluetooth Low Energy (BLE) signals or a recorder which saves interstitial glucose information to be uploaded after use. The sensor is composed of a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. In this study, a glucose sensor is paired with a glucose sensor recorder and/or transmitter capturing interstitial glucose information that will be uploaded from the device to a personal computer (PC) using appropriate software by the Investigational Center staff.

The Medtronic® MiniMed®, Inc. (d/b/a "Medtronic") family of Continuous Glucose Monitoring Systems (CGMS) measures subcutaneous glucose continuously over various ranges of time. The newest generation Guardian Sensor (3) was approved by the Food and Drug Administration (FDA) for commercialization as part of Medtronic MiniMed 670G system in September 2016. The Guardian Sensor (3) is intended for use with the MiniMed 670G system to continuously monitor glucose levels in persons with diabetes. It is intended to be used for detecting trends and tracking patterns in persons aged

fourteen years and older, and to be used by the MiniMed 670G system to automatically adjust basal insulin levels.

In this study, Guardian Sensor (3) will be tested on human subjects. The sensors are inserted into the user's subcutaneous tissue with a single patient, multi-use One-Press Serter. The Guardian Sensor (3) has the traditional one working electrode for determining the subject's interstitial glucose value. The sensors are attached to a Glucose Sensor Transmitter (GST), referred to as the Guardian Link (3) or Guardian Connect Transmitter, which will store the raw sensor data until it is downloaded to the designated PC.

3. Study Objectives

The purpose of Phase 3 Group is to collect data on the performance of Guardian Sensor (3)s each connected to the Guardian Link (3) Transmitter(s) and/or Guardian Connect Transmitter(s) during 11 days of wear (approximately 264 hours) in subjects with insulin requiring diabetes, 18-75 years of age.

4. Investigation Plan

The study is a multi-center, prospective single-arm design without controls. All subjects will be assigned to treatment for 11 days of sensor wear. Each subject will wear 4 Guardian Sensor (3)s, and each will be connected to a Guardian Link (3) Transmitter and/or Guardian Connect Transmitter. The Investigational Center will be informed via email the specific details on the type and number of sensors connected to the transmitters. Subjects may not use SG values for diabetes management.

Each subject may self-insert and self-tape their study glucose sensors once trained or have them inserted, connected, and taped by the trained Investigational Center staff in the abdomen and/ or arm area.

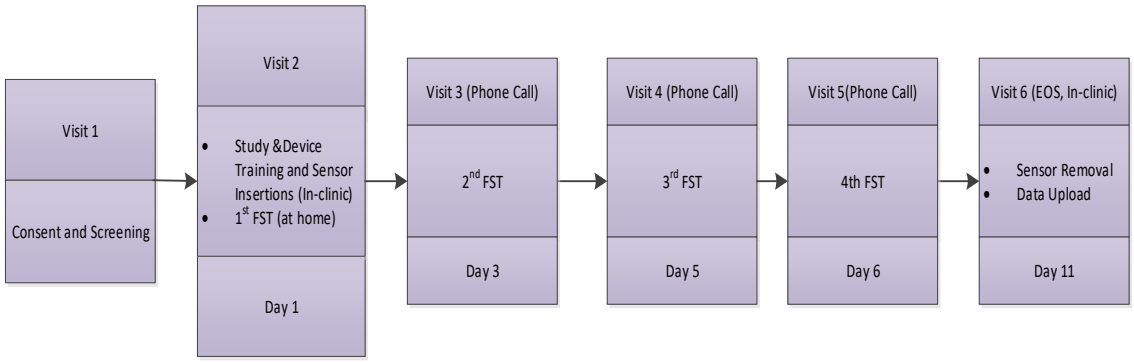
During the study, each subject will undergo 4 Frequent Sample Testings (FSTs) obtained by self-monitoring of blood glucose (SMBG) from fingerstick from Study Meter BG readings. Subject will be assigned to Phase 3 Group (Phase 3 Group will include only subjects 18 years of age and older).

Subjects will have all 4 FSTs occurring at home. Investigational Center staff will distribute and instruct subjects to take one gram of acetaminophen orally for FST Day 3, Day 5, and Day 6. During each FST, the subject will be asked to perform one SMBG measurement approximately every 20 minutes for 5 hours.

On Day 11, approximately 264 hours after last study sensor has been inserted, devices will be removed; data uploaded from the study meter and transmitter or recorder; skin assessment will be performed; and subject's participation in the study will be completed.

Phase 3 Group subjects will participate in 6 planned study visits, as presented in Phase 3 Group Figure 1 for 11 days of sensor wear with acetaminophen dosing.

Phase 3 Group Figure 1. Phase 3 Group: 11 Days of Sensor Wear with Acetaminophen Study Visit Schedule



- Phase 3 Group Visit 1: Consent and Screening
- Phase 3 Group Visit 2: Study & Device Training and Sensor Insertions:
    - Study Sensor Insertions (in-clinic)
    - 1st FST on Day 1 (at-home)
        - 5-hrs FST starting at approximately T=5 hours
- Phase 3 Group Visit 3 (Phone call): 2nd FST on Day 3 (approximately 72-90 hours) with 1gm Acetaminophen administered after first hour of FST at home
- Phase 3 Group Visit 4 (Phone call): 3rd FST on Day 5 (approximately 120-138 hours) with 1 gm Acetaminophen administered after first hour of FST at home
- Phase 3 Group Visit 5 (Phone call): 4th FST on Day 6 (approximately 144-162 hours) with 1 gm Acetaminophen administered after first hour of FST at home
- Phase 3 Group Visit 6 End of Study (EOS), In-clinic: Day 11 (approximately 264-282 hours)
    - Data upload

- Return study devices and Subject EZ Reference Guide and Diary

5. Determination of Sample Size

Given that this study is not statistically powered, no sample size calculation is performed. Up to 20 subjects will be enrolled in Phase 3 Group and demonstrate a feasibility study using the study sensors and transmitters.

6. Statistical Methods

6.1 Study Subjects

6.1.1 Disposition of Subjects

The number of subjects screened, enrolled, completed and withdrawn in the study will be presented. The reasons for subject's withdrawal will be summarized.

6.1.2 Clinical Investigation Plan (CIP) Deviations

All CIP deviations will be presented in the listings.

6.1.3 Analysis Sets

All enrolled subjects will be included in the accuracy analysis population and the safety analysis population.

6.2 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 report by Research and Development (R&D).

6.3 Center Pooling

Data will be pooled for analysis.

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

No imputation will be applied for the missing data.

6.5 Adjustments for Multiple Comparisons

No adjustments will be made.

6.6 Demographic and Other Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, duration of insulin requiring diabetes mellitus, type of diabetes mellitus, body fat percentage, and BMI (calculated based on provided height and weight) will be summarized by descriptive statistics.

6.7 Treatment Characteristics

Not applicable.

6.8 Interim Analyses

Not applicable.

6.9 Evaluation of Objectives

The primary objective of this feasibility study is to collect data to be used for development of Medtronic Diabetes devices and products.

6.9.1 Primary Endpoints

Accuracy (Mean absolute relative difference [MARD]) between the primary sensor values and meter BG values during the two hours (approximately 6 paired points per FST event) after ingestion of acetaminophen per subject will be described. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

6.9.2 Exploratory Analysis

Accuracy (MARD) between the primary sensor values and meter BG values during the two hours (approximately 6 paired points per FST event) after ingestion of acetaminophen per measurement will be described. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

The 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) between the primary sensor values and meter BG values during the two hours (at least 6 paired points per FST event) after ingestion of acetaminophen

per measurement will be calculated. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

6.10 Safety Evaluation

6.10.1 Safety

Descriptive summary will be used to characterize safety events

- Skin assessment of subject's glucose sensor insertion sites
- Adverse events (AE) to include:
  - Serious Adverse Events (SAE)
  - Device Related AEs
  - Procedure Related AEs
  - Serious Adverse Device Effect (SADEs)
  - UADE
  - Severe hypoglycemia
  - Diabetic Ketoacidosis (DKA)

6.10.2 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.
- All Investigational Center/subject reports of sensor damage, breakage or fracture will be included.

6.11 Health Outcomes Analyses

Not applicable.

6.12 Changes to Planned Analysis

Not applicable.

7. 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.

8. References

American Diabetes Association. Hyperglycemic Crises in Diabetes. Diabetes Care. 2004; 27(1): S94- S102.

American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes, Diabetes Care. 2005; 28: 1245-1249