This supplement contains the following items:

1. Original protocol, final protocol, and summary of changes
2. Original statistical plan, final statistical plan, and summary of changes

PROTOCOL VERSION 3: ACTIVE VERSION WHEN ENROLLLMENT INITIATED

Dexcom®

MOBILE

PROTOCOL

Continuous Glucose MOnitoring in T2D Basal InsuLin UsErs: The MOBILE Study

Protocol Number: PTL-902822

Study Sponsor: **Dexcom, Inc.**

Study Contact:

Version Date: **April 19, 2018**

Version Number: **003**

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1. Abbreviations and Definitions

AE	Adverse Event
BGM	Blood Glucose Meter
Blinded CGM	Receiver acts as a data collection tool and does not display CGM values, trends, or glucose alerts/alarms in real time. Receiver provides use prompts and features such as device failures, troubleshooting icons, event markers, etc.
CGM	Continuous Glucose Monitoring
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed Tomography
DCCT	Diabetes Control & Complications Trial
DKA	Diabetic Ketoacidosis (as defined by the DCCT) involves all of the following symptoms such as polyuria, polydipsia, nausea, or vomiting; serum ketones >1.5 mmol/L or large/moderate urine ketones; either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and treatment provided in a health care facility.
DM	Diabetes Mellitus
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate: a renal function test determined by a blood test for creatinine
GLP-1 agonist	Glucagon-like peptide-1 receptor agonists or incretin mimetics- A class of diabetes drugs used for the treatment of type 2 diabetes
HbA1c	Hemoglobin A1C. The hemoglobin A1C test provides the average level of blood glucose over the past 2 to 3 months. Also called glycated hemoglobin test, and Glycohemoglobin.
HCP	Health Care Professional
Hypoglycemia, Severe	**SH.** Results in seizure or loss of consciousness
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent to treat (analysis)
MDR	Medical Device Reporting
mg/dL	milligrams per deciliter
MRI	Magnetic Resonance Imaging
OAD	Oral Anti-Diabetic medications
PC	Personal computer, specifically using Intel hardware & Microsoft software; not Apple computers

Personal RT-CGM	Personal RT-CGM refers to frequent and continued use of CGM, owned by the user.
POC	Point of Care (Approved Guideline)
PP	Per Protocol (analysis)
PRO	Patient Reported Outcome
QoL	Quality of Life
RCT	Randomized Controlled Trial
RT-CGM	Real-Time Continuous Glucose Monitoring System
SAE	Serious Adverse Event
SGLT-2 inhibitors	Sodium-glucose transport protein 2 inhibitor used for the treatment of type 2 diabetes. They inhibit reabsorption of glucose in the kidneys and therefore lower blood glucose.
SMBG	**S**elf-Monitored Blood Glucose. Testing done with a glucose meter and capillary blood sample, typically from the person's fingertips.
SMBG Group	Uses a study-provided blood glucose meter to inform diabetes management decisions
SC	Study Coordinator
Study Clinician	Physician, Nurse Practitioner, Advanced Practice Nurse, Physician's Assistant, or Diabetes Educator, experienced in reviewing glucose data and making lifestyle recommendations or medication adjustments
T2D	Type 2 Diabetes Mellitus
UADE	Unanticipated Adverse Device Effect

2. Investigator Signature Sheet

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the study.

I will provide details of the protocol to all members of the study team responsible for conducting the study.

I will discuss the protocol with them to ensure that all participating staff members are fully informed regarding the study device and the conduct of the protocol.

Once the Institutional Review Board approves the protocol, I will not modify study procedures without obtaining prior approval of the Sponsor and, if required, of the Institutional Review Board (and FDA, as applicable).

I will submit any protocol and/or any informed consent modifications to the Sponsor and the Institutional Review Board (and FDA, as applicable) and approval will be obtained before any modifications are implemented.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

3. Protocol Synopsis

Title	Continuous Glucose **MO**nitoring in T2D **B**asal **I**nsu**L**in Us**E**rs: The MOBILE Study
Sponsor & Coordinating Center	Dexcom, Inc. and Jaeb Center for Health Research (JCHR)
Study Objectives	⇒ **Phase 1** **Primary:** Assess the benefit on glycemic control, using real time continuous glucose (RT-CGM) versus SMBG, in persons with Type 2 Diabetes (T2D) taking basal insulin with or without oral medications and/or GLP-1 analogue, not at their HbA1c goal. **Secondary:** • Assess quality of life (QoL) benefits of RT-CGM in basal insulin users • Assess frequency of hypoglycemia as determined by CGM ⇒ **Phase 2** **Primary:** Determine if glycemic control worsens upon withdrawal of RT-CGM **Secondary:** • Determine if glycemic benefits are sustainable for a longer period of time (14 months) • Assess QoL benefits of continuing or discontinuing RT-CGM • Assess frequency of hypoglycemia as determined by CGM
Study Design	Prospective, randomized, 2 phase parallel arm
Hypotheses	⇒ **Phase 1** In persons with T2D taking basal insulin (with or without oral medications and/or GLP-1 analogue) that are in poor control, CGM based decisions by the patients and their primary care physicians under advice from diabetes specialists, will result in better glycemic outcomes than blood glucose monitoring based decisions. ⇒ **Phase 2** Patients who discontinue RT-CGM will have a different time in target range (70-180 mg/dl) compared with patients who continue RT-CGM.

Study Devices:	Dexcom G6 CGM system, used in real time or blinded mode; a blue-tooth enabled blood glucose meter; CLARITY Data-management software; data management software compatible with the BG meter
Study Endpoints	⇒ **Phase 1 – Between group differences from baseline to Month 8, unless otherwise specified** **Primary Endpoint:** Change in HbA1c (Central lab) **Secondary & Other Endpoints** Numerous endpoints will be assessed for change between study groups. Endpoints include but are not limited to the following: • HbA1c metrics • CGM metrics • Diabetes medications • Non-HDL cholesterol • SMBG frequency • Patient Reported Outcomes (PRO)/surveys ⇒ **Phase 2 –** • **Between group differences for the Phase 1 CGM Group re-randomized to Discontinue CGM (use SMBG only) and Continue CGM from Month 8 to Month 14** • **Between group differences for the Continue CGM and the Continue SMBG groups from baseline to Month 14** **Primary Endpoint:** Change in CGM time in target range (70-180 mg/dL) for the Discontinue CGM and Continue CGM Groups (Month 8-14) **Secondary & Other Endpoints** Numerous endpoints will be assessed for change between study groups. Endpoints include but are not limited to the following: • CGM metrics • Diabetes medications • HbA1c metrics • Non-HDL cholesterol • SMBG frequency • PRO/surveys
Sample Size	Each study phase will be independently powered. ⇒ **Phase 1:** N=207 • For Phase 1, a 2:1 randomization scheme will be utilized- CGM: SMBG. A sample size of 165 participants is required to detect a difference in HbA1c with 85% power if the true difference between groups is 0.4%.

	Assuming a drop-out rate of 20%, up to 207 participants may be randomized into the study and up to 300 may be enrolled into screening. ⇒ **Phase 2:** N= approximately 74 • For Phase 2, a 1:1 randomization scheme will be utilized to re-randomize the Phase 1 CGM Group- Continue CGM: Discontinue CGM. All participants in the SMBG group from Phase 1 will continue in the study without re-randomization. The goal is for up to 92 participants from the Phase 1 CGM Group to enter Phase 2 (with approximately 74 completing Phase 2) to evaluate between group differences for time in range (70-180 mg/dL). There will be 85% power to detect a difference in time in range (70-180 mg/dL) if the true difference between groups is 5% and 74 participants complete Phase 2.
Study Sites	Up to 30 sites from across North America Target multi-specialty clinics/systems or endocrinology centers with a large referral base that possess research capabilities and have clinicians in the research site experienced in interpreting CGM and SMBG data.
Study Population	Adult T2D patients followed by a primary care physician for their diabetes, who are currently on basal insulin therapy with or without oral anti-diabetic therapy and/or GLP-1 analogue injections, sub-optimally controlled.
Inclusion Criteria	• Age at least 30 years • Type 2 diabetes by clinical history • Using 1-2 injections of basal or intermediate acting insulin daily • HbA1c between 8.0-11.5% inclusive at enrollment (by POC or local lab) • Assessment by clinician that patient is thought to be able and willing to wear a CGM device • Naïve to RT-CGM (may have used professional CGM) or intermittent scanned (Flash) continuous glucose monitoring • Has been self-monitoring on average at least 3 times per week (self-reported) during the prior month to entry • Stable medication regimen (medication classes) during the 3 months prior to entry • On basal insulin for ≥ 6 months prior to entry • Has a smart phone compatible with CGM and BGM systems and is willing to utilize a study issued blood glucose meter • Access to a computer for data transfer to clinical site • Has their diabetes managed by a primary care physician or nurse practitioner/ physician assistant (not an endocrinologist or diabetes specialist)

Exclusion Criteria	• Regular use of short acting insulin in the 3 months prior to study entry or planning to initiate prandial or short acting insulin. • Pregnancy (as demonstrated by a positive test at study entry) at time of screening or are planning to become pregnant during the study. • Planned or currently using weight reduction medications, programs or surgery. Defined as 1) using or planning on using weight loss prescription medication during the study; 2) currently using or planning on initiating a modified fasting program (e.g. protein-sparing diet plans) during the study; or 3) bariatric surgical procedure within the past year or plans for undergoing bariatric surgery during the study. **Note:** participation in non-physician directed plans such as Weight Watchers or Jenny Craig program are not exclusionary. • Concomitant disease or condition that may compromise patient safety including but not limited to severe mental illness, a diagnosed or suspected eating disorder or any uncontrolled long-term medical/ psychiatric condition that would interfere with study related tasks or visits. These assessments/conditions are made at investigator's discretion. • Known (or suspected) significant allergy to medical grade adhesives • Renal disease defined as estimated Glomerular Filtration Rate eGFR <30. **Note:** may use historical value, if obtained within 4 months of entry visit • Anticipated acute uses of glucocorticoids (oral, injectable, or IV), that will affect glycemic control and impact HbA1c • Acute conditions that impact the stability of a HbA1c measurement such as GI blood loss, recent (within 3 months of study entry), anticipated red blood cell transfusion or erythropoietin administration • Followed for their diabetes management by a study PI or sub-investigator • Diabetes (glucose) management, under the guidance of a diabetes specialist (endocrinologist, diabetologist, or advanced practice nurse) in the 6 months prior to study entry • Participation in another pharmaceutical or device trial at the time of enrollment or during the study
Study Overview	Investigators' role (and the investigator's clinical team/ study clinician) in the study is largely advisory in nature, such that they will provide insights and interpretation of the glucose data obtained from the BGM or CGM devices and formally communicate medication recommendations to the participant and their treating community clinician. The study clinician may provide the participant recommendations on lifestyle and self-titration modifications. Targeted participants will be recruited from outside the investigator team's diabetes and endocrine practice. **Run-In Period:** At the time of enrollment, participants will undergo a run-in period of blinded CGM to assess continuance in the study and to collect baseline CGM data. They will also receive and be trained on a study-assigned BG meter and supplies to be used in the run-in period. Baseline PRO tools

	and surveys will be administered at time of enrollment. Screening labs will be drawn and assessed for participant's study eligibility. Participants will wear blinded CGM for one sensor session (10 days). Criteria for participants to continue with randomization are 1) willingness and ability to use the CGM device, and 2) CGM adherence, defined as at least 70% usage (i.e. at least 7 days of CGM readings). The CGM data will NOT be shared with participants, clinicians at the research site, or the treating community clinician. Participants will all undergo or be referred for one or two general diabetes education session(s) (individual or group) during the run-in period, per site's usual diabetes educational program. The sessions will be documented and include review or discussion of the following: o Glucose targets (individualized) including fasting and pre-meal range and post meal o Basics of basal insulin titration o Basics of meal planning o Hypoglycemia management o Importance of medication adherence **Phase 1:** Those willing to participate and meeting eligibility criteria will be randomized 2:1 to either CGM (CGM Group) or SMBG (SMBG Group). Baseline labs will be drawn. Phase 1 is of 8 months duration. For the CGM Group, it comprises 4 scheduled clinic visits: at week 2, month 1, month 3 and month 8. For the SMBG Group, it comprises 5 scheduled clinic visits: at week 2, month 1, month 3, pre-month 8 (~ 10 days prior to Month 8 visit) and month 8. There will be phone/ remote visits at months 2, 4 and 6 in both groups. HbA1c will be measured by Central lab and POC/local lab at baseline, 3 months and 8 months. Visits and phone contacts involve assessment of glucose data for clinical decision making, with documented formal advice to the treating community clinician and participant. Participants in the SMBG Group will undergo periodic blinded CGM use (Month 3 and 8) to allow for a comparison of CGM metrics. During phone contacts and at the Month 8 clinic visit, self-reported therapy changes will be documented (medications and visits to primary care physician). **Phase 2:** Consists of 3 groups: 1) participants continuing use of SMBG since the beginning of Phase 1; 2) participants re-randomized from the Phase 1 CGM Group and assigned to SMBG; 3) participants re-randomized from Phase 1 CGM Group and assigned to CGM. This phase involves 1 phone contact and either 2 visits at Month 14 for SMBG participants to wear blinded CGM or one visit for CGM participants. For all participants, study participation will end upon completion of Month 14 visit. **Additional details:** • At each visit/contact study related procedures will be performed by a clinical coordinator and glucose data review will be made by a study clinician with experience in reviewing and interpreting glucose data.

	• Additional visits – number of education and phone discussions related to CGM (by the research site) - will be tracked by the study staff on CRFs. • Blinded CGM data should not be reviewed 1) by clinicians that are part of the investigator team, 2) with participants in the SMBG group or 3) by the community treating clinician. An exception is the final study visit at Month 14. • Additional communication to the community treating clinician will be encouraged (e.g. as a follow-up to letters sent), such as phone calls or messaging via electronic medical record. • If at any point during the study the community treating clinician believes referral to an endocrinologist is warranted, he/she will be encouraged to refer participant to an endocrinologist within their normal referral pattern. However, the PI or sub-investigators should be excluded from formal consultation and from providing ongoing diabetes management to participants during the study.
Duration of participation	14 months

4. Introduction

Diabetes mellitus is a group of diseases characterized by abnormally high blood glucose levels. There are two major classifications of diabetes mellitus: Type 1 Diabetes Mellitus (T1DM), autoimmune destruction of the insulin producing pancreatic beta cells resulting in diminished or absent insulin secretion; and Type 2 Diabetes Mellitus (T2DM), resulting from constellation of defects including but not limited to impaired insulin action, decreased insulin production, and enhanced hepatic glucose production.[1] The Centers for Disease Control and Prevention reported that diabetes affects approximately 30.3 million people in the United States, or roughly 9.4% of the population, with approximately 1.5 million new cases being diagnosed each year. There are also 79 million people in the United States with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).[2] The global prevalence of diabetes in 2015 in adults was 415 million and it is projected that 642 million people will have diabetes by the year 2040.[3]

Large-scale, randomized, prospective trials of various interventional therapies in patients with both T1DM and T2DM have clearly shown that improved glycemic control significantly reduces the development and progression of microvascular complications of diabetes in both adults and adolescents. The Diabetes Control and Complications Trial (DCCT) and the Kumamoto Trials showed that intensive treatment methods reduced the incidence of these complications by approximately 50 to 70%.[4,5,6] These studies have demonstrated that intensive monitoring and better control of blood glucose in people with T1DM and T2DM both delays the onset and reduces the progression of diabetic retinopathy, nephropathy, and neuropathy.

Advances in medications and medical devices over the years have not significantly impacted clinical goals for patients, with less than 8% of them at recommended treatment goal for glucose, blood pressure and lipids.[7] Achieving optimal glycemic control for persons with advanced T2DM often involves use of insulin therapy; however roughly a third of T2DM patients do not adhere to the prescribed insulin regimens.[8] Furthermore, many T2DM patients using insulin perform SMBG testing at suboptimal levels.[9,10]

Use of real-time continuous glucose monitoring (RT-CGM) has been shown to improve glycemic control with a reduced risk of hypoglycemia in T1DM and T2DM patients on intensive insulin therapy. Only a few studies have studied RT-CGM's impact on glycemic control in T2DM with use of basal insulin, prandial insulin and oral anti-diabetic medications (OADs). Because once-daily basal insulin is the first step in initiating insulin therapy in T2DM, the need to evaluate the utility of RT-CGM with less intensive insulin regimens is warranted.

Use of RT-CGM demonstrated a benefit in a pilot observational study conducted by Manning et al. The study's objective was to assess persistence of RT-CGM use in T2DM patients treated with basal insulin and its potential impact on quality of life and glycemic control. Results showed that use of RT-CGM resulted in marked glycemic improvement. Psychosocial measures collected during the study suggested that RT-CGM did not appear to increase diabetes-related stress or add to the burden of diabetes management. Further, analyses showed that subjects' attitudes toward RT-CGM use tended to improve over the six-month study duration.[11]

Episodic RT-CGM use was evaluated in a randomized trial of 100 subjects by Vigersky et al. Adults with T2DM who were not on prandial insulin were followed for 52 weeks to compare the long-term effects of RT-CGM versus SMBG on glycemic control. The results of this study showed a significant decline in HbA1c in the RT-CGM group compared to the SMBG group (0.8% vs 0.2% @ week 52). Vigersky concluded that persons with T2DM not on prandial insulin who used RT-CGM intermittently have sustained improvement in glycemic control during a long term follow up period (52 weeks).[12] The improvement in glycemic control observed in this study was similar to improvements achieved by pharmacologic interventions with oral agents.

No prospective randomized controlled studies have been conducted, exploring the clinical benefits of RT-CGM used daily for poorly-controlled, non-intensive insulin users compared with those who use SMBG as their glycemia monitoring tool. Therefore, this study will examine the potential benefit of adding RT-CGM to and utilizing RT-CGM data in patients with sub-optimal glycemic control using basal insulin therapy.

5. Study Objectives

For Phase 1 of the study, the objectives are as follows:

⇒ **Primary**:

Assess the benefit on glycemic control, using real time continuous glucose (RT-CGM) versus SMBG, in persons with Type 2 Diabetes (T2D) taking basal insulin with or without oral medications and/or GLP-1 analogue, not at their HbA1c goal.

⇒ **Secondary**:

- Assess quality of life (QoL) benefits of RT-CGM
- Assess frequency of hypoglycemia as determined by CGM

For Phase 2 of the study, the objectives are as follows:

⇒ **Primary**:

Determine if glycemic control worsens upon withdrawal of RT-CGM

⇒ **Secondary**:

- Determine if glycemic benefits of RT-CGM use are sustainable for a long period of time (14 months)
- Assess QoL benefits of continuing or discontinuing RT-CGM
- Assess frequency of hypoglycemia as determined by CGM

6. Hypotheses

⇒ **Phase 1**

In persons with T2D taking basal insulin (with or without oral medications and/or GLP-1 analogue) that are in poor control, CGM based decisions by the patients and their primary care physicians under advice from diabetes specialists, will result in better glycemic outcomes than blood glucose monitoring based decisions.

⇒ **Phase 2**

Patients who discontinue RT-CGM will have a different time in target range (70-180 mg/dL) compared with patients who continue RT-CGM.

7. Primary Endpoints

⇒ **Phase 1**: Between group differences (CGM and SMBG) for the change in HbA1c (from Central lab) from baseline to Month 8

⇒ **Phase 2**: Between group differences for the Phase 1 CGM Group re-randomized to Discontinue CGM (use SMBG only) or to Continue CGM for the change in time in target range (70-180 mg/dL) from Month 8 to Month 14

8. Secondary Endpoints

⇒ **Phase 1**: Between group differences (CGM and SMBG) from baseline to Month 8. All treatment group comparisons of CGM metrics will use the blinded CGM data collected for the SMBG Group participants and a similar time period of data for the CGM Group participants.

- Change in CGM time in target range, defined as 70-180 mg/dL
- Percent decreasing HbA1c by ≥0.5% (absolute)
- Percent adding or removing diabetes medications (starting or stopping medication)
- Change in HbA1c based on their baseline HbA1c (restricted to participants with baseline HbA1c ≥10.0%, ≥9.5%, ≥9.0%, ≥8.5%; only performed if primary analysis is significant)
- Change in CGM time-hyperglycemic, defined as >250 mg/dL
- Change in CGM measured coefficient of variation
- Change in CGM time-hypoglycemic, defined as <70 mg/dL

Additional outcomes are listed in the Statistical Analysis Plan.

⇒ **Phase 2**: Between group differences for the Phase 1 CGM Group re-randomized to the Discontinue CGM Group (use SMBG only) versus the Continue CGM Group from Month 8 to Month 14. Between group differences for the Continue CGM and the Continue SMBG groups from baseline to Month 14

- Change in HbA1c (Central lab)
- Change in CGM time-hyperglycemic, defined as >250 mg/dL
- Percent decreasing HbA1c by ≥0.5% (absolute)
- Percent adding or removing diabetes medications (starting or stopping medication)
- Change in CGM measured coefficient of variation
- Change in CGM time-hypoglycemic, defined as <70 mg/dL

Additional outcomes may be listed in the Statistical Analysis Plan.

9. Other Endpoints

Exploratory analyses will be performed on the outcomes listed below to better understand the effect of CGM on this population. Additional outcomes may be listed in the Statistical Analysis Plan.

⇒ **Phase 1**:

Between group differences (CGM and SMBG) from baseline to Month 8

- Other HbA1c outcomes:
  - Percent reaching target HbA1c (<7.0%)
  - Percent with HbA1c <7.5%
  - Percent decreasing HbA1c by ≥1.0% (absolute)
  - Percent decreasing HbA1c by ≥1.0% (absolute) OR reaching target HbA1c (<7.0%)
  - Percent decreasing HbA1c by >10% (relative)
- Change in SMBG frequency (self-reported)
- Number of visits to primary care physician for glucose management (self-reported)
- Changes in Quality of Life (QoL) and other survey outcomes:
  - Diabetes Distress Scale (DDS)
  - Glucose Monitoring Satisfaction Survey, (GMSS) - Type 2 Version

- Clinician Communication Rating Scale
- Fear of Hypoglycemia, Worry & Behavior Subscales
- Hill-Bone Medication Adherence Scale
- SF12 Health Survey
- WHO-5 Well-Being Index
- Toobert's Scale, Modified (SDSCA) - Diet and Exercise
- Perceived Benefit Questionnaire
- CGM Satisfaction Survey (CGM Group only)

⇒ **Phase 2**:

Between group differences for the Phase 1 CGM Group re-randomized to the Discontinue CGM Group (use SMBG only) and Continue CGM Group from Month 8 to Month 14

Between group differences for the Continue CGM and the Continue SMBG groups from baseline to Month 14

- Other HbA1c outcomes:
  - Percent reaching target HbA1c (<7.0%)
  - Percent with HbA1c <7.5%
  - Percent decreasing HbA1c by ≥1.0% (absolute), from baseline to Month 14
  - Percent decreasing HbA1c by ≥1.0% (absolute) OR reaching target HbA1c (<7.0%), from baseline to Month 14
  - Percent decreasing HbA1c by >10% (relative), from baseline to Month 14
- Change in SMBG frequency (self-reported)
- Number of visits to primary care physician for glucose management (self-reported)
- Changes in Quality of Life (QoL) and other survey outcomes:
  - Diabetes Distress Scale (DDS)
  - Glucose Monitoring Satisfaction Survey, (GMSS) - Type 2 Version
  - Clinician Communication Rating Scale
  - Fear of Hypoglycemia, Worry & Behavior Subscales
  - Hill-Bone Medication Adherence Scale
  - SF12 Health Survey
  - WHO-5 Well-Being Index
  - Toobert's Scale, Modified (SDSCA) - Diet and Exercise
  - Perceived Benefit Questionnaire
  - CGM Satisfaction Survey (CGM Group only)

10. Study Population

Adult T2D patients followed by a primary care physician, who are currently on basal insulin therapy with or without oral anti-diabetic therapy and/or GLP-1 analogue injections and who are sub-optimally controlled. Participants will be recruited from within the network or the referral base of the research site.

11. Study Eligibility

11.1. Inclusion Criteria

- Age at least 30 years
- Type 2 diabetes by clinical history
- Using 1-2 injections of basal or intermediate acting insulin daily
- HbA1c between 8.0-11.5% inclusive at enrollment (by site's POC or local lab)

- Assessment by clinician that patient is able and willing to wear a CGM device
- Naïve to RT-CGM (may have used professional CGM) or Flash glucose monitoring
- Self-monitors blood glucose on average at least 3 times per week (self-reported) during the month prior to entry visit
- Stable medication regimen (medication class) during the 3 months prior to entry visit
- On basal insulin for ≥ 6 months prior to entry visit
- Has a smart phone compatible with CGM and BGM systems and is willing to utilize a study issued blood glucose meter
- Access to a computer for data transfer to clinical site
- Has their diabetes managed by a primary care physician or nurse practitioner/ physician assistant (not an endocrinologist or diabetes specialist)

11.2. Exclusion Criteria

- Regular use of short acting insulin in the 3 months prior to entry visit or planning to initiate prandial insulin or short acting insulin. Regular use of short acting insulin defined as 1 or more injections/day for more than 1 week. **Note:** Short term use in a hospital setting or for correction of isolated hyperglycemia is not an exclusion.
- Pregnancy (as demonstrated by a positive test at study entry) at time of screening or are planning to become pregnant during the study
- Weight reduction medications, programs or surgery. Defined as 1) using or planning on using weight loss prescription medication during the study; 2) currently using or planning on initiating a modified fasting program (e.g. protein-sparing diet plans) during the study; or 3) bariatric surgical procedure within the past year or plans for undergoing bariatric surgery during the study. **Note:** participation in non-physician directed plans such as Weight Watchers or Jenny Craig program are not exclusionary.
- Concomitant disease or condition that may compromise patient safety including and not limited to severe mental illness, a diagnosed or suspected eating disorder or any uncontrolled long-term medical/ psychiatric condition that would interfere with study related tasks or visits. These assessments/conditions are made at the investigator's discretion.
- Known (or suspected) significant allergy to medical grade adhesives
- Renal disease defined as estimated Glomerular Filtration Rate eGFR <30 **Note:** may use historical value, if obtained within 4 months of entry visit
- Anticipated acute uses of glucocorticoids (oral, injectable, or IV), that will affect glycemic control and impact HbA1c – such as frequent steroid bursts required for inflammatory arthritis or inflammatory bowel disease, recurrent lumbar epidural steroid injections, etc. (Long-term stable glucocorticoid doses are allowed, such as when used for the treatment of rheumatoid arthritis or Addison's disease).
- Acute conditions that could impact the stability of an HbA1c measurement such as GI blood loss, recent (with 3 months of entry visit) or anticipated red blood cell transfusion or erythropoietin administration.
- Followed by for their diabetes management by a study PI or sub-investigator
- Diabetes (glucose) management in the prior 6 months (study entry) under the guidance of a diabetes specialist (endocrinologist, diabetologist or advanced practice nurse)
- Participation in another pharmaceutical or device trial at the time of enrollment or during the study

12. Study Design

Prospective, randomized, 2 phase parallel arm with a run-in period. The Investigators' role in the study with respect to diabetes management is advisory in nature, such that they will provide insights and interpretation of the glucose data obtained from the BGM or CGM devices and formally communicate recommendations to the participant and their treating community clinician. The study clinician may provide recommendations on lifestyle and self-titration modifications to the participant. Any recommendations for medication changes will be provided to the treating community clinician.

Targeted participants will be recruited from outside the investigator team's diabetes and endocrine practice and will be followed for their diabetes management by a primary care physician.

After providing consent, all potential participants will be assessed for eligibility**.** At the time of enrollment, participants will undergo a run-in period (10 days) of blinded CGM to assess continuance in the study and to collect baseline CGM data. Training will be provided for use of study-assigned meter. Screening labs and surveys will be administered at time of enrollment (See **Table 1. Schedule of Events**).

Criteria for participants to continue with randomization are 1) willingness and ability to use the CGM device, 2) and CGM adherence, defined as a minimum of 70% usage (e.g. at least 7 days of CGM readings). The CGM data will NOT be shared with participants, clinicians at the research site, or the treating community clinician.

Participants will undergo or be referred for one or two general diabetes education session(s) (individual or group) during the run-in period, per site's usual diabetes educational program. The sessions may include review or discussion of the following:

- Glucose targets (individualized) including fasting and pre-meal range and post meal
- Basics of basal insulin titration
- Basics of meal planning
- Hypoglycemia management
- Importance of medication adherence

Those willing to participate and meeting eligibility criteria will be assigned to 1 of 2 groups in Phase 1, using a 2:1 randomization scheme, to either CGM (CGM Group) or SMBG (SMBG Group). Randomization will be stratified by site using a permuted blocks design. Randomization to group assignment will be obtained from a study website after all enrollment data have been entered and eligibility verified. Baseline labs will be drawn (Non-HDL cholesterol, C-peptide if historical lab not available and Central and POC/local lab HbA1c).

Phase 1 is of 8 months duration. For the CGM Group, it comprises 4 scheduled clinic visits: at week 2, month 1, month 3 and month 8. For the SMBG Group, it comprises 5 scheduled clinic visits: at week 2, month 1, month 3, pre-month 8 (~ 10 days prior to Month 8 visit) and month 8. There will be phone/ remote visits at months 2, 4 and 6 in both groups. HbA1c will be measured by Central lab and POC/local lab at baseline, 3 months and 8 months.

A visit specific communication letter will be sent by the study clinician to the community treating clinician informing them of the patient's participation and the limited role of the study clinician-providing lifestyle recommendations to the patient. The study clinician may also provide guidance on self-titration of basal insulin, and report glucose trends to patients and clinicians (with treatment considerations to the community treating clinician, such as discontinuation of any medications that may be causing hypoglycemia or resulting in significant side effects).

Description of study groups:

SMBG Group

1. Participants will be provided a blue-tooth enabled blood glucose meter and testing supplies

2. A BGM account will be established and linked to the research site
3. Participants will be asked to perform SMBG testing from 1- 3x daily. Testing should involve a minimum of once daily test and include some fasting and some post-prandial measurements
4. Blinded CGM will be worn at intervals as described in **Section 20, Study Procedures**

CGM Group

1. The G6 CGM app will be installed on participant's smart phone.
2. A CLARITY mobile account will be set up and linked to the research site.
3. Participants will use CGM data for their diabetes management. Blood glucose monitoring will be performed if CGM readings do not match a participant's symptoms.
4. Participants will perform SMBG testing as needed with a study-provided blue-tooth enabled blood glucose meter, including testing supplies.
5. Participants will set CGM threshold alerts at values that will minimize alerts. These should be tightened/ adjusted during the study as glucose control improves.
6. Participants may have CLARITY push notifications enabled during the study.

During clinic visits, the study clinician will discuss any device issues requiring troubleshooting, upload the glucose data from the CGM and BGM as applicable, provide suggestions to the participant on self-titration of basal insulin (at Week 2 and at subsequent phone encounters and clinic visits), provide treatment guidelines based on observed glucose patterns, and encourage lifestyle experimentation and modifications to minimize glycemic excursions. A study-provided Tips for Success sheet (either CGM or BGM relevant) will be reviewed with the participant during some clinic visits. CGM users may have alert settings adjusted, will be encouraged to share their glucose data with the CGM Share app and indicate the number of followers in which they are sharing their glucose data. The Month 3 clinic visit involves only collection of Central and POC/local lab HbA1c and having the SMBG Group participants wear blinded CGM for one session wear.

During phone/remote contacts by the study clinician, any therapy changes (including any new/changing medications and visits to the primary care physician) that have been made by the community treating clinician, as self-reported by participants, will be documented. The study clinician will use a study-provided guidance document for conducting the phone/remote contacts. This document provides a structured approach to the remote visits.

At the conclusion of Phase 1 (Month 8), participants will have completed PROs/surveys and had blood drawn for lab data collection (HbA1c-Central and local and Non-HDL cholesterol). The blinded CGM data obtained in the SMBG Group will *not* be used by the research site staff and will *not* be reviewed with the participant or sent to the community treating clinician.

At each visit/contact (except Month 3) the study clinician will send the glucose data record (CGM for the CGM Group and SMBG for the SMBG Group) and communicate via letter with the community treating clinician interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments, and any lifestyle recommendations. The letter will contain discussion of glucose patterns that are elucidated and considerations for therapy changes based on patterns. However, any therapy changes would occur outside the study and be made by the community treating clinician, unless deemed clinically warranted by study clinician (e.g. for immediate safety purposes such as frequent or problematic hypoglycemia). A copy of the glucose data (summary CGM data for CGM Group and SMBG data for the SMBG Group, per Investigator discretion), interpretation and recommendations will also be provided to the participant for use in discussions with their community treating clinician.

For Phase 2, participants from the Phase 1 CGM Group will be re-randomized 1:1 to continue CGM use (Continue CGM Group) or to use SMBG (Discontinue CGM Group). CGM devices will be

collected from participants discontinuing CGM use in Phase 2. Participants from the Phase 1 SMBG Group will continue SMBG (Continue SMBG Group). Randomization to group assignment will be obtained from a study website after the Month 8 visit is completed. Tips for Success with CGM or SMBG will be provided.

Phase 2 comprises either 1 visit and 1 phone contact (Continue CGM Group) or 2 visits and 1 phone contact (Discontinue CGM Group and Continue SMBG Group). Participants in all 3 groups will continue study participation for an additional 6 months. BG testing supplies will continue to be provided.

During the phone/remote contact at Month 11, study staff will document any therapy changes (including any new/changing medications and visits to the primary care physician) that have been made by the community treating clinician, as self-reported by participants. They will discuss any device issues requiring troubleshooting, upload the glucose data, provide suggestions on self-titration of basal insulin, and encourage lifestyle experimentation and modifications. CGM users may have alert settings adjusted, will be encouraged to share their glucose data with the CGM Share app and indicate the number of followers in which they are sharing their glucose data.

The study clinician will send the glucose data record (CGM data for Continue CGM Group and SMBG data for both SMBG groups) and communicate via letter with the community treating clinician about the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments or significant post-meal hyperglycemia that may require additional therapy, and any lifestyle recommendations. The letter will contain discussion of glucose patterns that are elucidated and considerations for therapy changes based on patterns. However, any therapy changes would occur outside the study and be made by the community treating clinician. A copy of the glucose data (CGM data for Continue CGM Group and SMBG data for both SMBG groups) and recommendations will also be provided to the participant.

At the Pre-Month 14 visit, participants in both SMBG groups (Discontinue CGM Group and Continue SMBG Group) will wear blinded CGM for one session wear and complete PROs/surveys.

At the final Month 14 clinic visit, a blood draw will be done for Central and POC/local lab HbA1c and Non-HDL cholesterol, devices will be downloaded and surveys will be administered (CGM Group only). CGM devices used that are not approved by FDA will be collected. Blinded CGM data can be reviewed with the participants in both SMBG groups.

Additional details:

- At each visit/contact study related procedures will be performed by a clinical coordinator and glucose data review will be made by a study clinician with experience in reviewing and interpreting glucose data.
- Blinded CGM data should not be reviewed 1) by clinicians who are part of the investigator team, 2) with participants in any of the SMBG groups or 3) by the community treating clinician. An exception is the final study visit at Month 14.
- Additional visits – number of education and phone discussions related to CGM (by the research site) - will be tracked by the study staff.
- Additional communication to the community treating clinician will be encouraged (e.g. as a follow-up to letters sent), such as phone calls messaging via electronic medical record.
- If at any point during the study the community treating clinician believes referral to an endocrinologist is warranted, he/she will be encouraged to refer participant to an endocrinologist within their normal referral pattern. However, the PI or sub-investigators should be excluded from formal consultation and ongoing diabetes management during the study.

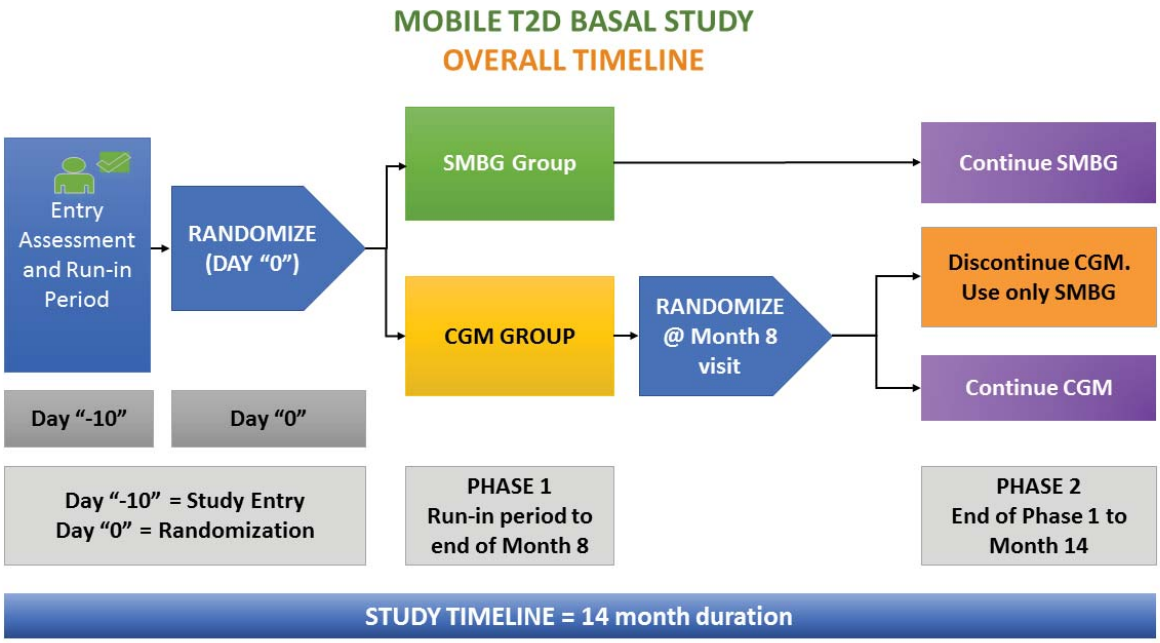

Figure 1. Study Design Diagram

13. Duration of Study Participation

Participants' duration in study for both phases is 14 months. Phase 1 duration is 8 months. Phase 2 duration is 6 months.

14. Study Duration

The estimated time for study completion is 3 years, includes recruitment and completion of Phase 2 follow up period.

15. Clinical Research Sites

Up to 30 sites from across North America

Targeted sites will be multi-specialty clinics/systems or endocrinology centers from a mixture of academic and community sites that are part of a health system or that have a strong referral base. These centers will have research capabilities and have clinicians in the research site experienced in interpreting CGM and SMBG data. Clinicians (CDE, NP, PA or equivalent, or MD) will interpret data and provide data and suggestions to the participant and participant's community treating clinician, using study provided correspondence and treatment guidelines.

16. Overview of Study Devices

The Dexcom G6 Continuous Monitoring System will be used during the study. Commercially cleared blood glucose meters will be assigned to participants to collect relevant study data. Study participants will receive guide materials for the both devices.

16.1. Dexcom G6 Continuous Glucose Monitoring System

The Dexcom G6™ Continuous Glucose Monitoring System (the G6 CGM System) is intended for single-patient use. The G6 CGM System is a Class II device that has been cleared by the FDA for

commercialization (DEN 170088). Its intended use is for the management of diabetes in persons age 2 years and older.

The Dexcom G6 System is intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G6 System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6 System also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments.

The Dexcom G6 System is also intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. The Dexcom G6 System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes. Refer to the Indications for Use document prior to device use. It measures and displays glucose values and trends for patients with diabetes. The system provides continuous glucose readings at five-minute intervals for up to 10 days of use. The system does not require calibration with blood glucose measurements taken with a self-monitoring blood glucose meter.

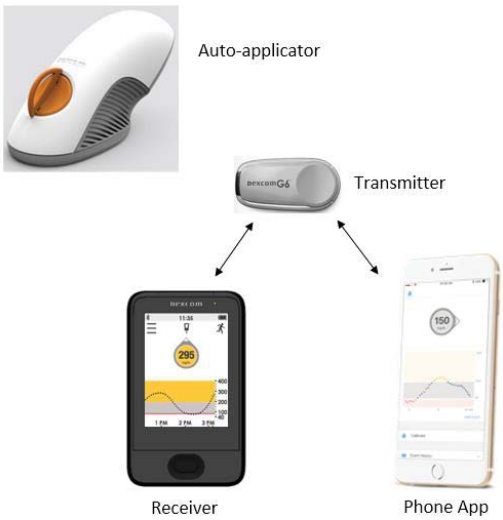

Figure 2. Dexcom G6 Continuous Monitoring System

The system (**Figure 2**) consists of a sensor, transmitter, receiver, and mobile app. The sensor is a small, flexible wire inserted into subcutaneous tissue where it converts glucose into electrical current. The sensor incorporates an interferent layer that minimizes the effect of potential electroactive interferents, such as acetaminophen, by preventing it from reaching the sensor wire surface. The benefit of this interferent layer in blocking the effects of acetaminophen prevents falsely high glucose readings. Thus, users may ingest acetaminophen while wearing the G6 CGM system.

The transmitter, which is connected to the sensor and worn on the body, samples the electrical current produced by the sensor and converts the measurement into a glucose reading using an onboard algorithm. The receiver and/or the app displays the glucose reading along with a rate of change arrow and a trend graph. Additionally, the receiver and/or app issues alarms and alerts to notify the patient of glucose level changes and other important system conditions. The app provides the additional capability to share data using the Dexcom Share service.

The receiver can be put into a blinded mode. In this mode, users are unable to see the CGM data or receive CGM alerts.

16.2. CGM Ancillary Devices

Dexcom CLARITY is an accessory to users of the Dexcom CGM system. It is a software program that allows the transfer of glucose data from the CGM system to Dexcom remote servers for data management to allow use of the CGM data by the user and study clinicians. Both participants and study sites will use CLARITY to transfer glucose data between user and study site, whether CGM is used in blinded or real-time mode.

16.3. Blood Glucose Meter (BGM) Devices

Each participant will be assigned a blue-tooth enabled study meter to record their blood glucose values during the study. The meter has FDA 510K clearance and is commercially available in the US. They will receive an ample supply of meter test materials based on quantities routinely used. This meter system includes a wireless meter, a smartphone app, and an online portal that allows users to share data with their clinical site personnel. The wireless meter transmits blood glucose results to the app on the user's smartphone using *Bluetooth*® technology. Users can also store and access information securely via an online portal account. Software used in conjunction with the BGM will be utilized for downloading data at the sites and use for study analysis.

17. PRO Measurements & Surveys

PRO measures and surveys will be administered during the study. All eligible participants will complete PRO measures and surveys at baseline. During follow-up, the PRO measures and surveys will be completed at Month 8 and 14 for the CGM Group and at the Pre-month 8 and 14 visits for the SMBG Group. The PRO measures and surveys may be completed by participants at home, up to 1-week prior to reduce participant burden during clinic visits. They assess QoL dimensions – health state, psychological well-being, diabetes management, and interaction with CGM; and treatment satisfaction and behavioral changes throughout the study, as well as capture health economic benefits.

The following PRO measures and surveys will be administered during the study:

17.1. Diabetes Distress Scale (DDS)[13]

CGM Group: Entry, Month 8, and Month 14; SMBG Groups: Entry, Pre-Month 8 & Pre-Month 14

This scale lists 17 potential problem areas that people with diabetes may experience and can denote the degree to which they are or are not affected. The DDS has a consistent, generalizable factor structure and good internal reliability and validity. The instrument serves as a valuable measure of diabetes-related emotional distress for use in research and clinical practice.

17.2. Glucose Monitoring Satisfaction Survey, (GMSS)[14]

CGM Group: Entry, Month 8, and Month 14; SMBG Groups: Entry, Pre-Month 8 & Pre-Month 14

This 15-question survey, which includes four subscales, is a reliable, validated measure of glucose device satisfaction in both its T1D form and its insulin-using T2D form. Subscales include Openness, Emotional Burden, Behavioral Burden and Worthwhileness. It can be used in clinical care and research.

17.3. Hill-Bone Medication Adherence Scale[15]

CGM Group: Entry, Month 8, and Month 14; SMBG Groups: Entry, Pre-Month 8 & Pre-Month 14

This scale is scored on a 4-point Likert scale and queries how a person with diabetes self manages their medication regimen. The original scale comprised three subscales (medication adherence, reduced sodium intake, appointment keeping) and was designed for use with patients taking hypertensive medication. In the modified, un-validated form used for this study, the word 'diabetes' was substituted. This change would not affect the psychometric properties of the scale.

17.4. Clinician Communication Rating[16]

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

This is a brief survey that assesses the perceived quality of the interaction between the participant and their community treating clinician.

17.5. Toobert's Scale, Modified (SDSCA Diet and Exercise)[17]

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

The SDSCA measure is a brief self-report questionnaire of diabetes self-management that includes items assessing the following aspects of the diabetes regimen: general diet, specific diet, exercise, blood-glucose testing, foot care, and smoking. This study will utilize the diet and exercise portions of the questionnaire.

17.6. Fear of Hypoglycemia Survey[18] Worry & Behavior Subscales

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

This validated short survey consists of 11 questions which measure several dimensions of worry and behavior surrounding hypoglycemia among adults with diabetes.

17.7. SF-12 Health Survey[19]

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

The SF-12 has become the most widely used measure of general health in clinical studies throughout the world. The survey is a 12-item validated questionnaire used to assess health outcomes from the patient's perspective. PRO measures like the SF-12 assess general health and well-being or health-related quality of life (HRQOL), including the impact of illnesses on a broad range of functional domains. The SF-12 comprises a subset of 12 items from the SF-36 Health Survey that covers the same eight domains of health outcomes, including physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Whilst such scores provide an excellent means for judging the effectiveness of health care interventions, they have only a limited application in economic evaluation because they are not based on preferences. The SF-6D provides a means for using the SF-12 in economic evaluation by estimating a preference-based single index measure for health from these data using general population values. The SF-6D allows the analyst to obtain quality adjusted life years (QALYs) from the SF-12 for use in cost utility analysis.

17.8. WHO-5 Well-Being Index[20]

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

This is a validated, 5-question scale, utilized to assess general outlook and overall well-being. This scale also examines aspects other than just the absence of depressive symptoms.

17.9. CGM Satisfaction Survey[21] (CGM users)

CGM Group: Month 8 and Month 14

The CGM Satisfaction Survey is a validated tool which consists of 44 questions which assesses satisfaction regarding various aspects of CGM use.

17.10. Perceived Benefit Questionnaire

CGM Group: Month 8 and Month 14; SMBG Group: Pre-Month 8 & Pre-Month 14

This 2-question questionnaire queries the participant on any perceived benefit of the glucose monitoring device they are using.

17.11. Subjective Numeracy Scale[22]

All participants: Entry

A validated tool that subjectively measures (i.e., self-assessment) person's quantitative ability that distinguishes low- and high-numerate individuals. Four items measure people's beliefs about their skill in performing various mathematical operations, and 4 items measure people's preferences regarding the presentation of numerical information.

18. Data Collection and Management

Data collected during the study will be documented on electronic case report forms (e-CRFs). The Investigator or designee is responsible for completing the Case Report Forms (CRFs). The electronic data capture (EDC) system will be validated prior to study commencement. Sites will be trained on use of the EDC system by sponsor or designee. Good Documentation Practices principles will be required. Participants who fail the Run-In Phase will not undergo randomization and thus will be withdrawn from the study, with documentation provided on a termination CRF.

A database system, Part 11 compliant, will be created using Jaeb Center's custom built EDC system for data entry and verification of the data inputted by site personnel.

19. Statistical Considerations

Most of the details in the following section apply to both Phase 1 and Phase 2 but some sub-sections give separate details for each phase.

19.1. Statistical and Analytical Plans

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

19.2. Statistical Hypotheses

Phase 1:

- Null hypothesis: There is no difference in the mean change in Central lab measured HbA1c over 8 months between patients making CGM based decisions about their diabetes and patients making blood glucose monitoring based decisions

- Alternate hypothesis: Patients making CGM based decisions about their diabetes have a different mean change in Central lab measured HbA1c over patients making blood glucose monitoring based decisions

Phase 2:

- Null hypothesis: There is no difference in the mean change in CGM measured time in the target range (70-180 mg/dL) over 6 months between patients who continue making CGM based decisions about their diabetes (after the initial 8 months) and patients who switch from making CGM based decisions to making blood glucose monitoring based decisions
- Alternate hypothesis: Patients who switch from making CGM based decisions to making blood glucose monitoring based decisions about their diabetes have a different mean CGM measured time in the target range over patients who continue making CGM based decisions (after the initial 8 months)

19.3. Sample Size

Phase 1 is formally powered and the Phase 2 sample size is dependent on the number in the CGM group in Phase 1 who continue into Phase 2.

For Phase 1, the DIaMonD T2D RCT data were used to estimate the mean and standard deviation for HbA1c at baseline and 6 months. Data were taken from 121 participants with T2D who met the current protocol's eligibility criteria for HbA1c (8.0-11.5%). Based on an effective standard deviation of 0.80% (adjusting for baseline HbA1c as a covariate) and a true treatment effect of 0.4%, the total sample size was estimated to be 165 to have at least 85% power with alpha=0.05 and 2:1 randomization. However, in order to account for a 20% dropout rate, a total sample size of 207 was selected (138 for the CGM Group and 69 for the SMBG Group) with up to 300 enrolled into screening.

For Phase 2, the DIaMonD Phase 2 RCT data (which includes only T1D participants) were used to estimate the mean and standard deviation for the percent time in the target range (70-180 mg/dL) at 6 and 12 months. Data were taken from 38 participants in the CGM+MDI Group. Assuming 138 subjects were randomized to the current protocol's Phase 1 CGM Group and a 20% dropout rate, we expect at least 74 participants to enter and complete Phase 2. Based on an effective standard deviation at 12 months of 7% (adjusting for 6-month time in range as a covariate) and a treatment effect of 5%, there will be 85% power to detect a difference in the time in range between the Continue CGM and the Discontinue CGM groups, with alpha=0.05 and 1:1 randomization.

19.4. Study Endpoints

The primary and secondary endpoints for both phases are listed in Sections 7 and 8 and won't be repeated here. Other exploratory endpoints are listed in Section 9. Additional analysis details are listed within this section.

19.5. Description of Statistical Methods

19.5.1. General Approach

All covariates obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that a variable does not have a linear relationship with the outcome. In such a case, categorization and/or transformation will be explored. All p-values will be two-sided.

Details for CGM Metrics

All treatment group comparisons of CGM metrics will use the blinded CGM data collected for the SMBG Group participants and a similar time period of data for the CGM Group participants. Additional details will be given in the Statistical Analysis Plan.

19.5.2. Analysis Cohorts

- All randomized participants will be analyzed for the Intention-to-Treat (ITT) Analysis.
- Safety outcomes will be reported for all enrolled participants, irrespective of whether the study was completed.
- Per-protocol analyses will be conducted for Phase 1 and for Phase 2 separately. The details will be discussed in the Statistical Analysis Plan.

19.5.3. Analysis of the Primary Outcome

Phase 1:

Summary statistics for HbA1c (from Central lab) appropriate to the distribution will be calculated separately by treatment group. The method of direct likelihood will be used by fitting a longitudinal mixed effects linear regression model including HbA1c values measured at baseline, 3 months and 8 months. The model will include a term for treatment arm, but the two arms will be forced to have the same predicted value at baseline (due to randomization). Separate treatment effects will be estimated at 3 and 8 months (treatment by time interaction) and inference will focus on the estimate at 8 months, which is the primary outcome. A risk-adjusted point-estimate, 95% confidence interval and p-value will be reported for the treatment arm difference at 8 months. The model will adjust for clinical site as a random effect and include the local HbA1c as an auxiliary variable.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead.

The risk adjusted difference and 95% confidence interval will be reported based on the least squares mean from this model.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated as a sensitivity analysis by including factors potentially associated with HbA1c for which there is an imbalance between groups.

Missing HbA1c Data for Phase 1

It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. Our goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used. Different techniques (summarized below) will therefore be utilized to determine whether they reach similar conclusions:

- Primary Analysis: Missing HbA1c values will be handled using direct likelihood as described above
- Sensitivity Analyses: Analyses will also be conducted using the following methods to handle missing HbA1c values:
    - Rubin's multiple imputation
    - Available cases only

Phase 2:

Summary statistics for the time in target range appropriate to the distribution will be calculated separately by treatment group. A mixed effects linear regression model will be used to compare the change in time in target range among the two treatment groups. The model will adjust for baseline time in target range as a fixed effect and include random effects for clinical site.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead.

If values are approximately normal, then a risk adjusted difference and 95% confidence interval will be reported based on the least squares mean from this model.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in the primary analysis by including factors potentially associated with time in target range for which there is an imbalance between groups.

Missing CGM Data in Phase 2

There will be no minimum requirement of CGM data to be included in the CGM analyses so all participants with CGM data will be included in the analysis.

19.5.4. Analysis of the Secondary Endpoints

For continuous variables, summary statistics appropriate to the distribution will be calculated separately by treatment group. For discrete variables, number and % will be calculated separately by treatment group.

All the binary measures will be compared between treatment groups using a logistic regression model and all the continuous measures will be compared using a linear regression model. All models will adjust for the baseline value as a fixed effect and include random effects for clinical site. In addition to these factors, the model for body weight will also adjust for age and gender.

For the continuous outcomes, residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead. If the distribution is approximately normal then the adjusted mean difference and confidence interval will be reported.

For the binary outcomes, the risk adjusted difference in percentages and the confidence interval will be reported. The adjusted difference in percentages will be calculated as in Kleinman and Norton[1] and the confidence interval will be calculated using a bootstrap.

Missing Data for Secondary Outcomes
Only participants with outcome data at baseline and follow-up will be included in the analysis (i.e. available cases only). There will be no minimum requirement of CGM data to be included in the CGM analyses.

19.5.5. Safety Analyses

All adverse events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. In addition, the following outcomes will be analyzed when the number of events is sufficient for a meaningful analysis and the analysis methods are described below:

1. Number of events per person (SH and DKA, separately)
2. Percentage of participants with at least one event (SH and DKA, separately)
3. Kaplan-Meier incidence rate (SH and DKA, separately)
4. Incidence rate per 100 person-years (SH and DKA, separately)
5. Number of events (any event) per person thought by investigator to be related to study intervention

Outcome #1 above will be compared between treatment groups using ordered logistic regression adjusting for the baseline value (whether or not the participant had an event in the previous year) as a fixed effect and clinical site as a random effect. Outcome #3 will be compared between treatment groups using a logrank test. Outcome #4 will be compared between treatment groups using Poisson regression adjusting for the baseline value (whether or not the participant had an event in the previous year) as a fixed effect and clinical site as a random effect. If there are outliers, then robust Poisson regression will be used.

SH and DKA Incidence Rate Calculation: The incidence rate per 100 person-years will be calculated by dividing the number of events in follow-up (including any events after the last visit) by the number of follow-up years from randomization until the latter of the last visit and the last adverse event and multiplying by 100.

19.5.6. Other Tabulations

For both Phase 1 and Phase 2, the following analyses will also be done:

- Tabulate summary statistics for the CGM use frequency for each visit and overall (CGM Group)
- Tabulate summary statistics for the CGM Satisfaction Survey for the CGM Group
- Tabulate diabetes medication changes for the participants who switched, added, or dropped a diabetes medication
- Tabulate the number of clinic visits and calls by treatment group
- Tabulate the number of and reasons for unscheduled visits by treatment group

- Construct a flowchart accounting for all subjects according to treatment group for each visit
- Tabulate the number of protocol and procedural deviations by treatment group

19.5.7. Baseline Descriptive Statistics

For each phase, summary statistics appropriate to the distribution will be given for characteristics at randomization by treatment group.

19.5.8. Planned Interim Analysis

Re-estimation of the sample size for Phase 1 will be undertaken when approximately 75 participants have completed the Month 3 visit. The analysis will involve assessment of the Month 3 HbA1c (Central lab) variance from both treatment groups combined.

19.5.9. Subgroup Analyses

Subgroup analyses will be conducted to determine whether a similar trend to the overall treatment effect for the primary outcome is seen in these subgroups. The study is not expected to have sufficient statistical power for definitive conclusions in subgroups and statistical power will be low to formally assess for the presence of interaction. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment effect. In the absence of any significant treatment effects in the primary analysis, assessment of subgroups will be considered exploratory and used to suggest hypotheses for further investigation in future studies.

The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the linear model used for the primary analysis. For continuous factors, the interaction term will use the continuous version of the variable.

The planned subgroups defined by factors measured at baseline are listed below. These subgroups will be used in both Phase 1 and Phase 2:

- HbA1c
- Time in target range (70-180 mg/dL)
- Age
- Diabetes duration
- Education
- Use of GLP1 or SGLT2 medications

Note: subgroups above will only be analyzed if there are at least 10 participants in each treatment group for each subgroup.

19.5.10. Multiple Comparisons/Multiplicity

The primary analyses for both Phase 1 and Phase 2 involve a single treatment arm comparison for a single outcome measure so no correction for multiple comparisons will be performed.

For the secondary analyses and exploratory analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure. Details will be given in the formal SAP.

19.5.11. Exploratory Analyses

The endpoints listed in Section 9 are considered exploratory analyses. Additional endpoints may be given in the Statistical Analysis Plan.

20. Study Procedures

General instructions for each visit are provided to ensure consistency in conducting the study across multiple sites and include:

1. At each visit/contact study related procedures will be performed by a clinical coordinator and glucose data review and interpretation will be made by a study clinician with experience in reviewing and interpreting glucose data.
2. Additional visits – number of education and phone discussions related to CGM (by the research site) - will be tracked by the study staff.
3. Blinded CGM data should not be reviewed 1) by clinicians who are part of the investigator team, 2) with participants in the SMBG groups or 3) by the community treating clinician. An exception is the final study visit at Month 14.
4. Additional communication to the community treating clinician will be encouraged (e.g. as a follow-up to letters sent), such as phone calls messaging via electronic medical record.
5. If at any point during the study the community treating clinician believes referral to an endocrinologist is warranted, he/she will be encouraged to refer participant to an endocrinologist within their normal referral pattern. However, the PI or sub-investigators should be excluded from formal consultation and ongoing diabetes management during the study.

Table 1 (**Schedule of Events**) indicates study staff and participant requirements per visit. **Table 2** (**Questionnaire Details**) provides the schedule for administration of the various PROs and surveys during the study.

20.1. Study Entry & Run-In Visit:

At the time of enrollment, participants will undergo a run-in period of blinded CGM wear to assess continuance in the study and to collect baseline CGM data. The following procedures occur during the initial visit and run-in period:

1. Obtain Informed Consent
2. Assess for eligibility per Inclusion/Exclusion criteria
    i. Obtain screening labs (pregnancy, eGFR, POC/local HbA1c) **Note**: for eGFR may use historical, if obtained within 4 months of study entry
3. Obtain height and weight (BMI)
4. Collect demographics, socioeconomic and diabetes history
5. Collect diabetes medications
6. Schedule participants for one or two general diabetes education session(s) (individual or group) during the run-in, which will include a review or discussion of the following using developed, study-assigned teaching tools:
    i. Glucose targets (individualized) including fasting and pre-meal range and post meal
    ii. Basics of basal insulin titration
    iii. Basics of meal planning
    iv. Hypoglycemia management
    v. Importance of medication adherence

7. Assign blinded CGM to participant and train participant on use of the device in blinded mode.
8. Assign study BGM and provide testing supplies to participant and train participant on use of the device
9. Administer baseline PRO/surveys
10. Schedule return visit to assess for eligibility to enter Phase 1 of the study

20.2. Phase 1 (End of Run-in Period) -: T= 0

At the end of the run-in period, participants will be assessed for eligibility to proceed to randomization. Those willing to participate and meeting eligibility criteria will be randomized to either the CGM (CGM Group) or SMBG (SMBG Group).

1. Download CGM device to assess for CGM adherence: at least 70% usage (e.g. at least 7 days of CGM readings collected). **Note[1]:** In the event the participant was unable to collect a minimum of 7 days of CGM data *due to device issues, not compliance issues* (i.e., adhesive or sensor failures) they may have their sensor wear run-in period extended in order to collect the required number of days. This extension will be at the discretion of the investigator. **Note[2]:** CGM data will NOT be shared with participants, clinicians at the research site, or the treating community clinician.
2. Obtain baseline labs:
   i. Central lab HbA1c
   ii. POC/local HbA1c
   iii. C-peptide, fasting or non-fasting **Note:** For C-peptide, may use historical, if obtained within 6 months of study entry
   iv. Non-HDL cholesterol, derived from non-fasting Lipid Panel
3. Assess for any AEs.
4. Obtain randomization group assignment from coordinating center and perform the following, per group designation:

   SMBG Group
   - Instruct participant to continue use of study-provided blue-tooth enabled blood glucose meter with testing supplies
   - Establish a BGM account and link to the research site
   - Instruct participant to perform SMBG testing from 1- 3x daily. Testing should involve a minimum of once daily testing and includes some fasting and some post-prandial measurements

   CGM Group
   - Install the G6 CGM app on participant's smart phone
   - Establish a CLARITY mobile account and link to the research site
   - Instruct participants to use CGM non-adjunctively (i.e. for diabetes management without confirmatory SMBG testing)
   - Instruct participants to perform SMBG testing as with the study assigned blue-tooth enabled blood glucose meter, including testing supplies.
   - Set CGM threshold alerts at values that will minimize alerts. These should be tightened/ adjusted during the study as glucose control improves.
   - Enable CLARITY push notifications and document type

5. Review group-specific study provided Tips for Success sheet
6. Study Clinician: Send visit specific communication letter to the community treating clinician, informing them of the patient's participation and the role of the

study site. The letter informs the community clinician that the study site will identify glucose trends, provide lifestyle recommendations for the participant, provide guidance on self-titration of basal insulin, and provide considerations to optimize medications. A template will be provided. Document date letter sent.

7. Provide ample supplies for use until next visit
8. Schedule next visit

20.3. Phase 1-Week 2 Visit (both groups) (14 +/- 4 day window)

1. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
2. Assess for any AEs.
3. Study Clinician Discussion:
   i. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   ii. Review glucose targets.
   iii. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   iv. Review group-specific study provided Tips for Success sheet
   v. Send visit specific communication letter to the community treating clinician (copy to participant), together with the glucose data record and interpretation (CGM data for CGM Group and SMBG data for the SMBG Group) of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any medication changes should occur outside the study and be made by the community treating clinician, unless deemed clinically warranted by study clinician (e.g. for safety purposes such as frequent or problematic hypoglycemia.
   vi. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.
4. Provide ample supplies until next visit
5. Schedule next visit.

20.4. Phase 1-Month 1 Visit (both groups) (30 +/- 5 day window)

1. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
2. Assess for any AEs.
3. Study Clinician Discussion:
   i. If sufficient glucose data is available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   ii. Review glucose targets.
   iii. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   iv. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
   v. Review group-specific study provided Tips for Success sheet.
   vi. Send visit specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for

CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made ONLY by the community treating clinician, unless deemed clinically warranted by study clinician (e.g. for safety purposes such as severe hypoglycemia events).

vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.

4. Provide ample supplies until next visit
5. Schedule initial phone contact.

20.5. Phase 1-Phone/remote Contact- Month 2 (both groups) (60 +/- 5 day window)

1. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
2. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
3. Study Clinician Discussion:
   i. Use the study provided Guidance for Phone Contact & Documentation to guide these discussions.
   ii. If sufficient glucose data are available, encourage self-titration of basal. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   iii. Review glucose targets.
   iv. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   v. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
   vi. Send a contact specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note:** any therapy changes should occur outside the study and be made only by the community treating clinician, unless deemed clinically warranted by study clinician for safety purposes.
   vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.
4. Schedule next visit.

20.6. Phase 1-Month 3 Visit (both groups) (90 +/- 5 day window)

During this visit, glucose data will not be reviewed. Blinded CGM data is obtained for the purposes of documenting CGM metrics in the SMBG group

1. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).

2. Obtain labs
    i. Central lab HbA1c
    ii. POC/local HbA1c
3. Assess for any AEs.
4. Provide group-specific study provided Tips for Success (discussion of glucose targets not required).
5. Dispense blinded CGM devices to the SMBG Group for one blinded CGM wear period, with instructions for return of device to the clinical site. **Note:** A second sensor session may be warranted if device issues occur (i.e., adhesive or sensor failures), resulting in the session ending before Day 4 of wear.
6. Download returned CGM device from SMBG Group participants upon receipt of the returned system. Store the CGM system for next blinded use by the participant.
7. Obtain BGM data from both groups
8. Provide ample supplies until next visit
9. Schedule next phone contact.

20.7. Phase 1-Phone/remote Contact- Month 4 (both group) (120 +/- 5 day window)

1. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
2. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
3. Study Clinician Discussion:
    i. Use the study provided Guidance for Phone Contact & Documentation to guide these discussions.
    ii. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
    iii. Review glucose targets.
    iv. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
    v. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
    vi. Send a contact specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made by the community treating clinician, unless deemed clinically warranted by study clinician (e.g. for safety purposes.
    vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.
4. Schedule next phone contact.

20.8. Phase 1-Phone/remote Contact- Month 6 (both groups) (180 +/- 5 day window)

1. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
2. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
3. Study Clinician Discussion:
   i. Use the study provided Guidance for Phone Contact & Documentation to guide these discussions.
   ii. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   iii. Review glucose targets.
   iv. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   v. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
   vi. Send a contact specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made only by the community treating clinician, unless deemed clinically warranted by study clinician for safety purposes
   vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.
4. Schedule next visit.

20.9. Phase 1-Pre-Month 8 Visit (SMBG Group only) (230 +/- 3 day window)

This visit is scheduled approximately 10 days prior to Month 8 Visit.

1. Administer PRO/surveys prior to dispensing blinded CGM, to minimize confounding the responses in this study group. The participant may complete PRO/surveys 1 week prior to Pre-Month 8 visit.
2. Dispense blinded CGM devices for one blinded CGM wear period, with instructions for return of device to the clinical site. **Note:** A second sensor session may be warranted if *device issues* occur (i.e., adhesive or sensor failures), resulting in the session ending before Day 4 of wear.
3. Schedule next visit.

20.10. Phase 1-Month 8 Visit & Phase 2 Randomization (both groups) (240 +/- 5 day window)

This visit concludes Phase 1 and begins Phase 2. The visit includes collection of data for Phase 1 analysis and re-randomization of the CGM Group participants into Continue CGM or Discontinue CGM (use SMBG only) groups. Participants in the Phase 1 SMBG Group will continue to Phase 2 (Continue SMBG Group) without any group re-assignment.

1. Download returned CGM device from SMBG Group participants upon receipt of the returned system. Store the CGM system for next blinded use by the participant
2. Obtain BGM data from both groups
3. Assess for any AEs
4. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
5. Administer PRO/surveys to CGM Group. The participant may complete PRO/surveys 1 week prior to Month 8 visit.
6. Obtain labs
   i. Central lab HbA1c
   ii. POC/local HbA1c
   iii. Non-HDL cholesterol (non-fasting Lipid panel)
7. Obtain height and weight (BMI)
8. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
9. Re-randomize the CGM Group from Phase 1. Obtain randomization group assignment from study website and perform the following, per group designation:

   Discontinue CGM Group (use SMBG only)
   - A BGM account will be established and linked to the research site
   - Review study provided Tips for Success with SMBG sheet
   - Instruct participant to perform SMBG testing from 1- 3x daily with study provided meter. Testing should involve a minimum of once daily testing and includes some fasting and some post-prandial measurements

   Continue CGM Group
   - No changes from Phase 1. Participants will perform SMBG testing as needed

10. Study Clinician Discussion:
    i. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated. **Note:** The blinded CGM data obtained in the SMBG group will not be used by the research site staff and will not be reviewed with the participant or sent to the community treating clinician.
    ii. Review glucose targets.
    iii. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
    iv. Review group-specific study provided Tips for Success sheet
    v. Send a visit specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. Inform the community treating clinician of participant entering Phase 2 of the study. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made by only the community treating clinician, unless deemed clinically warranted by study clinician for safety purposes.

vi. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.

11. Provide ample supplies until next contact
12. Schedule next phone contact.

20.11. Phase 2-Phone/remote Contact- Month 11 (all 3 groups) (330 +/- 5 day window)

1. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
2. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
3. Study Clinician Discussion:
   i. Use the study provided Guidance for Phone Contact & Documentation to guide these discussions.
   ii. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   iii. Review glucose targets.
   iv. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   v. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
   vi. Send a contact specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made only by the community treating clinician, unless deemed clinically warranted by study clinician for safety purposes.
   vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.
4. Schedule next visit.

20.12. Phase 2-Pre-Month 14 Visit (Discontinue CGM and SMBG Groups only) (410 +/- 3 day window

This visit is scheduled approximately 10 days prior to Month 14 Visit.

1. Administer PRO/surveys prior to dispensing blinded CGM, to minimize confounding the responses in this study group. The participant may complete PRO/surveys 1 week prior to Pre-Month 14 visit.
2. Dispense blinded CGM devices for one blinded CGM wear period, with instructions for return of device to the clinical site. **Note:** A second sensor session may be warranted if device issues occur (i.e., adhesive or sensor failures), resulting in the session ending before Day 14 of wear.
3. Provide ample supplies until next visit
4. Schedule next visit.

20.13. Phase 2-Month 14 Visit & (all groups) (420 +/- 5 day window)

This visit concludes Phase 2 and participation in the study.

1. Download returned CGM device from both SMBG group participants upon receipt of the returned system.
2. Obtain BGM data from both groups
3. Assess for any AEs
4. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
5. Administer PRO/surveys to Continued CGM Group. The participant may complete PRO/surveys 1 week prior to Month 14 visit.
6. Obtain labs
   i. Central lab HbA1c
   ii. POC/local HbA1c
   iii. Non-HDL cholesterol (non-fasting Lipid panel)
7. Obtain height and weight (BMI)
8. Study Clinician Discussion:
   i. Review blinded CGM data with participants in the SMBG groups and CGM data with the CGM Group.
   ii. Document the number of followers on CRF.
9. Participants may be offered their CGM systems with a month's supply of sensors. Document the number of participants who accept or decline on CRF.

Table 1. Schedule of Study Event

		Start of Run In period	Randomization	PHASE 1								PHASE 2		
STUDY DAY NUMBER -->		minus 10	0	14	30	60	90	120	180	230	240	330	410	420
Permitted Visit Windows -->		--	--	±4	± 5	± 5	± 5	± 5	± 5	± 3	± 5	± 5	± 3	± 5
	Line Item	Enrollment and Start of Run In period	End of Run-in and Day 0 Clinic Visit (Randomize)	Wk 2 Clinic Visit	M1 Clinic Visit	M2 Phone Contact	M3 Clinic Visit; *Plus 10 day Blinded Wear at M3 Visit for SMBG Group*	M4 Phone Contact	M6 Phone Contact	SMBG GRP: *Pre-Mon 8 Blinded Wear (10 days before M8 visit)*	M8 Clinic Visit (Randomize)	M11 Phone Contact	SMBG GRP: *Pre-Mon 14 Blinded Wear (10 days before M14 visit)*	M14 Final Clinic Visit
ALL SUBJECTS														
1	(1) Informed Consent, (2) Eligibility Criteria, (3) Demographics, (4) Payer, (5) Pregnancy test, (6) Socioeconomic, (7) Vital Signs, (8) Diabetes Education Session(s)	●												
2	Collect diabetes history	●	●	●	●	●	●	●	●		●	●		●
3	Height/Weight Assessment	●									●			●
4	Labs (1) POC/local A1C	●	●				●				●			●
5	Labs (2) Central Lab HbA1c		●				●				●			●
6	Labs (3) eGFR (acceptable if w/in 4 mon)	●												
7	Labs (4) Non HDL Chol		●								●			●
8	Labs (5) C-peptide (acceptable if w/in 6 mon)		●											
9	Blinded CGM Wear & Training	●												
10	Dispense Blue-tooth BGM/Install software	●												
11	Confirm completion of PROs/Surveys	●								●	●		●	●
12	Communication letter to treating community physician		●	●	●	●		●	●		●	●		●
13	Document therapy changes					●		●	●		●	●		●
14	Download BGM device						●				●			●
15	Return CGM system		●								●			
16	AE/Device Assessment		●	●	●		●				●			●
17	Device troubleshooting			●	●	●	●	●	●	●	●	●		
18	Ensure upload/review of glucose data/goals			●	●	●		●	●		●	●		●
19	CGM and BGM Tips for Success			●	●		●				●			
CGM GROUP SUBJECTS														
20	CLINIC VISITS/CONTACTS		●	●	●	●	●	●	●		●	●		●
21	(1) Dispense unblinded CGM device (2) Install/Set-up device APP on participant smart phone		●								●			
22	Encourage CGM users to share CGM data with followers & document number of followers		●	●	●	●		●	●		●	●		●
SMBG GROUP SUBJECTS														
23	CLINIC VISITS/CONTACTS		●	●	●	●	●	●	●	●	●	●	●	●
24	Dispense blinded CGM supplies						●			●			●	

Table 2. Questionnaire Details

CGM GROUP: Quality of Life and Other Surveys (between group differences)		**Screening**	**Phase 1**		**Phase 2**	
		Screening Visit 1 (Start Run-in)	Pre Month 8 (10 days before Month 8 visit) Blinded wear period	**Month 8 Clinic Visit**	Pre Month 14 (10 days before Month 14 visit) Blinded wear period	**Month 14 Clinic Visit**
1	Diabetes Distress Scale (DDS)	●		●		●
2	Glucose Monitoring Satisfaction Survey, (GMSS) - Type 2 Version	●		●		●
3	Hill-Bone Medication Adherence Scale	●		●		●
4	Clinician Communication Rating	●		●		●
5	Toobert's scale – SDSCA Diet and Exercise	●		●		●
6	Fear of Hypoglycemia, Worry & Behavior Subscales	●		●		●
7	SF-12 Health Survey	●		●		●
8	WHO-5 Well-Being Index	●		●		●
9	CGM Satisfaction Survey			●		●
10	Perceived Benefit Questionnaire			●		●
11	Subjective Numeracy Scale (SNS)	●				

SMBG GROUP: Quality of Life and Other Surveys (between group differences)		**Screening**	**Phase 1**		**Phase 2**	
		Screening Visit 1 (Start Run-in)	Pre Month 8 (10 days before Month 8 visit) Blinded wear period	**Month 8 Clinic Visit**	Pre Month 14 (10 days before Month 14 visit) Blinded wear period	**Month 14 Clinic Visit**
1	Diabetes Distress Scale (DDS)	●	●		●	
2	Glucose Monitoring Satisfaction Survey, (GMSS) - Type 2 Version	●	●		●	
3	Hill-Bone Medication Adherence Scale	●	●		●	
4	Clinician Communication Rating	●	●		●	
5	Toobert's scale – SDSCA Diet and Exercise	●	●		●	
6	Fear of Hypoglycemia, Worry & Behavior Subscales	●	●		●	
7	SF-12 Health Survey	●	●		●	
8	WHO-5 Well-Being Index	●	●		●	
9	CGM Satisfaction Survey					
10	Perceived Benefit Questionnaire		●		●	
11	Subjective Numeracy Scale (SNS)	●				

21. Risks & Mitigation

21.1. CGM

The instructions for use includes the following use information to minimize risk to the user:

- Interpretation of the Dexcom CGM system results should be based on the glucose trends and several sequential readings over time. The Dexcom CGM device also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments.
- Failure to use the Dexcom CGM systems and its components according to the instructions for use and all indications, contraindications, warnings, precautions, and cautions may result in missing a severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) occurrence and/or making a treatment decision that may result in injury.
- Do not ignore symptoms of low or high glucose. If glucose alerts and readings do not match symptoms or expectations, a SMBG value should be obtained from a blood glucose meter to make diabetes treatment decisions or seek immediate medical attention.

Insertion of the sensors into the skin may result in pain, erythema, and/or edema at the insertion sites. Infection, excessive bleeding, or hematoma are also possible side effects of device use; however, the expected frequency of these events is low based on data obtained from similar devices and adverse event information from more than five previous Dexcom studies where the device was inserted from 12 hours to 15 days.

After removal of the sensors, participants may experience irritation due to the medical adhesive used to apply the sensor pod and any bandages that may be placed over the device. This reaction is self-limiting and should resolve within hours and not more than a week post-removal. Participants may experience some itching in the area during the healing process, which is normal.

Rarely, participants may develop an allergic reaction to one or more of the components of the sensor and/or transmitter. This is similar to allergies that can occur due to contact with medical tape.

Sensors may fracture or be retained in situ on rare occasions. In these rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation. In the event that signs and/or symptoms of infection or inflammation arise such as redness, swelling, and pain participants should consult with the investigator or prescribing physician for the best course of action. If there is no portion of the broken sensor wire fragment or retained sensor wire visible above the skin, attempts to remove it without medical guidance are not advised.

21.2. Hypoglycemia/Hyperglycemia

Treatment of diabetes is associated with increased risk of hypoglycemia. Hypoglycemia may be associated with reduced cognitive function, diaphoresis, tachycardia, coma, and seizure. These complications are an inherent risk of having diabetes. Participants will be trained on proper use of the device, which include the instructions listed above.

During the study instances of hypoglycemia will be captured as an AE, together with a severity rating, if requiring home treatment, assistance of a third party for treatment or involves seizure or loss of consciousness. Instances of severe hypoglycemia are anticipated to be low, due to the patient population in the study, that is, persons that are not intensively treated with insulin. However, any hypoglycemic event involving seizure or loss of consciousness will be captured as severe and potentially as a serious adverse event if it meets the definition of a SAE as defined in the protocol.

Instances of symptomatic hyperglycemia that are outside a confirmed diagnosis of diabetic ketoacidosis (DKA) will be captured as an AE if emergency evaluation or treatment is obtained from a health care provider.

Instances of severe hypoglycemia and DKA are anticipated to be low, due to the patient population in the study, that is, persons that are not intensively treated with insulin. Diabetic ketoacidosis is a serious complication of diabetes that occurs when the liver produces high levels of ketones, which are an acid. Diabetic ketoacidosis develops when there is insulin deficiency; in response, the body switches to burning fatty acids and producing acidic ketone bodies that cause most of the symptoms and complications. Vomiting, dehydration, tachypnea, confusion and occasionally coma are symptoms. DKA will be captured as a serious adverse event if confirmed, treated and meets definition of an SAE.

22. Adverse Events

For the purpose of this protocol, AEs will be captured on the AE CRF form if causality is related to the study, disease or device.

At all study visits, study staff will determine if any device, disease or study-related adverse events (AEs) have occurred. Disease related events that are *chronic in nature and occur as part of the progression of the diabetes disease state* (i.e. diagnoses of retinopathy, nephropathy, and neuropathy) *will not* be captured as adverse events in this study. Instances of hypo- or hyperglycemia will be captured as AEs if event meets details, as stated in Section 21.2.

All study, disease or device-related AEs will be monitored until adequately resolved or stable.

22.1. Adverse Events (AE)

Any clinically significant undesirable experience (sign, symptom, illness, or other medical event) meeting the causality definition above that appears or worsens in a participant during a clinical study. A clinically significant event is any event (sign, symptom, lab/imaging abnormality, or diagnosis) that is noteworthy enough to merit documentation in standard medical records (e.g. history and physical, progress notes, clinic visit notes, etc.). Other non-clinically significant events (e.g. colds, minor headaches, etc.) *may* be documented on the comments CRF.

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

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

22.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening; (substantial risk of dying at the time of the adverse event or suspicion that continued use of the device would result in a participant's death
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Requires medical or surgical intervention to prevent permanent impairment or damage

Any SAE, including death, due to any cause (related or unrelated to the device), that may occur during a clinical study must be reported immediately (within 1 working day of learning of the event). Details of the SAE submitted via eCRF will result in an automatic email generated and forwarded to the Sponsor. The Sponsor contact for SAE review:

Dexcom Clinical Affairs personnel will document SAE details and assessment by Clinical Affairs management in a timely manner.

22.3. Severity of Adverse Events

The following definitions may be used to rate severity of AEs:

Mild

Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.

Example: hypoglycemia with at home treatment.

Moderate

Discomfort severe enough to cause interference with usual activities, requiring treatment but not requiring urgent care or hospitalization.

Example: hypoglycemia, requiring third party assistance for treatment.

Severe

Incapacitating, causing inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical evaluation and/or treatment at a health care facility

Example: hypoglycemia with loss of consciousness or seizure involvement

22.4. Relationship of Adverse Event to Study, Disease or Device

The investigator will categorize the relationship of the event to the study, disease, or study device as follows:

Not related

AE is due to an underlying disease state or concomitant medication or therapy not related to the device, disease or study.

Probably Not Related

AE has minimum or no temporal relationship to the study device, disease or study participation and/or a more likely alternative etiology exists.

Possibly Related

AE has a strong temporal relationship to the study device, disease or study procedures and alternative etiology is equally or less likely compared to the potential relationship to the device, disease or study.

Probably Related

AE has a strong temporal relationship to the study device, disease or study and another etiology is unlikely.

Related

AE has a strong temporal relationship to the study device, study procedures or disease and another etiology does not exist.

22.5. Anticipated Device-related Adverse Events

The following events have been identified as possible device-related adverse events of **sensor insertion and wear**:

- Excessive pain or discomfort from either system deployment or during wear period (8 or greater on a 10-point Likert scale)
- Excessive bleeding, defined as requires removal of the device to stop bleeding
- Hematoma (ecchymosis is a known consequence of needle skin puncture or pressure from sensor pod and will not be captured as an AE)
- Edema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Erythema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Local infection, defined as presence of pus at either sensor wire or sensor pod site
- Sensor or introducer needle fracture during insertion/wear/removal

Information regarding device-related AEs that occur during the study will be entered into appropriate CRFs. Such information will include, at a minimum:

- Date of event
- Severity
- Outcome
- Resolution of event

22.6. Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is not expected to occur. An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, the informed consent document, other study-related documents), or any other

unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of participants.

During the review of a reported SAE, if Clinical Affairs management with the Investigator input determines the severity or extent of the event was not cited in this protocol or associated protocol materials, and the event was classified as, 'possibly related' to the device, the event will be documented as an UADE. If the event is classified as an UADE, the Investigator must notify the IRB and Dexcom will notify the FDA within ten (10) working days of the original SAE notification.

If determined that the UADE presents an unreasonable risk to participants, Dexcom will terminate all investigations or parts of investigations presenting that risk as soon as possible, but not later than 5 working days after such determination is made and not later than 15 working days after Dexcom first receives notice of the original SAE. Dexcom will not resume a terminated study without IRB and FDA approval.

22.7. Device Issues & MDR Reportable Events/MDR Reporting

A device issue, whether related to a complaint or not, is an allegation from the participant or study personnel regarding an indication of the failure of a device to meet user expectations for quality or performance specifications. Device issues will be recorded onto appropriate CRFs by site personnel. Dexcom personnel will process device issues, regardless of any associated adverse event details, per Dexcom's Complaint Handling procedures for any Dexcom FDA approved devices used in the study. For purposes of this protocol, the CGM devices are currently marketed. Therefore, the sponsor will follow the required reporting regulations if a MDR reportable event occurs, according to Sponsor SOP and FDA guidelines. (US MDR Reporting; Code of Federal Regulations Title 21 Part 803) and Dexcom Quality Assurance procedures related to complaint handling.

MDR reportable events are events that manufacturers become aware of that reasonably suggest one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device would likely cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.3).

23. Ethical Considerations

23.1. Informed Consent

Informed consent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50. Participants will be asked to sign state specific forms, such as Subject's Bill of Rights, or equivalent, (if applicable) and HIPAA authorization form, if not included in the site's consent template. Participants will be provided the opportunity to review these documents prior to coming to the clinical site. The Investigator or designee will explain the purpose and duration of the study, the study procedures and participant requirements, and the potential risks and benefits. Study staff will attempt to answer all questions the participant may have. Consenting process will be documented in the participant's source documents. A copy of the consent will be provided to the participant.

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the 1983 amendment per FDA's Guidance for Industry: Acceptance of Foreign Clinical Studies written in March, 2001.

Participants will receive a stipend for being in the study and offered the study-assigned meter following completion of their participation in the study.

23.2. Institutional Review Board

The protocol, informed consent document, and participant training materials for this study will be reviewed and approved by a duly constituted Institutional Review Board (IRB) before participants are screened.

The Investigator will ensure that all aspects of the IRB review are conducted in accordance with current institutional, local, and national regulations. An IRB approval letter will be provided to the Sponsor prior to study initiation. Protocol amendments must adhere to the same requirements as the original protocol. The Investigator will submit all IRB-required reports and updates, including any continuing review and/or final closeout reports. The Investigator will inform the IRB of any reportable AEs as per the IRB reporting rules.

24. Device Accountability

The Investigator(s) will store devices in a secure location at the clinical site. An accurate and current accounting of the dispensing for the Dexcom and other device components will be maintained by a member of the study site staff on the "Device Accountability Log". All used and unused devices must be returned to the Dexcom Clinical Affairs department (or accounted for if lost) upon completion of enrollment or upon request of the Sponsor.

25. Monitoring

Monitoring will be conducted by trained and experienced Clinical Research Associates (CRAs) in accordance with Dexcom's standard operating procedures. CRAs will evaluate study conduct and documentation on an ongoing basis. Assessment of site performance will be reviewed with Clinical Affairs management to determine the level of monitoring required. All informed consent documents will be source verified along with key data fields related to safety and performance indicators. All CRF data will be collected via the EDC system designated for the study for analysis. A risk-based monitoring plan will be developed consistent with the Food and Drug Administration (FDA) Guidance for Industry: Oversight of Clinical Investigations—A Risk-based Approach to Monitoring (August 2013). This approach focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study. Monitoring is separated into Central (remote) monitoring and On-Site monitoring (site visits). Considerable focus is placed on real-time centralized monitoring methods.

26. Study Termination

Participation in the clinical study will be terminated for each participant following the last visit or when all AEs have been resolved or considered ongoing but stable. Prior to this time, participants may voluntarily withdraw at any point in the study or the Investigator and/or Sponsor may determine that it is in the best interest of the participant to be terminated from the study. Reasons for withdrawal of participant from the study include, but are not limited, to the following:

a) In the opinion of the Investigator, the participant's health or safety would be compromised by continuing in the study
b) In the opinion of the Investigator, it is in the participant's best interest to discontinue participation in the study
c) During the study, (female) participant becomes pregnant

However, discontinuation of the study intervention (CGM) does not equate with discontinuation from the study and every effort will be made to retain participants in the study for the primary outcome assessment, even if CGM is discontinued.

The clinical study in its entirety will be considered complete upon receipt of reports from study monitoring activities, completion of site closeout visits, and issuance of a clinical study report. The clinical study report will include all safety and efficacy data.

27. Investigator Responsibilities

The Investigator's signature(s) on this protocol confirms that the Investigator is familiar with all sections of the protocol and agrees to conduct this study in accordance with the provisions of the protocol and applicable regulations. The Investigator(s) must sign this protocol prior to commencement of any study-related activities (e.g. screening).

The Investigator(s) are responsible for protecting the rights, safety, and welfare of participants under their care. The Investigator(s) are also responsible for obtaining IRB approval prior to study start and the written informed consent of each participant before participation in this study. The informed consent must comply with FDA regulations (21 CFR 50) and be approved by the IRB.

The Investigator(s) are responsible for ensuring completion of the CRFs per the study timelines discussed in the site initiation visit and subsequent monitoring visits.

Dexcom and/or the IRB retain the right to disqualify an Investigational Site and remove all study materials at any time. Specific instances, which may precipitate clinical site disqualification, include but are not limited to:

a) Unsatisfactory participant enrollment with regard to quality and quantity.
b) Persistent non-compliance related to protocol procedures by the Investigator/Investigational Center.
c) Inaccurate, incomplete, and/or untimely data recording on a recurrent basis.
d) The incidence and/or severity of adverse experiences in this or other studies indicating inadequate oversight
e) Unsatisfactory accountability of study devices.

28. Sponsor Responsibilities

The Sponsor is responsible for selecting qualified Investigators and providing them with the information needed to properly conduct the study. The Sponsor will ensure proper monitoring of the study and that IRB approval has been obtained prior to the Investigator commencing study-related activities. The Sponsor is also responsible for ensuring that the reviewing IRB(s) and FDA, if applicable, are promptly informed of significant new information.

29. Confidentiality of Records

All records and documents pertaining to this study will be retained for a period of no less than 2 years by Dexcom, Inc. and will be available for inspection by FDA or other regulatory agencies at any time. All records containing personal identification or information that identifies a study participant will be handled confidentially within the law.

These records will be coded and kept in locked files. No individual identities will be used in any reports or publications resulting from this study.

Neither the site nor participants will disclose, share, or use any information gathered during the course of the clinical study. All information about the study, including the study product and study procedures, is confidential. Any publication about the products or the study by print or electronic format (e.g. blogging) is strictly prohibited.

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MOBILE PROTOCOL VERSION 5

Dexcom®

MOBILE

PROTOCOL

Continuous Glucose MOnitoring in T2D Basal InsuLin UsErs: The MOBILE Study

Protocol Number: PTL-902822

Study Sponsor: **Dexcom, Inc.**

Study Contact:

Version Date: December 03, 2018

Version Number: 005

TABLE OF CONTENTS

1. Abbreviations and Definitions

AE	Adverse Event
BGM	Blood Glucose Meter
Blinded CGM	Receiver acts as a data collection tool and does not display CGM values, trends, or glucose alerts/alarms in real time. Receiver provides use prompts and features such as device failures, troubleshooting icons, event markers, etc.
CGM	Continuous Glucose Monitoring
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed Tomography
DCCT	Diabetes Control & Complications Trial
DKA	Diabetic Ketoacidosis (as defined by the DCCT) involves all of the following symptoms such as polyuria, polydipsia, nausea, or vomiting; serum ketones >1.5 mmol/L or large/moderate urine ketones; either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and treatment provided in a health care facility.
DM	Diabetes Mellitus
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate: a renal function test determined by a blood test for creatinine
GLP-1 agonist	Glucagon-like peptide-1 receptor agonists or incretin mimetics- A class of diabetes drugs used for the treatment of type 2 diabetes
HbA1c	Hemoglobin A1C. The hemoglobin A1C test provides the average level of blood glucose over the past 2 to 3 months. Also called glycated hemoglobin test, and Glycohemoglobin.
HCP	Health Care Professional
Hypoglycemia, Severe	**SH.** Results in seizure or loss of consciousness
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent to treat (analysis)
MDR	Medical Device Reporting
mg/dL	milligrams per deciliter
MRI	Magnetic Resonance Imaging
OAD	Oral Anti-Diabetic medications
PC	Personal computer, specifically using Intel hardware & Microsoft software; not Apple computers

Personal RT-CGM	Personal RT-CGM refers to frequent and continued use of CGM, owned by the user.
POC	Point of Care (Approved Guideline)
PP	Per Protocol (analysis)
PRO	Patient Reported Outcome
QoL	Quality of Life
RCT	Randomized Controlled Trial
RT-CGM	Real-Time Continuous Glucose Monitoring System
SAE	Serious Adverse Event
SGLT-2 inhibitors	Sodium-glucose transport protein 2 inhibitor used for the treatment of type 2 diabetes. They inhibit reabsorption of glucose in the kidneys and therefore lower blood glucose.
SMBG	**S**elf-Monitored Blood Glucose. Testing done with a glucose meter and capillary blood sample, typically from the person's fingertips.
SMBG Group	Uses a study-provided blood glucose meter to inform diabetes management decisions
SC	Study Coordinator
Study Clinician	Physician, Nurse Practitioner, Advanced Practice Nurse, Physician's Assistant, or Diabetes Educator, experienced in reviewing glucose data and making lifestyle recommendations or medication adjustments
T2D	Type 2 Diabetes Mellitus
UADE	Unanticipated Adverse Device Effect

2. Investigator Signature Sheet

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the study.

I will provide details of the protocol to all members of the study team responsible for conducting the study.

I will discuss the protocol with them to ensure that all participating staff members are fully informed regarding the study device and the conduct of the protocol.

Once the Institutional Review Board approves the protocol, I will not modify study procedures without obtaining prior approval of the Sponsor and, if required, of the Institutional Review Board (and FDA, as applicable).

I will submit any protocol and/or any informed consent modifications to the Sponsor and the Institutional Review Board (and FDA, as applicable) and approval will be obtained before any modifications are implemented.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

3. Protocol Synopsis

Title	Continuous Glucose **MO**nitoring in T2D **B**asal **I**nsu**L**in Us**E**rs: The MOBILE Study
Sponsor & Coordinating Center	Dexcom, Inc. and Jaeb Center for Health Research (JCHR)
Study Objectives	⇒ **Phase 1** **Primary:** Assess the benefit on glycemic control, using real time continuous glucose (RT-CGM) versus SMBG, in persons with Type 2 Diabetes (T2D) taking basal insulin with or without oral medications and/or GLP-1 analogue, not at their HbA1c goal. **Secondary:** • Assess quality of life (QoL) benefits of RT-CGM in basal insulin users • Assess frequency of hypoglycemia as determined by CGM ⇒ **Phase 2** **Primary:** Determine if glycemic control worsens upon withdrawal of RT-CGM **Secondary:** • Determine if glycemic benefits are sustainable for a longer period of time (14 months) • Assess QoL benefits of continuing or discontinuing RT-CGM • Assess frequency of hypoglycemia as determined by CGM
Study Design	Prospective, randomized, 2 phase parallel arm
Hypotheses	⇒ **Phase 1** In persons with T2D taking basal insulin (with or without oral medications and/or GLP-1 analogue) that are in poor control, CGM based decisions by the patients and their primary care physicians under advice from diabetes specialists, will result in better glycemic outcomes than blood glucose monitoring based decisions. ⇒ **Phase 2** Patients who discontinue RT-CGM will have a different time in target range (70-180 mg/dl) compared with patients who continue RT-CGM.

Study Devices:	Dexcom G6 CGM system, used in real time or blinded mode; a blue-tooth enabled blood glucose meter; CLARITY Data-management software; data management software compatible with the BG meter
Study Endpoints	⇒ **Phase 1 – Between group differences from baseline to Month 8, unless otherwise specified** **Primary Endpoint:** Change in HbA1c (Central lab) **Secondary & Other Endpoints** Numerous endpoints will be assessed for change between study groups. Endpoints include but are not limited to the following: • HbA1c metrics • CGM metrics • Diabetes medications • Non-HDL cholesterol • SMBG frequency • Patient Reported Outcomes (PRO)/surveys ⇒ **Phase 2 –** • **Between group differences for the Phase 1 CGM Group re-randomized to Discontinue CGM (use SMBG only) and Continue CGM from Month 8 to Month 14** • **Between group differences for the Continue CGM and the Continue SMBG groups from baseline to Month 14** **Primary Endpoint:** Change in CGM time in target range (70-180 mg/dL) for the Discontinue CGM and Continue CGM Groups (Month 8-14) **Secondary & Other Endpoints** Numerous endpoints will be assessed for change between study groups. Endpoints include but are not limited to the following: • CGM metrics • Diabetes medications • HbA1c metrics • Non-HDL cholesterol • SMBG frequency • PRO/surveys
Sample Size	Each study phase will be independently powered. ⇒ **Phase 1:** N=207 • For Phase 1, a 2:1 randomization scheme will be utilized- CGM: SMBG. A sample size of 165 participants is required to detect a difference in HbA1c with 85% power if the true difference between groups is 0.4%.

	Assuming a drop-out rate of 20%, up to 207 participants may be randomized into the study and up to 300 may be enrolled into screening. ⇒ **Phase 2:** N= approximately 74 • For Phase 2, a 1:1 randomization scheme will be utilized to re-randomize the Phase 1 CGM Group- Continue CGM: Discontinue CGM. All participants in the SMBG group from Phase 1 will continue in the study without re-randomization. The goal is for up to 92 participants from the Phase 1 CGM Group to enter Phase 2 (with approximately 74 completing Phase 2) to evaluate between group differences for time in range (70-180 mg/dL). There will be 85% power to detect a difference in time in range (70-180 mg/dL) if the true difference between groups is 5% and 74 participants complete Phase 2.
Study Sites	Up to 30 sites from across North America Target multi-specialty clinics/systems or endocrinology centers with a large referral base that possess research capabilities and have clinicians in the research site experienced in interpreting CGM and SMBG data. Clinical research sites with on-site access to diabetes experts will also be considered to participate in the study.
Study Population	Adult T2D patients followed by a primary care physician for their diabetes, who are currently on basal insulin therapy with or without oral anti-diabetic therapy and/or GLP-1 analogue injections, sub-optimally controlled.
Inclusion Criteria	• Age at least 30 years • Type 2 diabetes by clinical history • Comprehends written and spoken English • Using 1-2 injections of basal or intermediate acting insulin daily • HbA1c between 7.8-11.5% inclusive at enrollment (by POC or local lab) • Assessment by clinician that patient is thought to be able and willing to wear a CGM device • Naïve to RT-CGM (No personal RT-CGM use within 3 months of study entry; may have used professional CGM or intermittent scanned (Flash) continuous glucose monitoring) • Has been self-monitoring on average at least 3 times per week (self-reported) during the prior month to entry • Stable medication regimen (medication classes) during the 3 months prior to entry • On basal insulin for ≥ 6 months prior to entry • Has a smart phone compatible with CGM and BGM systems and is willing to utilize a study issued blood glucose meter • Has their diabetes managed by a primary care physician or nurse practitioner/ physician assistant

Exclusion Criteria	• Regular use of short acting insulin in the 3 months prior to study entry or planning to initiate prandial or short acting insulin. • Pregnancy (as demonstrated by a positive test at study entry) at time of screening or are planning to become pregnant during the study. • Planned or currently using weight reduction medications, programs or surgery. Defined as 1) using weight loss medications and losing weight (e.g. chronic use of weight loss medications with stable weight is not exclusionary) or planning on using weight loss prescription medication during the study; 2) currently using or planning on initiating a modified fasting program (e.g. protein-sparing diet plans) during the study; or 3) bariatric surgical procedure within the past year or plans for undergoing bariatric surgery during the study. **Note:** participation in non-physician directed plans such as Weight Watchers or Jenny Craig program are not exclusionary. • Concomitant disease or condition that may compromise patient safety including but not limited to severe mental illness, a diagnosed or suspected eating disorder or any uncontrolled long-term medical/ psychiatric condition that would interfere with study related tasks or visits. These assessments/conditions are made at investigator's discretion. • Known (or suspected) significant allergy to medical grade adhesives • Renal disease defined as estimated Glomerular Filtration Rate eGFR <30. **Note:** may use historical value, if obtained within 4 months of entry visit • Anticipated acute uses of glucocorticoids (oral, injectable, or IV), that will affect glycemic control and impact HbA1c • Acute conditions that impact the stability of a HbA1c measurement such as GI blood loss, recent (within 3 months of study entry), anticipated red blood cell transfusion or erythropoietin administration • Followed for their diabetes management by a study PI or sub-investigator • Diabetes (glucose) management in the 6 months prior to study entry under the guidance of a diabetes specialist • Participation in another pharmaceutical or device trial at the time of enrollment or during the study
Study Overview	Investigators' role (and the investigator's clinical team/ study clinician) in the study is largely advisory in nature, such that they will provide insights and interpretation of the glucose data obtained from the BGM or CGM devices and formally communicate medication recommendations to the participant and their treating community clinician. The study clinician may provide the participant recommendations on lifestyle and self-titration modifications. Targeted participants will be recruited from outside the investigator team's diabetes and endocrine practice. Clinical research sites with on-site access to diabetes experts will also be considered to participate in the study. **Run-In Period:**

	At the time of enrollment, participants will undergo a run-in period of blinded CGM to assess continuance in the study and to collect baseline CGM data. They will also receive and be trained on a study-assigned BG meter and supplies to be used in the run-in period. Baseline PRO tools and surveys will be administered at time of enrollment. Screening labs will be drawn and assessed for participant's study eligibility. Participants will wear blinded CGM for one sensor session (10 days). Criteria for participants to continue with randomization are 1) willingness and ability to use the CGM device, and 2) CGM adherence, defined as at least 70% usage (i.e. at least 7 days of CGM readings). The CGM data will NOT be shared with participants, clinicians at the research site, or the treating community clinician. Participants will all undergo or be referred for one or two general diabetes education session(s) (individual or group) during the run-in period, per site's usual diabetes educational program. The sessions will be documented and include review or discussion of the following: o Glucose targets (individualized) including fasting and pre-meal range and post meal o Basics of basal insulin titration o Basics of meal planning o Hypoglycemia management o Importance of medication adherence **Phase 1:** Those willing to participate and meeting eligibility criteria will be randomized 2:1 to either CGM (CGM Group) or SMBG (SMBG Group). Baseline labs will be drawn. Phase 1 is of 8 months duration. For the CGM Group, it comprises 4 scheduled clinic visits: at week 2, month 1, month 3 and month 8. For the SMBG Group, it comprises 5 scheduled clinic visits: at week 2, month 1, month 3, pre-month 8 (~ 10 days prior to Month 8 visit) and month 8. There will be phone/ remote visits at months 2, 4 and 6 in both groups. HbA1c will be measured by Central lab and POC/local lab at baseline, 3 months and 8 months. Visits and phone contacts involve assessment of glucose data for clinical decision making, with documented formal advice to the treating community clinician and participant. Participants in the SMBG Group will undergo periodic blinded CGM use (Month 3 and 8) to allow for a comparison of CGM metrics. During phone contacts and at the Month 8 clinic visit, self-reported therapy changes will be documented (medications and visits to primary care physician). **Phase 2:** Consists of 3 groups: 1) participants continuing use of SMBG since the beginning of Phase 1; 2) participants re-randomized from the Phase 1 CGM Group and assigned to SMBG; 3) participants re-randomized from Phase 1 CGM Group and assigned to CGM. This phase involves 1 phone contact and either 2 visits at Month 14 for SMBG participants to wear blinded CGM or one visit for CGM participants. For all participants, study participation will end upon completion of Month 14 visit.

	Additional details: • At each visit/contact study related procedures will be performed by a clinical coordinator and glucose data review will be made by a study clinician with experience in reviewing and interpreting glucose data. • Additional visits – number of education and phone discussions related to CGM (by the research site) - will be tracked by the study staff on CRFs. • Blinded CGM data should not be reviewed 1) by clinicians that are part of the investigator team, 2) with participants in the SMBG group or 3) by the community treating clinician. An exception is the final study visit at Month 14. • Additional communication to the community treating clinician will be encouraged (e.g. as a follow-up to letters sent), such as phone calls or messaging via electronic medical record. • If at any point during the study the community treating clinician believes referral to an endocrinologist is warranted, he/she will be encouraged to refer participant to an endocrinologist within their normal referral pattern. However, the PI or sub-investigators should be excluded from formal consultation and from providing ongoing diabetes management to participants during the study.
Duration of participation	14 months

4. Introduction

Diabetes mellitus is a group of diseases characterized by abnormally high blood glucose levels. There are two major classifications of diabetes mellitus: Type 1 Diabetes Mellitus (T1DM), autoimmune destruction of the insulin producing pancreatic beta cells resulting in diminished or absent insulin secretion; and Type 2 Diabetes Mellitus (T2DM), resulting from constellation of defects including but not limited to impaired insulin action, decreased insulin production, and enhanced hepatic glucose production.[1] The Centers for Disease Control and Prevention reported that diabetes affects approximately 30.3 million people in the United States, or roughly 9.4% of the population, with approximately 1.5 million new cases being diagnosed each year. There are also 79 million people in the United States with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).[2] The global prevalence of diabetes in 2015 in adults was 415 million and it is projected that 642 million people will have diabetes by the year 2040.[3]

Large-scale, randomized, prospective trials of various interventional therapies in patients with both T1DM and T2DM have clearly shown that improved glycemic control significantly reduces the development and progression of microvascular complications of diabetes in both adults and adolescents. The Diabetes Control and Complications Trial (DCCT) and the Kumamoto Trials showed that intensive treatment methods reduced the incidence of these complications by approximately 50 to 70%.[4,5,6] These studies have demonstrated that intensive monitoring and better control of blood glucose in people with T1DM and T2DM both delays the onset and reduces the progression of diabetic retinopathy, nephropathy, and neuropathy.

Advances in medications and medical devices over the years have not significantly impacted clinical goals for patients, with less than 8% of them at recommended treatment goal for glucose, blood pressure and lipids.[7] Achieving optimal glycemic control for persons with advanced T2DM often involves use of insulin therapy; however roughly a third of T2DM patients do not adhere to the prescribed insulin regimens.[8] Furthermore, many T2DM patients using insulin perform SMBG testing at suboptimal levels.[9,10]

Use of real-time continuous glucose monitoring (RT-CGM) has been shown to improve glycemic control with a reduced risk of hypoglycemia in T1DM and T2DM patients on intensive insulin therapy. Only a few studies have studied RT-CGM's impact on glycemic control in T2DM with use of basal insulin, prandial insulin and oral anti-diabetic medications (OADs). Because once-daily basal insulin is the first step in initiating insulin therapy in T2DM, the need to evaluate the utility of RT-CGM with less intensive insulin regimens is warranted.

Use of RT-CGM demonstrated a benefit in a pilot observational study conducted by Manning et al. The study's objective was to assess persistence of RT-CGM use in T2DM patients treated with basal insulin and its potential impact on quality of life and glycemic control. Results showed that use of RT-CGM resulted in marked glycemic improvement. Psychosocial measures collected during the study suggested that RT-CGM did not appear to increase diabetes-related stress or add to the burden of diabetes management. Further, analyses showed that subjects' attitudes toward RT-CGM use tended to improve over the six-month study duration.[11]

Episodic RT-CGM use was evaluated in a randomized trial of 100 subjects by Vigersky et al. Adults with T2DM who were not on prandial insulin were followed for 52 weeks to compare the long-term effects of RT-CGM versus SMBG on glycemic control. The results of this study showed a significant decline in HbA1c in the RT-CGM group compared to the SMBG group (0.8% vs 0.2% @ week 52). Vigersky concluded that persons with T2DM not on prandial insulin who used RT-CGM intermittently have sustained improvement in glycemic control during a long term follow up period (52 weeks).[12] The improvement in glycemic control observed in this study was similar to improvements achieved by pharmacologic interventions with oral agents.

No prospective randomized controlled studies have been conducted, exploring the clinical benefits of RT-CGM used daily for poorly-controlled, non-intensive insulin users compared with those who use SMBG as their glycemia monitoring tool. Therefore, this study will examine the potential benefit of adding RT-CGM to and utilizing RT-CGM data in patients with sub-optimal glycemic control using basal insulin therapy.

5. Study Objectives

For Phase 1 of the study, the objectives are as follows:

⇒ **Primary**:

Assess the benefit on glycemic control, using real time continuous glucose (RT-CGM) versus SMBG, in persons with Type 2 Diabetes (T2D) taking basal insulin with or without oral medications and/or GLP-1 analogue, not at their HbA1c goal.

⇒ **Secondary**:

- Assess quality of life (QoL) benefits of RT-CGM
- Assess frequency of hypoglycemia as determined by CGM

For Phase 2 of the study, the objectives are as follows:

⇒ **Primary**:

Determine if glycemic control worsens upon withdrawal of RT-CGM

⇒ **Secondary**:

- Determine if glycemic benefits of RT-CGM use are sustainable for a long period of time (14 months)
- Assess QoL benefits of continuing or discontinuing RT-CGM
- Assess frequency of hypoglycemia as determined by CGM

6. Hypotheses

⇒ **Phase 1**

In persons with T2D taking basal insulin (with or without oral medications and/or GLP-1 analogue) that are in poor control, CGM based decisions by the patients and their primary care physicians under advice from diabetes specialists, will result in better glycemic outcomes than blood glucose monitoring based decisions.

⇒ **Phase 2**

Patients who discontinue RT-CGM will have a different time in target range (70-180 mg/dL) compared with patients who continue RT-CGM.

7. Primary Endpoints

⇒ **Phase 1**: Between group differences (CGM and SMBG) for the change in HbA1c (from Central lab) from baseline to Month 8

⇒ **Phase 2**: Between group differences for the Phase 1 CGM Group re-randomized to Discontinue CGM (use SMBG only) or to Continue CGM for the change in time in target range (70-180 mg/dL) from Month 8 to Month 14

8. Secondary Endpoints

⇒ **Phase 1**: Between group differences (CGM and SMBG) from baseline to Month 8. All treatment group comparisons of CGM metrics will use the blinded CGM data collected for the SMBG Group participants and a similar time period of data for the CGM Group participants.

- Change in CGM time in target range, defined as 70-180 mg/dL
- Percent decreasing HbA1c by ≥0.5% (absolute)
- Percent adding or removing diabetes medications (starting or stopping medication)
- Change in HbA1c based on their baseline HbA1c (restricted to participants with baseline HbA1c ≥10.0%, ≥9.5%, ≥9.0%, ≥8.5%; only performed if primary analysis is significant)
- Change in CGM time-hyperglycemic, defined as >250 mg/dL
- Change in CGM measured coefficient of variation
- Change in CGM time-hypoglycemic, defined as <70 mg/dL

Additional outcomes are listed in the Statistical Analysis Plan.

⇒ **Phase 2**: Between group differences for the Phase 1 CGM Group re-randomized to the Discontinue CGM Group (use SMBG only) versus the Continue CGM Group from Month 8 to Month 14. Between group differences for the Continue CGM and the Continue SMBG groups from baseline to Month 14

- Change in HbA1c (Central lab)
- Change in CGM time-hyperglycemic, defined as >250 mg/dL
- Percent decreasing HbA1c by ≥0.5% (absolute)
- Percent adding or removing diabetes medications (starting or stopping medication)
- Change in CGM measured coefficient of variation
- Change in CGM time-hypoglycemic, defined as <70 mg/dL

Additional outcomes may be listed in the Statistical Analysis Plan.

9. Other Endpoints

Exploratory analyses will be performed on the outcomes listed below to better understand the effect of CGM on this population. Additional outcomes may be listed in the Statistical Analysis Plan.

⇒ **Phase 1**:

Between group differences (CGM and SMBG) from baseline to Month 8

- Other HbA1c outcomes:
  - Percent reaching target HbA1c (<7.0%)
  - Percent with HbA1c <7.5%
  - Percent decreasing HbA1c by ≥1.0% (absolute)
  - Percent decreasing HbA1c by ≥1.0% (absolute) OR reaching target HbA1c (<7.0%)
  - Percent decreasing HbA1c by >10% (relative)
- Change in SMBG frequency (self-reported)
- Number of visits to primary care physician for glucose management (self-reported)
- Changes in Quality of Life (QoL) and other survey outcomes:
  - Diabetes Distress Scale (DDS)
  - Glucose Monitoring Satisfaction Survey, (GMSS) - Type 2 Version

- Clinician Communication Rating Scale
- Fear of Hypoglycemia, Worry & Behavior Subscales
- Hill-Bone Medication Adherence Scale
- SF12 Health Survey
- WHO-5 Well-Being Index
- Toobert's Scale, Modified (SDSCA) - Diet and Exercise
- Perceived Benefit Questionnaire
- CGM Satisfaction Survey (CGM Group only)

⇒ **Phase 2**:

Between group differences for the Phase 1 CGM Group re-randomized to the Discontinue CGM Group (use SMBG only) and Continue CGM Group from Month 8 to Month 14

Between group differences for the Continue CGM and the Continue SMBG groups from baseline to Month 14

- Other HbA1c outcomes:
  - Percent reaching target HbA1c (<7.0%)
  - Percent with HbA1c <7.5%
  - Percent decreasing HbA1c by ≥1.0% (absolute), from baseline to Month 14
  - Percent decreasing HbA1c by ≥1.0% (absolute) OR reaching target HbA1c (<7.0%), from baseline to Month 14
  - Percent decreasing HbA1c by >10% (relative), from baseline to Month 14
- Change in SMBG frequency (self-reported)
- Number of visits to primary care physician for glucose management (self-reported)
- Changes in Quality of Life (QoL) and other survey outcomes:
  - Diabetes Distress Scale (DDS)
  - Glucose Monitoring Satisfaction Survey, (GMSS) - Type 2 Version
  - Clinician Communication Rating Scale
  - Fear of Hypoglycemia, Worry & Behavior Subscales
  - Hill-Bone Medication Adherence Scale
  - SF12 Health Survey
  - WHO-5 Well-Being Index
  - Toobert's Scale, Modified (SDSCA) - Diet and Exercise
  - Perceived Benefit Questionnaire
  - CGM Satisfaction Survey (CGM Group only)

10. Study Population

Adult T2D patients followed by a primary care physician, who are currently on basal insulin therapy with or without oral anti-diabetic therapy and/or GLP-1 analogue injections and who are sub-optimally controlled. Participants will be recruited from within the network or the referral base of the research site. Clinical research sites with on-site access to diabetes experts will also be considered to participate in the study.

11. Study Eligibility

11.1. Inclusion Criteria

- Age at least 30 years
- Type 2 diabetes by clinical history

- Comprehends written and spoken English
- Using 1-2 injections of basal or intermediate acting insulin daily
- HbA1c between 7.8-11.5% inclusive at enrollment (by site's POC or local lab)
- Assessment by clinician that patient is able and willing to wear a CGM device
- Naïve to RT-CGM (No personal RT-CGM use within 3 months of study entry; may have used professional CGM or Flash glucose monitoring)
- Self-monitors blood glucose on average at least 3 times per week (self-reported) during the month prior to entry visit
- Stable medication regimen (medication class) during the 3 months prior to entry visit
- On basal insulin for ≥ 6 months prior to entry visit
- Has a smart phone compatible with CGM and BGM systems and is willing to utilize a study issued blood glucose meter
- Has their diabetes managed by a primary care physician or nurse practitioner/ physician assistant

11.2. Exclusion Criteria

- Regular use of short acting insulin in the 3 months prior to entry visit or planning to initiate prandial insulin or short acting insulin. Regular use of short acting insulin defined as 1 or more injections/day for more than 1 week. **Note:** Short term use in a hospital setting or for correction of isolated hyperglycemia is not an exclusion.
- Pregnancy (as demonstrated by a positive test at study entry) at time of screening or are planning to become pregnant during the study
- Weight reduction medications, programs or surgery. Defined as 1) using weight loss medications and losing weight (e.g. chronic use of weight loss medications with stable weight is not exclusionary) or planning on using weight loss prescription medication during the study; 2) currently using or planning on initiating a modified fasting program (e.g. protein-sparing diet plans) during the study; or 3) bariatric surgical procedure within the past year or plans for undergoing bariatric surgery during the study. **Note:** participation in non-physician directed plans such as Weight Watchers or Jenny Craig program are not exclusionary.
- Concomitant disease or condition that may compromise patient safety including and not limited to severe mental illness, a diagnosed or suspected eating disorder or any uncontrolled long-term medical/ psychiatric condition that would interfere with study related tasks or visits. These assessments/conditions are made at the investigator's discretion.
- Known (or suspected) significant allergy to medical grade adhesives
- Renal disease defined as estimated Glomerular Filtration Rate eGFR <30 **Note:** may use historical value, if obtained within 4 months of entry visit
- Anticipated acute uses of glucocorticoids (oral, injectable, or IV), that will affect glycemic control and impact HbA1c – such as frequent steroid bursts required for inflammatory arthritis or inflammatory bowel disease, recurrent lumbar epidural steroid injections, etc. (Long-term stable glucocorticoid doses are allowed, such as when used for the treatment of rheumatoid arthritis or Addison's disease).
- Acute conditions that could impact the stability of an HbA1c measurement such as GI blood loss, recent (with 3 months of entry visit) or anticipated red blood cell transfusion or erythropoietin administration.
- Followed by for their diabetes management by a study PI or sub-investigator
- Diabetes (glucose) management in the prior 6 months (study entry) under the guidance of a diabetes specialist

- Participation in another pharmaceutical or device trial at the time of enrollment or during the study

12. Study Design

Prospective, randomized, 2 phase parallel arm with a run-in period. The Investigators' role in the study with respect to diabetes management is advisory in nature, such that they will provide insights and interpretation of the glucose data obtained from the BGM or CGM devices and formally communicate recommendations to the participant and their treating community clinician. The study clinician may provide recommendations on lifestyle and self-titration modifications to the participant. Any recommendations for medication changes will be provided to the treating community clinician.

Targeted participants will be recruited from outside the investigator team's diabetes and endocrine practice and will be followed for their diabetes management by a primary care physician. Clinical research sites with on-site access to diabetes experts will also be considered to participate in the study.

After providing consent, all potential participants will be assessed for eligibility**.** At the time of enrollment, participants will undergo a run-in period (10 days) of blinded CGM to assess continuance in the study and to collect baseline CGM data. Training will be provided for use of study-assigned meter. Screening labs and surveys will be administered at time of enrollment (See **Table 1. Schedule of Events**).

Criteria for participants to continue with randomization are 1) willingness and ability to use the CGM device, 2) and CGM adherence, defined as a minimum of 70% usage (e.g. at least 7 days of CGM readings). The CGM data will NOT be shared with participants, clinicians at the research site, or the treating community clinician.

Participants will undergo or be referred for one or two general diabetes education session(s) (individual or group) during the run-in period, per site's usual diabetes educational program. The sessions may include review or discussion of the following:

- Glucose targets (individualized) including fasting and pre-meal range and post meal
- Basics of basal insulin titration
- Basics of meal planning
- Hypoglycemia management
- Importance of medication adherence

Those willing to participate and meeting eligibility criteria will be assigned to 1 of 2 groups in Phase 1, using a 2:1 randomization scheme, to either CGM (CGM Group) or SMBG (SMBG Group). Randomization will be stratified by site using a permuted blocks design. Randomization to group assignment will be obtained from a study website after all enrollment data have been entered and eligibility verified. Baseline labs will be drawn (Non-HDL cholesterol, C-peptide if historical lab not available and Central and POC/local lab HbA1c).

Phase 1 is of 8 months duration. For the CGM Group, it comprises 4 scheduled clinic visits: at week 2, month 1, month 3 and month 8. For the SMBG Group, it comprises 5 scheduled clinic visits: at week 2, month 1, month 3, pre-month 8 (~ 10 days prior to Month 8 visit) and month 8. There will be phone/ remote visits at months 2, 4 and 6 in both groups. HbA1c will be measured by Central lab and POC/local lab at baseline, 3 months and 8 months.

A visit specific communication letter will be sent by the study clinician to the community treating clinician informing them of the patient's participation and the limited role of the study clinician-

providing lifestyle recommendations to the patient. The study clinician may also provide guidance on self-titration of basal insulin, and report glucose trends to patients and clinicians (with treatment considerations to the community treating clinician, such as discontinuation of any medications that may be causing hypoglycemia or resulting in significant side effects).

Description of study groups:

SMBG Group

1. Participants will be provided a blue-tooth enabled blood glucose meter and testing supplies
2. A BGM account will be established and linked to the research site
3. Participants will be asked to perform SMBG testing from 1- 3x daily. Testing should involve a minimum of once daily test and include some fasting and some post-prandial measurements
4. Blinded CGM will be worn at intervals as described in **Section 20, Study Procedures**

CGM Group

1. The G6 CGM app will be installed on participant's smart phone.
2. A CLARITY mobile account will be set up and linked to the research site.
3. Participants will use CGM data for their diabetes management. Blood glucose monitoring will be performed if CGM readings do not match a participant's symptoms.
4. Participants will perform SMBG testing as needed with a study-provided blue-tooth enabled blood glucose meter, including testing supplies.
5. Participants will set CGM threshold alerts at values that will minimize alerts. These should be tightened/ adjusted during the study as glucose control improves.
6. Participants may have CLARITY push notifications enabled during the study.

During clinic visits, the study clinician will discuss any device issues requiring troubleshooting, upload the glucose data from the CGM and BGM as applicable, provide suggestions to the participant on self-titration of basal insulin (at Week 2 and at subsequent phone encounters and clinic visits), provide treatment guidelines based on observed glucose patterns, and encourage lifestyle experimentation and modifications to minimize glycemic excursions. A study-provided Tips for Success sheet (either CGM or BGM relevant) will be reviewed with the participant during some clinic visits. CGM users may have alert settings adjusted, will be encouraged to share their glucose data with the CGM Share app and indicate the number of followers in which they are sharing their glucose data. The Month 3 clinic visit involves only collection of Central and POC/local lab HbA1c and having the SMBG Group participants wear blinded CGM for one session wear.

During phone/remote contacts by the study clinician, any therapy changes (including any new/changing medications and visits to the primary care physician) that have been made by the community treating clinician, as self-reported by participants, will be documented. The study clinician will use a study-provided guidance document for conducting the phone/remote contacts. This document provides a structured approach to the remote visits.

At the conclusion of Phase 1 (Month 8), participants will have completed PROs/surveys and had blood drawn for lab data collection (HbA1c-Central and local and Non-HDL cholesterol). The blinded CGM data obtained in the SMBG Group will *not* be used by the research site staff and will *not* be reviewed with the participant or sent to the community treating clinician.

At each visit/contact (except Month 3) the study clinician will send the glucose data record (CGM for the CGM Group and SMBG for the SMBG Group) and communicate via letter with the community treating clinician interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments, and any lifestyle recommendations. The letter will contain discussion of glucose patterns that are elucidated and considerations for therapy changes based on patterns. However, any therapy changes would occur

outside the study and be made by the community treating clinician, unless deemed clinically warranted by study clinician (e.g. for immediate safety purposes such as frequent or problematic hypoglycemia). A copy of the glucose data (summary CGM data for CGM Group and SMBG data for the SMBG Group, per Investigator discretion), interpretation and recommendations will also be provided to the participant for use in discussions with their community treating clinician.

For Phase 2, participants from the Phase 1 CGM Group will be re-randomized 1:1 to continue CGM use (Continue CGM Group) or to use SMBG (Discontinue CGM Group). CGM devices will be collected from participants discontinuing CGM use in Phase 2. Participants from the Phase 1 SMBG Group will continue SMBG (Continue SMBG Group). Randomization to group assignment will be obtained from a study website after the Month 8 visit is completed. Tips for Success with CGM or SMBG will be provided.

Phase 2 comprises either 1 visit and 1 phone contact (Continue CGM Group) or 2 visits and 1 phone contact (Discontinue CGM Group and Continue SMBG Group). Participants in all 3 groups will continue study participation for an additional 6 months. BG testing supplies will continue to be provided.

During the phone/remote contact at Month 11, study staff will document any therapy changes (including any new/changing medications and visits to the primary care physician) that have been made by the community treating clinician, as self-reported by participants. They will discuss any device issues requiring troubleshooting, upload the glucose data, provide suggestions on self-titration of basal insulin, and encourage lifestyle experimentation and modifications. CGM users may have alert settings adjusted, will be encouraged to share their glucose data with the CGM Share app and indicate the number of followers in which they are sharing their glucose data.

The study clinician will send the glucose data record (CGM data for Continue CGM Group and SMBG data for both SMBG groups) and communicate via letter with the community treating clinician about the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments or significant post-meal hyperglycemia that may require additional therapy, and any lifestyle recommendations. The letter will contain discussion of glucose patterns that are elucidated and considerations for therapy changes based on patterns. However, any therapy changes would occur outside the study and be made by the community treating clinician. A copy of the glucose data (CGM data for Continue CGM Group and SMBG data for both SMBG groups) and recommendations will also be provided to the participant.

At the Pre-Month 14 visit, participants in both SMBG groups (Discontinue CGM Group and Continue SMBG Group) will wear blinded CGM for one session wear and complete PROs/surveys.

At the final Month 14 clinic visit, a blood draw will be done for Central and POC/local lab HbA1c and Non-HDL cholesterol, devices will be downloaded, and surveys will be administered (CGM Group only). CGM devices used during the study will be offered to the participant with a month supply of sensors. Blinded CGM data can be reviewed with the participants in both SMBG groups.

Additional details:

- At each visit/contact study related procedures will be performed by a clinical coordinator and glucose data review will be made by a study clinician with experience in reviewing and interpreting glucose data.
- Blinded CGM data should not be reviewed 1) by clinicians who are part of the investigator team, 2) with participants in any of the SMBG groups or 3) by the community treating clinician. An exception is the final study visit at Month 14.
- Additional visits – number of education and phone discussions related to CGM (by the research site) - will be tracked by the study staff.

- Additional communication to the community treating clinician will be encouraged (e.g. as a follow-up to letters sent), such as phone calls messaging via electronic medical record.
- If at any point during the study the community treating clinician believes referral to an endocrinologist is warranted, he/she will be encouraged to refer participant to an endocrinologist within their normal referral pattern. However, the PI or sub-investigators should be excluded from formal consultation and ongoing diabetes management during the study.

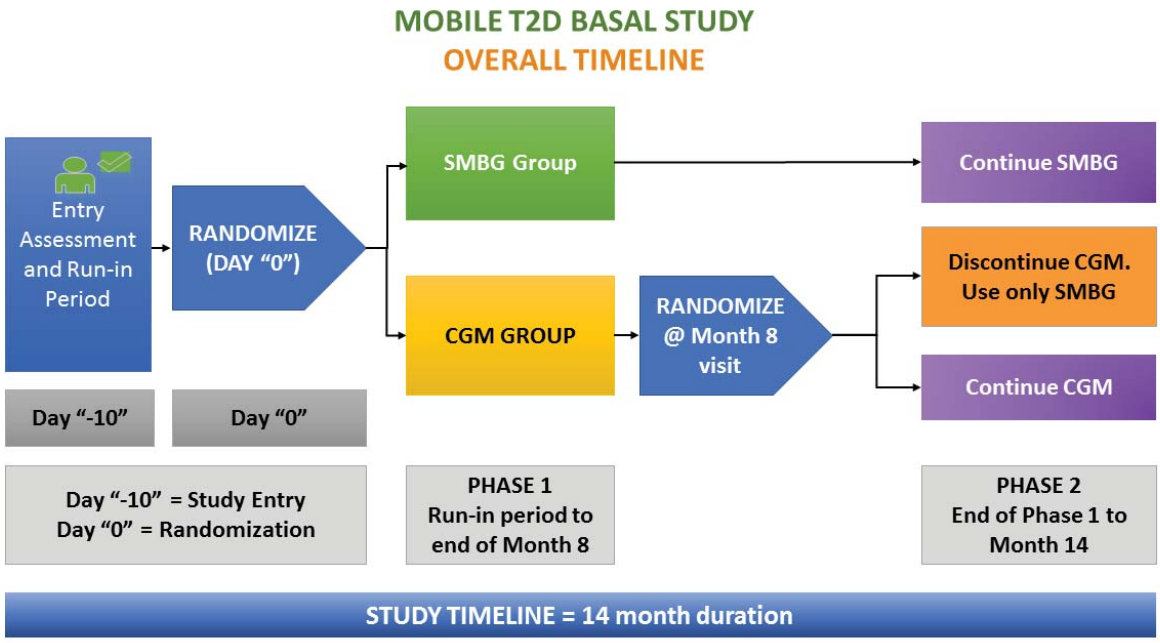

Figure 1. Study Design Diagram

13. Duration of Study Participation

Participants' duration in the study for both phases is 14 months. Phase 1 duration is 8 months. Phase 2 duration is 6 months.

14. Study Duration

The estimated time for study completion is 3 years, includes recruitment and completion of Phase 2 follow up period.

15. Clinical Research Sites

Up to 30 sites from across North America

Targeted sites will be multi-specialty clinics/systems or endocrinology centers from a mixture of academic and community sites that are part of a health system or that have a strong referral base. Clinical research sites with on-site access to diabetes experts will also be considered to participate in the study. These centers will have research capabilities and have clinicians in the research site experienced in interpreting CGM and SMBG data. Clinicians (CDE, NP, PA or equivalent, or MD) will interpret data and provide data and suggestions to the participant and participant's community treating clinician, using study provided correspondence and treatment guidelines.

16. Overview of Study Devices

The Dexcom G6 Continuous Monitoring System will be used during the study. Commercially cleared blood glucose meters will be assigned to participants to collect relevant study data. Study participants will receive guide materials for the both devices.

16.1. Dexcom G6 Continuous Glucose Monitoring System

The Dexcom G6™ Continuous Glucose Monitoring System (the G6 CGM System) is intended for single-patient use. The G6 CGM System is a Class II device that has been cleared by the FDA for commercialization (DEN 170088). Its intended use is for the management of diabetes in persons age 2 years and older.

The Dexcom G6 System is intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G6 System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6 System also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments.

The Dexcom G6 System is also intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. The Dexcom G6 System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes. Refer to the Indications for Use document prior to device use. It measures and displays glucose values and trends for patients with diabetes. The system provides continuous glucose readings at five-minute intervals for up to 10 days of use. The system does not require calibration with blood glucose measurements taken with a self-monitoring blood glucose meter.

Figure 2. Dexcom G6 Continuous Monitoring System

The system (**Figure 2**) consists of a sensor, transmitter, receiver, and mobile app. The sensor is a small, flexible wire inserted into subcutaneous tissue where it converts glucose into electrical current. The sensor incorporates an interferent layer that minimizes the effect of potential electroactive interferents, such as acetaminophen, by preventing it from reaching the sensor wire surface. The benefit of this interferent layer in blocking the effects of acetaminophen prevents falsely high glucose readings. Thus, users may ingest acetaminophen while wearing the G6 CGM system.

The transmitter, which is connected to the sensor and worn on the body, samples the electrical current produced by the sensor and converts the measurement into a glucose reading using an onboard algorithm. The receiver and/or the app displays the glucose reading along with a rate of change arrow and a trend graph. Additionally, the receiver and/or app issues alarms and alerts to notify the patient of glucose level changes and other important system conditions. The app provides the additional capability to share data using the Dexcom Share service.

The receiver can be put into a blinded mode. In this mode, users are unable to see the CGM data or receive CGM alerts.

16.2. CGM Ancillary Devices

Dexcom CLARITY is an accessory to users of the Dexcom CGM system. It is a software program that allows the transfer of glucose data from the CGM system to Dexcom remote servers for data management to allow use of the CGM data by the user and study clinicians. Both participants and study sites will use CLARITY to transfer glucose data between user and study site, whether CGM is used in blinded or real-time mode.

16.3. Blood Glucose Meter (BGM) Devices

Each participant will be assigned a blue-tooth enabled study meter to record their blood glucose values during the study. The meter has FDA 510K clearance and is commercially available in the US. They will receive an ample supply of meter test materials based on quantities routinely used. This meter system includes a wireless meter, a smartphone app, and an online portal that allows users to share data with their clinical site personnel. The wireless meter transmits blood glucose results to the app on the user's smartphone using *Bluetooth*® technology. Users can also store and access information securely via an online portal account. Software used in conjunction with the BGM will be utilized for downloading data at the sites and use for study analysis.

17. PRO Measurements & Surveys

PRO measures and surveys will be administered during the study. All eligible participants will complete PRO measures and surveys at baseline. During follow-up, the PRO measures and surveys will be completed at Month 8 and 14 for the CGM Group and at the Pre-month 8 and 14 visits for the SMBG Group. The PRO measures and surveys may be completed by participants at home, up to 1-week prior to reduce participant burden during clinic visits. They assess QoL dimensions – health state, psychological well-being, diabetes management, and interaction with CGM; and treatment satisfaction and behavioral changes throughout the study, as well as capture health economic benefits.

The following PRO measures and surveys will be administered during the study:

17.1. Diabetes Distress Scale (DDS)[13]

CGM Group: Entry, Month 8, and Month 14; SMBG Groups: Entry, Pre-Month 8 & Pre-Month 14

This scale lists 17 potential problem areas that people with diabetes may experience and can denote the degree to which they are or are not affected. The DDS has a consistent, generalizable factor structure and good internal reliability and validity. The instrument serves as a valuable measure of diabetes-related emotional distress for use in research and clinical practice.

17.2. Glucose Monitoring Satisfaction Survey, (GMSS)[14]

CGM Group: Entry, Month 8, and Month 14; SMBG Groups: Entry, Pre-Month 8 & Pre-Month 14

This 15-question survey, which includes four subscales, is a reliable, validated measure of glucose device satisfaction in both its T1D form and its insulin-using T2D form. Subscales include Openness, Emotional Burden, Behavioral Burden and Worthwhileness. It can be used in clinical care and research.

17.3. Hill-Bone Medication Adherence Scale[15]

CGM Group: Entry, Month 8, and Month 14; SMBG Groups: Entry, Pre-Month 8 & Pre-Month 14

This scale is scored on a 4-point Likert scale and queries how a person with diabetes self manages their medication regimen. The original scale comprised three subscales (medication adherence, reduced sodium intake, appointment keeping) and was designed for use with patients taking hypertensive medication. In the modified, un-validated form used for this study, the word 'diabetes' was substituted. This change would not affect the psychometric properties of the scale.

17.4. Clinician Communication Rating[16]

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

This is a brief survey that assesses the perceived quality of the interaction between the participant and their community treating clinician.

17.5. Toobert's Scale, Modified (SDSCA Diet and Exercise)[17]

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

The SDSCA measure is a brief self-report questionnaire of diabetes self-management that includes items assessing the following aspects of the diabetes regimen: general diet, specific diet, exercise, blood-glucose testing, foot care, and smoking. This study will utilize the diet and exercise portions of the questionnaire.

17.6. Fear of Hypoglycemia Survey[18] Worry & Behavior Subscales

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

This validated short survey consists of 11 questions which measure several dimensions of worry and behavior surrounding hypoglycemia among adults with diabetes.

17.7. SF-12 Health Survey[19]

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

The SF-12 has become the most widely used measure of general health in clinical studies throughout the world. The survey is a 12-item validated questionnaire used to assess health outcomes from the patient's perspective. PRO measures like the SF-12 assess general health and well-being or health-related quality of life (HRQOL), including the impact of illnesses on a broad range of functional domains. The SF-12 comprises a subset of 12 items from the SF-36 Health Survey that covers the same eight domains of health outcomes, including physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH).

Whilst such scores provide an excellent means for judging the effectiveness of health care interventions, they have only a limited application in economic evaluation because they are not based on preferences. The SF-6D provides a means for using the SF-12 in economic evaluation by estimating a preference-based single index measure for health from these data using general population values. The SF-6D allows the analyst to obtain quality adjusted life years (QALYs) from the SF-12 for use in cost utility analysis.

17.8. WHO-5 Well-Being Index[20]

CGM Group: Entry, Month 8, and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

This is a validated, 5-question scale, utilized to assess general outlook and overall well-being. This scale also examines aspects other than just the absence of depressive symptoms.

17.9. CGM Satisfaction Survey[21] (CGM users)

CGM Group: Month 8 and Month 14

The CGM Satisfaction Survey is a validated tool which consists of 44 questions which assesses satisfaction regarding various aspects of CGM use.

17.10. Perceived Benefit Questionnaire

CGM Group: Month 8 and Month 14; SMBG Group: Pre-Month 8 & Pre-Month 14

This 2-question questionnaire queries the participant on any perceived benefit of the glucose monitoring device they are using.

17.11. Subjective Numeracy Scale[22]

All participants: Entry

A validated tool that subjectively measures (i.e., self-assessment) person's quantitative ability that distinguishes low- and high-numerate individuals. Four items measure people's beliefs about their skill in performing various mathematical operations, and 4 items measure people's preferences regarding the presentation of numerical information.

17.12. Work Productivity and Activity Impairment Instrument[23]

CGM Group: Entry, Month 8 and Month 14; SMBG Group: Entry, Pre-Month 8 & Pre-Month 14

A 6-question validated tool that measures time missed from work, impairment of work and regular activities due to overall health and symptoms.

18. Data Collection and Management

Data collected during the study will be documented on electronic case report forms (e-CRFs). The Investigator or designee is responsible for completing the Case Report Forms (CRFs). The electronic data capture (EDC) system will be validated prior to study commencement. Sites will be trained on use of the EDC system by sponsor or designee. Good Documentation Practices principles will be required. Participants who fail the Run-In Phase will not undergo randomization and thus will be withdrawn from the study, with documentation provided on a termination CRF.

A database system, Part 11 compliant, will be created using Jaeb Center's custom-built EDC system for data entry and verification of the data inputted by site personnel.

19. Statistical Considerations

Most of the details in the following section apply to both Phase 1 and Phase 2 but some sub-sections give separate details for each phase.

19.1. Statistical and Analytical Plans

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

19.2. Statistical Hypotheses

Phase 1:

- Null hypothesis: There is no difference in the mean change in Central lab measured HbA1c over 8 months between patients making CGM based decisions about their diabetes and patients making blood glucose monitoring based decisions
- Alternate hypothesis: Patients making CGM based decisions about their diabetes have a different mean change in Central lab measured HbA1c over patients making blood glucose monitoring based decisions

Phase 2:

- Null hypothesis: There is no difference in the mean change in CGM measured time in the target range (70-180 mg/dL) over 6 months between patients who continue making CGM based decisions about their diabetes (after the initial 8 months) and patients who switch from making CGM based decisions to making blood glucose monitoring based decisions
- Alternate hypothesis: Patients who switch from making CGM based decisions to making blood glucose monitoring based decisions about their diabetes have a different mean CGM measured time in the target range over patients who continue making CGM based decisions (after the initial 8 months)

19.3. Sample Size

Phase 1 is formally powered and the Phase 2 sample size is dependent on the number in the CGM group in Phase 1 who continue into Phase 2.

For Phase 1, the DIaMonD T2D RCT data were used to estimate the mean and standard deviation for HbA1c at baseline and 6 months. Data were taken from 121 participants with T2D who met the current protocol's eligibility criteria for HbA1c (8.0-11.5%). Based on an effective standard deviation of 0.80% (adjusting for baseline HbA1c as a covariate) and a true treatment effect of 0.4%, the total sample size was estimated to be 165 to have at least 85% power with alpha=0.05 and 2:1 randomization. However, in order to account for a 20% dropout rate, a total sample size of 207 was selected (138 for the CGM Group and 69 for the SMBG Group) with up to 300 enrolled into screening.

For Phase 2, the DIaMonD Phase 2 RCT data (which includes only T1D participants) were used to estimate the mean and standard deviation for the percent time in the target range (70-180 mg/dL) at 6 and 12 months. Data were taken from 38 participants in the CGM+MDI Group. Assuming 138 subjects were randomized to the current protocol's Phase 1 CGM Group and a 20% dropout rate, we expect at least 74 participants to enter and complete Phase 2. Based on an effective standard deviation at 12 months of 7% (adjusting for 6-month time in range as a covariate) and a treatment

effect of 5%, there will be 85% power to detect a difference in the time in range between the Continue CGM and the Discontinue CGM groups, with alpha=0.05 and 1:1 randomization.

19.4. Study Endpoints

The primary and secondary endpoints for both phases are listed in Sections 7 and 8 and won't be repeated here. Other exploratory endpoints are listed in Section 9. Additional analysis details are listed within this section.

19.5. Description of Statistical Methods

19.5.1. General Approach

All covariates obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that a variable does not have a linear relationship with the outcome. In such a case, categorization and/or transformation will be explored. All p-values will be two-sided.

Details for CGM Metrics

All treatment group comparisons of CGM metrics will use the blinded CGM data collected for the SMBG Group participants and a similar time period of data for the CGM Group participants. Additional details will be given in the Statistical Analysis Plan.

19.5.2. Analysis Cohorts

- All randomized participants will be analyzed for the Intention-to-Treat (ITT) Analysis.
- Safety outcomes will be reported for all enrolled participants, irrespective of whether the study was completed.
- Per-protocol analyses will be conducted for Phase 1 and for Phase 2 separately. The details will be discussed in the Statistical Analysis Plan.

19.5.3. Analysis of the Primary Outcome

Phase 1:

Summary statistics for HbA1c (from Central lab) appropriate to the distribution will be calculated separately by treatment group. The method of direct likelihood will be used by fitting a longitudinal mixed effects linear regression model including HbA1c values measured at baseline, 3 months and 8 months. The model will include a term for treatment arm, but the two arms will be forced to have the same predicted value at baseline (due to randomization). Separate treatment effects will be estimated at 3 and 8 months (treatment by time interaction) and inference will focus on the estimate at 8 months, which is the primary outcome. A risk-adjusted point-estimate, 95% confidence interval and p-value will be reported for the treatment arm difference at 8 months. The model will adjust for clinical site as a random effect and include the local HbA1c as an auxiliary variable.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead.

The risk adjusted difference and 95% confidence interval will be reported based on the least squares mean from this model.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated as a sensitivity analysis by including factors potentially associated with HbA1c for which there is an imbalance between groups.

Missing HbA1c Data for Phase 1

It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. Our goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used. Different techniques (summarized below) will therefore be utilized to determine whether they reach similar conclusions:

- Primary Analysis: Missing HbA1c values will be handled using direct likelihood as described above
- Sensitivity Analyses: Analyses will also be conducted using the following methods to handle missing HbA1c values:
    - Rubin's multiple imputation
    - Available cases only

Phase 2:

Summary statistics for the time in target range appropriate to the distribution will be calculated separately by treatment group. A mixed effects linear regression model will be used to compare the change in time in target range among the two treatment groups. The model will adjust for baseline time in target range as a fixed effect and include random effects for clinical site.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead.

If values are approximately normal, then a risk adjusted difference and 95% confidence interval will be reported based on the least squares mean from this model.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in the primary analysis by including factors potentially associated with time in target range for which there is an imbalance between groups.

Missing CGM Data in Phase 2

There will be no minimum requirement of CGM data to be included in the CGM analyses so all participants with CGM data will be included in the analysis.

19.5.4. Analysis of the Secondary Endpoints

For continuous variables, summary statistics appropriate to the distribution will be calculated separately by treatment group. For discrete variables, number and % will be calculated separately by treatment group.

All the binary measures will be compared between treatment groups using a logistic regression model and all the continuous measures will be compared using a linear regression model. All models will adjust for the baseline value as a fixed effect and include random effects for clinical site. In addition to these factors, the model for body weight will also adjust for age and gender.

For the continuous outcomes, residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead. If the distribution is approximately normal then the adjusted mean difference and confidence interval will be reported.

For the binary outcomes, the risk adjusted difference in percentages and the confidence interval will be reported. The adjusted difference in percentages will be calculated as in Kleinman and Norton[1] and the confidence interval will be calculated using a bootstrap.

Missing Data for Secondary Outcomes
Only participants with outcome data at baseline and follow-up will be included in the analysis (i.e. available cases only). There will be no minimum requirement of CGM data to be included in the CGM analyses.

19.5.5. Safety Analyses

All adverse events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. In addition, the following outcomes will be analyzed when the number of events is sufficient for a meaningful analysis and the analysis methods are described below:

1. Number of events per person (SH and DKA, separately)
2. Percentage of participants with at least one event (SH and DKA, separately)
3. Kaplan-Meier incidence rate (SH and DKA, separately)
4. Incidence rate per 100 person-years (SH and DKA, separately)
5. Number of events (any event) per person thought by investigator to be related to study intervention

Outcome #1 above will be compared between treatment groups using ordered logistic regression adjusting for the baseline value (whether or not the participant had an event in the previous year) as a fixed effect and clinical site as a random effect. Outcome #3 will be compared between treatment groups using a logrank test. Outcome #4 will be compared between treatment groups using Poisson regression adjusting for the baseline value (whether or not the participant had an event in the previous year) as a fixed effect and clinical site as a random effect. If there are outliers, then robust Poisson regression will be used.

SH and DKA Incidence Rate Calculation: The incidence rate per 100 person-years will be calculated by dividing the number of events in follow-up (including any events after the last visit)

by the number of follow-up years from randomization until the latter of the last visit and the last adverse event and multiplying by 100.

19.5.6. Other Tabulations

For both Phase 1 and Phase 2, the following analyses will also be done:

- Tabulate summary statistics for the CGM use frequency for each visit and overall (CGM Group)
- Tabulate summary statistics for the CGM Satisfaction Survey for the CGM Group
- Tabulate diabetes medication changes for the participants who switched, added, or dropped a diabetes medication
- Tabulate the number of clinic visits and calls by treatment group
- Tabulate the number of and reasons for unscheduled visits by treatment group
- Construct a flowchart accounting for all subjects according to treatment group for each visit
- Tabulate the number of protocol and procedural deviations by treatment group

19.5.7. Baseline Descriptive Statistics

For each phase, summary statistics appropriate to the distribution will be given for characteristics at randomization by treatment group.

19.5.8. Planned Interim Analysis

Re-estimation of the sample size for Phase 1 will be undertaken when approximately 75 participants have completed the Month 3 visit. The analysis will involve assessment of the Month 3 HbA1c (Central lab) variance from both treatment groups combined.

19.5.9. Subgroup Analyses

Subgroup analyses will be conducted to determine whether a similar trend to the overall treatment effect for the primary outcome is seen in these subgroups. The study is not expected to have sufficient statistical power for definitive conclusions in subgroups and statistical power will be low to formally assess for the presence of interaction. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment effect. In the absence of any significant treatment effects in the primary analysis, assessment of subgroups will be considered exploratory and used to suggest hypotheses for further investigation in future studies.

The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the linear model used for the primary analysis. For continuous factors, the interaction term will use the continuous version of the variable.

The planned subgroups defined by factors measured at baseline are listed below. These subgroups will be used in both Phase 1 and Phase 2:

- HbA1c
- Time in target range (70-180 mg/dL)
- Age
- Diabetes duration

- Education
- Use of GLP1 or SGLT2 medications

Note: subgroups above will only be analyzed if there are at least 10 participants in each treatment group for each subgroup.

19.5.10. Multiple Comparisons/Multiplicity

The primary analyses for both Phase 1 and Phase 2 involve a single treatment arm comparison for a single outcome measure so no correction for multiple comparisons will be performed.

For the secondary analyses and exploratory analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure. Details will be given in the formal SAP.

19.5.11. Exploratory Analyses

The endpoints listed in Section 9 are considered exploratory analyses. Additional endpoints may be given in the Statistical Analysis Plan.

20. Study Procedures

General instructions for each visit are provided to ensure consistency in conducting the study across multiple sites and include:

1. At each visit/contact study related procedures will be performed by a clinical coordinator and glucose data review and interpretation will be made by a study clinician with experience in reviewing and interpreting glucose data.
2. Additional visits – number of education and phone discussions related to CGM (by the research site) - will be tracked by the study staff.
3. Blinded CGM data should not be reviewed 1) by clinicians who are part of the investigator team, 2) with participants in the SMBG groups or 3) by the community treating clinician. An exception is the final study visit at Month 14.
4. Additional communication to the community treating clinician will be encouraged (e.g. as a follow-up to letters sent), such as phone calls messaging via electronic medical record.
5. If at any point during the study the community treating clinician believes referral to an endocrinologist is warranted, he/she will be encouraged to refer participant to an endocrinologist within their normal referral pattern. However, the PI or sub-investigators should be excluded from formal consultation and ongoing diabetes management during the study.

Table 1 (**Schedule of Events**) indicates study staff and participant requirements per visit. **Table 2** (**Questionnaire Details**) provides the schedule for administration of the various PROs and surveys during the study.

20.1. Study Entry & Run-In Visit:

At the time of enrollment, participants will undergo a run-in period of blinded CGM wear to assess continuance in the study and to collect baseline CGM data. The following procedures occur during the initial visit and run-in period:

1. Obtain Informed Consent
2. Assess for eligibility per Inclusion/Exclusion criteria

i. Obtain screening labs (pregnancy, eGFR, POC/local HbA1c) **Note**: for eGFR may use historical, if obtained within 4 months of study entry

3. Obtain height and weight (BMI)
4. Collect demographics, socioeconomic and diabetes history
5. Collect diabetes medications
6. Schedule participants for one or two general diabetes education session(s) (individual or group) during the run-in, which will include a review or discussion of the following using developed, study-assigned teaching tools:
    i. Glucose targets (individualized) including fasting and pre-meal range and post meal
    ii. Basics of basal insulin titration
    iii. Basics of meal planning
    iv. Hypoglycemia management
    v. Importance of medication adherence
7. Assign blinded CGM to participant and train participant on use of the device in blinded mode.
8. Assign study BGM and provide testing supplies to participant and train participant on use of the device
9. Administer baseline PRO/surveys
10. Schedule return visit to assess for eligibility to enter Phase 1 of the study

20.2. Phase 1 (End of Run-in Period) -: T= 0

At the end of the run-in period, participants will be assessed for eligibility to proceed to randomization. Those willing to participate and meeting eligibility criteria will be randomized to either the CGM (CGM Group) or SMBG (SMBG Group).

1. Download CGM device to assess for CGM adherence: at least 70% usage (e.g. at least 7 days of CGM readings collected). **Note[1]:** In the event the participant was unable to collect a minimum of 7 days of CGM data *due to device issues, not compliance issues* (i.e., adhesive or sensor failures) they may have their sensor wear run-in period extended in order to collect the required number of days. This extension will be at the discretion of the investigator. **Note[2]:** CGM data will NOT be shared with participants, clinicians at the research site, or the treating community clinician.
2. Obtain baseline labs:
    i. Central lab HbA1c
    ii. POC/local HbA1c
    iii. C-peptide, fasting or non-fasting **Note:** For C-peptide, may use historical, if obtained within 6 months of study entry
    iv. Non-HDL cholesterol, derived from non-fasting Lipid Panel
3. Assess for any AEs.
4. Obtain randomization group assignment from coordinating center and perform the following, per group designation:

    SMBG Group

    - Instruct participant to continue use of study-provided blue-tooth enabled blood glucose meter with testing supplies
    - Establish a BGM account and link to the research site
    - Instruct participant to perform SMBG testing from 1- 3x daily. Testing should involve a minimum of once daily testing and includes some fasting and some post-prandial measurements

CGM Group

- Install the G6 CGM app on participant's smart phone
- Establish a CLARITY mobile account and link to the research site
- Instruct participants to use CGM non-adjunctively (i.e. for diabetes management without confirmatory SMBG testing)
- Instruct participants to perform SMBG testing as with the study assigned blue-tooth enabled blood glucose meter, including testing supplies.
- Set CGM threshold alerts at values that will minimize alerts. These should be tightened/ adjusted during the study as glucose control improves.
- Enable CLARITY push notifications and document type

5. Review group-specific study provided Tips for Success sheet
6. Study Clinician: Send visit specific communication letter to the community treating clinician, informing them of the patient's participation and the role of the study site. The letter informs the community clinician that the study site will identify glucose trends, provide lifestyle recommendations for the participant, provide guidance on self-titration of basal insulin, and provide considerations to optimize medications. A template will be provided. Document date letter sent.
7. Provide ample supplies for use until next visit
8. Schedule next visit

20.3. Phase 1-Week 2 Visit (both groups) (14 +/- 4 day window)

1. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
2. Assess for any AEs.
3. Study Clinician Discussion:
   i. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   ii. Review glucose targets.
   iii. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   iv. Review group-specific study provided Tips for Success sheet
   v. Send visit specific communication letter to the community treating clinician (copy to participant), together with the glucose data record and interpretation (CGM data for CGM Group and SMBG data for the SMBG Group) of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any medication changes should occur outside the study and be made by the community treating clinician, unless deemed clinically warranted by study clinician (e.g. for safety purposes such as frequent or problematic hypoglycemia.
   vi. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.
4. Provide ample supplies until next visit
5. Schedule next visit.

20.4. Phase 1-Month 1 Visit (both groups) (30 +/- 5 day window)

1. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
2. Assess for any AEs.
3. Study Clinician Discussion:
   i. If sufficient glucose data is available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   ii. Review glucose targets.
   iii. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   iv. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
   v. Review group-specific study provided Tips for Success sheet.
   vi. Send visit specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made ONLY by the community treating clinician, unless deemed clinically warranted by study clinician (e.g. for safety purposes such as severe hypoglycemia events).
   vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.
4. Provide ample supplies until next visit
5. Schedule initial phone contact.

20.5. Phase 1-Phone/remote Contact- Month 2 (both groups) (60 +/- 5 day window)

1. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
2. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
3. Study Clinician Discussion:
   i. Use the study provided Guidance for Phone Contact & Documentation to guide these discussions.
   ii. If sufficient glucose data are available, encourage self-titration of basal. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   iii. Review glucose targets.
   iv. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   v. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
   vi. Send a contact specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and

interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note:** any therapy changes should occur outside the study and be made only by the community treating clinician, unless deemed clinically warranted by study clinician for safety purposes.

vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.

4. Schedule next visit.

20.6. Phase 1-Month 3 Visit (both groups) (90 +/- 5 day window)

During this visit, glucose data will not be reviewed. Blinded CGM data is obtained for the purposes of documenting CGM metrics in the SMBG group

1. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
2. Obtain labs
   i. Central lab HbA1c
   ii. POC/local HbA1c
3. Assess for any AEs.
4. Provide group-specific study provided Tips for Success (discussion of glucose targets not required).
5. Dispense blinded CGM devices to the SMBG Group for one blinded CGM wear period, with instructions for return of device to the clinical site. **Note:** A second sensor session may be warranted if device issues occur (i.e., adhesive or sensor failures), resulting in the session ending before Day 4 of wear.
6. Download returned CGM device from SMBG Group participants upon receipt of the returned system. Store the CGM system for next blinded use by the participant.
7. Obtain BGM data from both groups
8. Provide ample supplies until next visit
9. Schedule next phone contact.

20.7. Phase 1-Phone/remote Contact- Month 4 (both group) (120 +/- 5 day window)

1. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
2. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
3. Study Clinician Discussion:
   i. Use the study provided Guidance for Phone Contact & Documentation to guide these discussions.
   ii. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   iii. Review glucose targets.
   iv. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.

v. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
vi. Send a contact specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made by the community treating clinician, unless deemed clinically warranted by study clinician (e.g. for safety purposes.
vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.

4. Schedule next phone contact.

20.8. Phase 1-Phone/remote Contact- Month 6 (both groups) (180 +/- 5 day window)

1. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
2. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
3. Study Clinician Discussion:
   i. Use the study provided Guidance for Phone Contact & Documentation to guide these discussions.
   ii. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.
   iii. Review glucose targets.
   iv. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.
   v. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.
   vi. Send a contact specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made only by the community treating clinician, unless deemed clinically warranted by study clinician for safety purposes
   vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.
4. Schedule next visit.

20.9. Phase 1-Pre-Month 8 Visit (SMBG Group only) (230 +/- 3 day window)

This visit is scheduled approximately 10 days prior to Month 8 Visit.

1. Administer PRO/surveys prior to dispensing blinded CGM, to minimize confounding the responses in this study group. The participant may complete PRO/surveys 1 week prior to Pre-Month 8 visit.
2. Dispense blinded CGM devices for one blinded CGM wear period, with instructions for return of device to the clinical site. **Note:** A second sensor session may be warranted if *device issues* occur (i.e., adhesive or sensor failures), resulting in the session ending before Day 4 of wear.
3. Schedule next visit.

20.10. Phase 1-Month 8 Visit & Phase 2 Randomization (both groups) (240 +/- 5 day window)

This visit concludes Phase 1 and begins Phase 2. The visit includes collection of data for Phase 1 analysis and re-randomization of the CGM Group participants into Continue CGM or Discontinue CGM (use SMBG only) groups. Participants in the Phase 1 SMBG Group will continue to Phase 2 (Continue SMBG Group) without any group re-assignment.

1. Download returned CGM device from SMBG Group participants upon receipt of the returned system. Store the CGM system for next blinded use by the participant
2. Obtain BGM data from both groups
3. Assess for any AEs
4. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
5. Administer PRO/surveys to CGM Group. The participant may complete PRO/surveys 1 week prior to Month 8 visit.
6. Obtain labs
   i. Central lab HbA1c
   ii. POC/local HbA1c
   iii. Non-HDL cholesterol (non-fasting Lipid panel)
7. Obtain height and weight (BMI)
8. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).
9. Re-randomize the CGM Group from Phase 1. Obtain randomization group assignment from study website and perform the following, per group designation:

   Discontinue CGM Group (use SMBG only)
   - A BGM account will be established and linked to the research site
   - Review study provided Tips for Success with SMBG sheet
   - Instruct participant to perform SMBG testing from 1- 3x daily with study provided meter. Testing should involve a minimum of once daily testing and includes some fasting and some post-prandial measurements

   Continue CGM Group
   - No changes from Phase 1. Participants will perform SMBG testing as needed

10. Study Clinician Discussion:
    i. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated. **Note:** The blinded CGM data obtained in the SMBG group will not be used by the research site staff and

will not be reviewed with the participant or sent to the community treating clinician.

ii. Review glucose targets.

iii. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.

iv. Review group-specific study provided Tips for Success sheet

v. Send a visit specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. Inform the community treating clinician of participant entering Phase 2 of the study. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made by only the community treating clinician, unless deemed clinically warranted by study clinician for safety purposes.

vi. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.

11. Provide ample supplies until next contact

12. Schedule next phone contact.

20.11. Phase 2-Phone/remote Contact- Month 11 (all 3 groups) (330 +/- 5 day window)

1. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.

2. Trouble shoot for any device issues, confirming participant can upload glucose data from CGM or BGM (or the device is setup to auto uploads).

3. Study Clinician Discussion:

   i. Use the study provided Guidance for Phone Contact & Documentation to guide these discussions.

   ii. If sufficient glucose data are available, encourage self-titration of basal insulin. Encourage lifestyle experimentation and modifications based on glucose data and patterns that are elucidated.

   iii. Review glucose targets.

   iv. CGM users may have alert settings and/or CLARITY push notifications adjusted at clinician or subject's discretion.

   v. Discuss with participant challenges and learnings from their glucose monitoring device and any changes or planned changes in their diabetes management.

   vi. Send a contact specific communication letter to the community treating clinician (copy to participant), together with the glucose data record (CGM data for CGM Group and SMBG data for the SMBG Group) and interpretation of the glucose data, such as if there are patterns of overnight or fasting hyperglycemia detected that may require basal adjustments. A letter template and diabetes guidelines for diabetes management are provided. Document date letters sent. **Note**: any therapy changes should occur outside the study and be made only by the community treating clinician, unless deemed clinically warranted by study clinician for safety purposes.

   vii. Encourage CGM users to share CGM data with followers. Document the number of followers on CRF.

4. Schedule next visit.

20.12. Phase 2-Pre-Month 14 Visit (Discontinue CGM and SMBG Groups only) (410 +/- 3 day window

This visit is scheduled approximately 10 days prior to Month 14 Visit.

1. Administer PRO/surveys prior to dispensing blinded CGM, to minimize confounding the responses in this study group. The participant may complete PRO/surveys 1 week prior to Pre-Month 14 visit.
2. Dispense blinded CGM devices for one blinded CGM wear period, with instructions for return of device to the clinical site. **Note:** A second sensor session may be warranted if device issues occur (i.e., adhesive or sensor failures), resulting in the session ending before Day 4 of wear.
3. Provide ample supplies until next visit
4. Schedule next visit.

20.13. Phase 2-Month 14 Visit & (all groups) (420 +/- 5 day window)

This visit concludes Phase 2 and participation in the study.

1. Download returned CGM device from both SMBG group participants upon receipt of the returned system.
2. Obtain BGM data from both groups
3. Assess for any AEs
4. Document any therapy changes (including any new/changing medications and visits to primary care physician) that have been made by the community treating clinician, as self-reported by the participant.
5. Administer PRO/surveys to Continued CGM Group. The participant may complete PRO/surveys 1 week prior to Month 14 visit.
6. Obtain labs
   i. Central lab HbA1c
   ii. POC/local HbA1c
   iii. Non-HDL cholesterol (non-fasting Lipid panel)
7. Obtain height and weight (BMI)
8. Study Clinician Discussion:
   i. Review blinded CGM data with participants in the SMBG groups and CGM data with the CGM Group.
   ii. Document the number of followers on CRF.
9. Participants may be offered their CGM systems with a month's supply of sensors. Document the number of participants who accept or decline on CRF.

Table 1. Schedule of Study Event

		Start of Run In period	Randomization	PHASE 1								PHASE 2		
STUDY DAY NUMBER -->		minus 10	0	14	30	60	90	120	180	230	240	330	410	420
Permitted Visit Windows -->		--	--	±4	± 5	± 5	± 5	± 5	± 5	± 3	± 5	± 5	± 3	± 5
	Line Item	Enrollment and Start of Run In period	End of Run-in and Day 0 Clinic Visit (Randomize)	Wk 2 Clinic Visit	M1 Clinic Visit	M2 Phone Contact	M3 Clinic Visit; *Plus 10 day Blinded Wear at M3 Visit for SMBG Group*	M4 Phone Contact	M6 Phone Contact	SMBG GRP: *Pre-Mon 8 Blinded Wear (10 days before M8 visit)*	M8 Clinic Visit (Randomize)	M11 Phone Contact	SMBG GRP: *Pre-Mon 14 Blinded Wear (10 days before M14 visit)*	M14 Final Clinic Visit
ALL SUBJECTS														
1	(1) Informed Consent, (2) Eligibility Criteria, (3) Demographics, (4) Payer, (5) Pregnancy test, (6) Socioeconomic, (7) Vital Signs, (8) Diabetes Education Session(s)	●												
2	Collect diabetes history	●	●	●	●	●	●	●	●		●	●		●
3	Height/Weight Assessment	●									●			●
4	Labs (1) POC/local A1C	●	●				●				●			●
5	Labs (2) Central Lab HbA1c		●				●				●			●
6	Labs (3) eGFR (acceptable if w/in 4 mon)	●												
7	Labs (4) Non HDL Chol		●								●			●
8	Labs (5) C-peptide (acceptable if w/in 6 mon)		●											
9	Blinded CGM Wear & Training	●												
10	Dispense Blue-tooth BGM/Install software	●												
11	Confirm completion of PROs/Surveys	●								●	●		●	●
12	Communication letter to treating community physician		●	●	●	●		●	●		●	●		●
13	Document therapy changes					●		●	●		●	●		●
14	Download BGM device						●				●			●
15	Return CGM system		●								●			
16	AE/Device Assessment		●	●	●		●				●			●
17	Device troubleshooting			●	●	●	●	●	●	●	●	●		
18	Ensure upload/review of glucose data/goals			●	●	●		●	●		●	●		●
19	CGM and BGM Tips for Success			●	●		●				●			
CGM GROUP SUBJECTS														
20	CLINIC VISITS/CONTACTS		●	●	●	●	●	●	●		●	●		●
21	(1) Dispense unblinded CGM device (2) Install/Set-up device APP on participant smart phone		●								●			
22	Encourage CGM users to share CGM data with followers & document number of followers		●	●	●	●		●	●		●	●		●
SMBG GROUP SUBJECTS														
23	CLINIC VISITS/CONTACTS		●	●	●	●	●	●	●	●	●	●	●	●
24	Dispense blinded CGM supplies						●			●			●	

Table 2. Questionnaire Details

CGM GROUP: Quality of Life and Other Surveys (between group differences)		**Screening**	**Phase 1**		**Phase 2**	
		Screening Visit 1 (Start Run-in)	Pre Month 8 (10 days before Month 8 visit) Blinded wear period	**Month 8 Clinic Visit**	Pre Month 14 (10 days before Month 14 visit) Blinded wear period	**Month 14 Clinic Visit**
1	Diabetes Distress Scale (DDS)	●		●		●
2	Glucose Monitoring Satisfaction Survey, (GMSS) - Type 2 Version	●		●		●
3	Hill-Bone Medication Adherence Scale	●		●		●
4	Clinician Communication Rating	●		●		●
5	Toobert's scale – SDSCA Diet and Exercise	●		●		●
6	Fear of Hypoglycemia, Worry & Behavior Subscales	●		●		●
7	SF-12 Health Survey	●		●		●
8	WHO-5 Well-Being Index	●		●		●
9	CGM Satisfaction Survey			●		●
10	Perceived Benefit Questionnaire			●		●
11	Subjective Numeracy Scale (SNS)	●				
12	Work Productivity and Activity Impairement (WPAI)	●		●		●

SMBG GROUP: Quality of Life and Other Surveys (between group differences)		**Screening**	**Phase 1**		**Phase 2**	
		Screening Visit 1 (Start Run-in)	Pre Month 8 (10 days before Month 8 visit) Blinded wear period	**Month 8 Clinic Visit**	Pre Month 14 (10 days before Month 14 visit) Blinded wear period	**Month 14 Clinic Visit**
1	Diabetes Distress Scale (DDS)	●	●		●	
2	Glucose Monitoring Satisfaction Survey, (GMSS) - Type 2 Version	●	●		●	
3	Hill-Bone Medication Adherence Scale	●	●		●	
4	Clinician Communication Rating	●	●		●	
5	Toobert's scale – SDSCA Diet and Exercise	●	●		●	
6	Fear of Hypoglycemia, Worry & Behavior Subscales	●	●		●	
7	SF-12 Health Survey	●	●		●	
8	WHO-5 Well-Being Index	●	●		●	
9	CGM Satisfaction Survey					
10	Perceived Benefit Questionnaire		●		●	
11	Subjective Numeracy Scale (SNS)	●				
12	Work Productivity and Activity Impairement (WPAI)	●	●		●	

21. Risks & Mitigation

21.1. CGM

The instructions for use includes the following use information to minimize risk to the user:

- Interpretation of the Dexcom CGM system results should be based on the glucose trends and several sequential readings over time. The Dexcom CGM device also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments.
- Failure to use the Dexcom CGM systems and its components according to the instructions for use and all indications, contraindications, warnings, precautions, and cautions may result in missing a severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) occurrence and/or making a treatment decision that may result in injury.
- Do not ignore symptoms of low or high glucose. If glucose alerts and readings do not match symptoms or expectations, a SMBG value should be obtained from a blood glucose meter to make diabetes treatment decisions or seek immediate medical attention.

Insertion of the sensors into the skin may result in pain, erythema, and/or edema at the insertion sites. Infection, excessive bleeding, or hematoma are also possible side effects of device use; however, the expected frequency of these events is low based on data obtained from similar devices and adverse event information from more than five previous Dexcom studies where the device was inserted from 12 hours to 15 days.

After removal of the sensors, participants may experience irritation due to the medical adhesive used to apply the sensor pod and any bandages that may be placed over the device. This reaction is self-limiting and should resolve within hours and not more than a week post-removal. Participants may experience some itching in the area during the healing process, which is normal.

Rarely, participants may develop an allergic reaction to one or more of the components of the sensor and/or transmitter. This is similar to allergies that can occur due to contact with medical tape.

Sensors may fracture or be retained in situ on rare occasions. In these rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation. In the event that signs and/or symptoms of infection or inflammation arise such as redness, swelling, and pain participants should consult with the investigator or prescribing physician for the best course of action. If there is no portion of the broken sensor wire fragment or retained sensor wire visible above the skin, attempts to remove it without medical guidance are not advised.

21.2. Hypoglycemia/Hyperglycemia

Treatment of diabetes is associated with increased risk of hypoglycemia. Hypoglycemia may be associated with reduced cognitive function, diaphoresis, tachycardia, coma, and seizure. These complications are an inherent risk of having diabetes. Participants will be trained on proper use of the device, which include the instructions listed above.

During the study instances of hypoglycemia will be captured as an AE, together with a severity rating, if requiring home treatment, assistance of a third party for treatment or involves seizure or loss of consciousness. Instances of severe hypoglycemia are anticipated to be low, due to the patient population in the study, that is, persons that are not intensively treated with insulin. However, any hypoglycemic event involving seizure or loss of consciousness will be captured as severe and potentially as a serious adverse event if it meets the definition of a SAE as defined in the protocol.

Instances of symptomatic hyperglycemia that are outside a confirmed diagnosis of diabetic ketoacidosis (DKA) will be captured as an AE if emergency evaluation or treatment is obtained from a health care provider.

Instances of severe hypoglycemia and DKA are anticipated to be low, due to the patient population in the study, that is, persons that are not intensively treated with insulin. Diabetic ketoacidosis is a serious complication of diabetes that occurs when the liver produces high levels of ketones, which are an acid. Diabetic ketoacidosis develops when there is insulin deficiency; in response, the body switches to burning fatty acids and producing acidic ketone bodies that cause most of the symptoms and complications. Vomiting, dehydration, tachypnea, confusion and occasionally coma are symptoms. DKA will be captured as a serious adverse event if confirmed, treated and meets definition of an SAE.

22. Adverse Events

For the purpose of this protocol, AEs will be captured on the AE CRF form if causality is related to the study, disease or device.

At all study visits, study staff will determine if any device, disease or study-related adverse events (AEs) have occurred. Disease related events that are *chronic in nature and occur as part of the progression of the diabetes disease state* (i.e. diagnoses of retinopathy, nephropathy, and neuropathy) *will not* be captured as adverse events in this study. Instances of hypo- or hyperglycemia will be captured as AEs if event meets details, as stated in Section 21.2.

All study, disease or device-related AEs will be monitored until adequately resolved or stable.

22.1. Adverse Events (AE)

An AE is any clinically significant undesirable experience (sign, symptom, illness, or other medical event) meeting the causality definition above that appears or worsens in a participant during a clinical study. A clinically significant event is any event (sign, symptom, lab/imaging abnormality, or diagnosis) that is noteworthy enough to merit documentation in standard medical records (e.g. history and physical, progress notes, clinic visit notes, etc.). Other non-clinically significant events (e.g. colds, minor headaches, etc.) *may* be documented on the comments CRF. Mild hypoglycemia is expected in persons with diabetes using insulin and are typically self-limiting in nature; thus this will not be captured as an AE.

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

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

22.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening; (substantial risk of dying at the time of the adverse event or suspicion that continued use of the device would result in a participant's death

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Requires medical or surgical intervention to prevent permanent impairment or damage.

Exceptions to the SAE definition will include the following:

- Elective surgery
- A planned hospitalization for pre-existing condition, without a serious deterioration in health

Any SAE, including death, due to any cause (related or unrelated to the device), that may occur during a clinical study must be reported immediately (within 1 working day of learning of the event). Details of the SAE submitted via eCRF will result in an automatic email generated and forwarded to the Sponsor. The Sponsor contact for SAE review:

Dexcom Clinical Affairs personnel will document SAE details and assessment by Clinical Affairs management in a timely manner.

22.3. Severity of Adverse Events

The following definitions may be used to rate severity of AEs:

Mild

Awareness of signs or symptoms, but easily tolerated; are of minor irritant type that is outside the norm for the disease state or subject; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient. Mild hypoglycemia is expected in diabetes and will not be captured as an AE. **Example:** hypoglycemia with at home treatment.

Moderate

Discomfort severe enough to cause interference with usual activities, requiring treatment due to cognitive impairment, by family member or emergency personnel

Example: hypoglycemia with inability to self-treat, requiring third party assistance for treatment and/or an emergency room visit.

Severe

Incapacitating, causing inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical evaluation and/or treatment at a health care facility

Example: hypoglycemia with loss of consciousness or seizure involvement

22.4. Relationship of Adverse Event to Study, Disease or Device

The investigator will categorize the relationship of the event to the study, disease, or study device as follows:

Not related

AE is due to an underlying disease state or concomitant medication or therapy not related to the device, disease or study.

Probably Not Related

AE has minimum or no temporal relationship to the study device, disease or study participation and/or a more likely alternative etiology exists.

Possibly Related

AE has a strong temporal relationship to the study device, disease or study procedures and alternative etiology is equally or less likely compared to the potential relationship to the device, disease or study.

Probably Related

AE has a strong temporal relationship to the study device, disease or study and another etiology is unlikely.

Related

AE has a strong temporal relationship to the study device, study procedures or disease and another etiology does not exist.

22.5. Anticipated Device-related Adverse Events

The following events have been identified as possible device-related adverse events of **sensor insertion and wear**:

- Excessive pain or discomfort from either system deployment or during wear period (8 or greater on a 10-point Likert scale)
- Excessive bleeding, defined as requires removal of the device to stop bleeding
- Hematoma, defined as induration at the sensor insertion location (ecchymosis is a known consequence of needle skin puncture or pressure from sensor pod and will not be captured as an AE)
- Edema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Erythema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- Local infection, defined as presence of pus at either sensor wire or sensor pod site
- Sensor or introducer needle fracture during insertion/wear/removal

Information regarding device-related AEs that occur during the study will be entered into appropriate CRFs. Such information will include, at a minimum:

- Date of event
- Severity
- Outcome
- Resolution of event

22.6. Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is not expected to occur. An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, the informed consent document, other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of participants.

During the review of a reported SAE, if Clinical Affairs management with the Investigator input determines the severity or extent of the event was not cited in this protocol or associated protocol materials, and the event was classified as, 'possibly related' to the device, the event will be documented as an UADE. If the event is classified as an UADE, the Investigator must notify the IRB and Dexcom will notify the FDA within ten (10) working days of the original SAE notification.

If determined that the UADE presents an unreasonable risk to participants, Dexcom will terminate all investigations or parts of investigations presenting that risk as soon as possible, but not later than 5 working days after such determination is made and not later than 15 working days after Dexcom first receives notice of the original SAE. Dexcom will not resume a terminated study without IRB and FDA approval.

22.7. Device Issues & MDR Reportable Events/MDR Reporting

A device issue, whether related to a complaint or not, is an allegation from the participant or study personnel regarding an indication of the failure of a device to meet user expectations for quality or performance specifications. Device issues will be recorded onto appropriate CRFs by site personnel. Dexcom personnel will process device issues, regardless of any associated adverse event details, per Dexcom's Complaint Handling procedures for any Dexcom FDA approved devices used in the study. For purposes of this protocol, the CGM devices are currently marketed. Therefore, the sponsor will follow the required reporting regulations if a MDR reportable event occurs, according to Sponsor SOP and FDA guidelines. (US MDR Reporting; Code of Federal Regulations Title 21 Part 803) and Dexcom Quality Assurance procedures related to complaint handling.

MDR reportable events are events that manufacturers become aware of that reasonably suggest one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device would likely cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.3).

23. Ethical Considerations

23.1. Informed Consent

Informed consent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50. Participants will be asked to sign state specific forms, such as Subject's Bill of Rights, or equivalent, (if applicable) and HIPAA authorization form, if not included in the site's consent template. Participants will be provided the opportunity to review these documents prior to coming to the clinical site. The Investigator or designee will explain the purpose and duration of the study, the study procedures and participant requirements, and the potential risks and benefits. Study staff will attempt to answer all questions the participant may have. Consenting process will be

documented in the participant's source documents. A copy of the consent will be provided to the participant.

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the 1983 amendment per FDA's Guidance for Industry: Acceptance of Foreign Clinical Studies written in March, 2001.

Participants will receive a stipend for being in the study and offered the study-assigned meter following completion of their participation in the study.

23.2. Institutional Review Board

The protocol, informed consent document, and participant training materials for this study will be reviewed and approved by a duly constituted Institutional Review Board (IRB) before participants are screened.

The Investigator will ensure that all aspects of the IRB review are conducted in accordance with current institutional, local, and national regulations. An IRB approval letter will be provided to the Sponsor prior to study initiation. Protocol amendments must adhere to the same requirements as the original protocol. The Investigator will submit all IRB-required reports and updates, including any continuing review and/or final closeout reports. The Investigator will inform the IRB of any reportable AEs as per the IRB reporting rules.

24. Device Accountability

The Investigator(s) will store devices in a secure location at the clinical site. An accurate and current accounting of the dispensing for the Dexcom and other device components will be maintained by a member of the study site staff on the "Device Accountability Log". All used and unused devices must be returned to the Dexcom Clinical Affairs department (or accounted for if lost) upon completion of enrollment or upon request of the Sponsor.

25. Monitoring

Monitoring will be conducted by trained and experienced Clinical Research Associates (CRAs) in accordance with Dexcom's standard operating procedures. CRAs will evaluate study conduct and documentation on an ongoing basis. Assessment of site performance will be reviewed with Clinical Affairs management to determine the level of monitoring required. All informed consent documents will be source verified along with key data fields related to safety and performance indicators. All CRF data will be collected via the EDC system designated for the study for analysis. A risk-based monitoring plan will be developed consistent with the Food and Drug Administration (FDA) Guidance for Industry: Oversight of Clinical Investigations—A Risk-based Approach to Monitoring (August 2013). This approach focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study. Monitoring is separated into Central (remote) monitoring and On-Site monitoring (site visits). Considerable focus is placed on real-time centralized monitoring methods.

26. Study Termination

Participation in the clinical study will be terminated for each participant following the last visit or when all AEs have been resolved or considered ongoing but stable. Prior to this time, participants may voluntarily withdraw at any point in the study or the Investigator and/or Sponsor may determine that it is in the best interest of the participant to be terminated from the study. Reasons for withdrawal of participant from the study include, but are not limited, to the following:

a) In the opinion of the Investigator, the participant's health or safety would be compromised by continuing in the study
b) In the opinion of the Investigator, it is in the participant's best interest to discontinue participation in the study
c) During the study, (female) participant becomes pregnant

However, discontinuation of the study intervention (CGM) does not equate with discontinuation from the study and every effort will be made to retain participants in the study for the primary outcome assessment, even if CGM is discontinued.

The clinical study in its entirety will be considered complete upon receipt of reports from study monitoring activities, completion of site closeout visits, and issuance of a clinical study report. The clinical study report will include all safety and efficacy data.

27. Investigator Responsibilities

The Investigator's signature(s) on this protocol confirms that the Investigator is familiar with all sections of the protocol and agrees to conduct this study in accordance with the provisions of the protocol and applicable regulations. The Investigator(s) must sign this protocol prior to commencement of any study-related activities (e.g. screening).

The Investigator(s) are responsible for protecting the rights, safety, and welfare of participants under their care. The Investigator(s) are also responsible for obtaining IRB approval prior to study start and the written informed consent of each participant before participation in this study. The informed consent must comply with FDA regulations (21 CFR 50) and be approved by the IRB.

The Investigator(s) are responsible for ensuring completion of the CRFs per the study timelines discussed in the site initiation visit and subsequent monitoring visits.

Dexcom and/or the IRB retain the right to disqualify an Investigational Site and remove all study materials at any time. Specific instances, which may precipitate clinical site disqualification, include but are not limited to:

a) Unsatisfactory participant enrollment with regard to quality and quantity.
b) Persistent non-compliance related to protocol procedures by the Investigator/Investigational Center.
c) Inaccurate, incomplete, and/or untimely data recording on a recurrent basis.
d) The incidence and/or severity of adverse experiences in this or other studies indicating inadequate oversight
e) Unsatisfactory accountability of study devices.

28. Sponsor Responsibilities

The Sponsor is responsible for selecting qualified Investigators and providing them with the information needed to properly conduct the study. The Sponsor will ensure proper monitoring of the study and that IRB approval has been obtained prior to the Investigator commencing study-related activities. The Sponsor is also responsible for ensuring that the reviewing IRB(s) and FDA, if applicable, are promptly informed of significant new information.

29. Confidentiality of Records

All records and documents pertaining to this study will be retained for a period of no less than 2 years by Dexcom, Inc. and will be available for inspection by FDA or other regulatory agencies at any time. All records containing personal identification or information that identifies a study participant will be handled confidentially within the law.

These records will be coded and kept in locked files. No individual identities will be used in any reports or publications resulting from this study.

Neither the site nor participants will disclose, share, or use any information gathered during the course of the clinical study. All information about the study, including the study product and study procedures, is confidential. Any publication about the products or the study by print or electronic format (e.g. blogging) is strictly prohibited.

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Change Matrix V003 to V004

	Protocol PTL-902822 Change Matrix **V004 – 03August2018**			
	Affected Section(s)	**Page(s)**	**Description of Revision**	**Justification for Revision**
1	Global Change	All	Revision 003 to 004	Updates require a revision change for consistency and clarification
2	Synopsis and Inclusion Criteria	vi 4	Defining "Naïve to RT-CGM" as no personal RT-CGM use within the last 3 months	Sponsor discretion & clarification
3	12. Study Design	8	Clarifying that CGM devices will be offered to participants at the end of the study	Sponsor discretion & clarification
4	17. PRO Measurements & Surveys	13	Additional PRO related to measuring work productivity and activity impairments	Sponsor discretion
5	20.12 Phase 2 Pre-Month 14 Visit Procedures	27	Correcting that before Day 4, if device issue noted, participant can have additional time allotted to collect data for blinded wear	Sponsor discretion & clarification
6	Table 2. Questionnaire Details	29	Additional PRO – WPAI	Sponsor discretion
7	22. Adverse Events	31	Clarifying that Mild Hypoglycemic events will not be captured as an adverse event – these events are expected in persons with diabetes using insulin	Sponsor discretion
8	22.2. Serious Adverse Events (SAE)	32	Clarifying what events do not qualify as an SAE	Sponsor discretion & clarification
9	22.2. Severity of Adverse Events	32	Clarifying the Mild, and Moderate severity levels for AEs	Sponsor discretion & clarification

Change Matrix V003 to V004

10	22.5 Anticipated Device-related Adverse Events	33	Defining “Hematoma” as indurations at the sensor location	Sponsor clarification
11	31. References	37	Removal of reference not used in protocol document. Additional reference for new PRO #12 - WPAI	Sponsor discretion & clarification

Change Matrix V004 to V005

	Protocol PTL-902822 Change Matrix **V005 – 03December2018**			
	Affected Section(s)	**Page(s)**	**Description of Revision**	**Justification for Revision**
1.	Global Change	All	Revision 004 to 005	Updates require a revision change for consistency and clarification
2.	Front Page	0	Updated study contact information	Sponsor clarification
3.	Study Population Study Overview Study Design Clinical Research Sites	vi & 4 vii 6 9	Clarification on types of sites that will be recruited for the study	Sponsor discretion & clarification
4.	Synopsis Inclusion Criteria Exclusion Criteria	vi 4 5	• Additional Inclusion criterion – *"Comprehends written and spoken English"* • Change of A1c lower bound from 8.0% to 7.8% • Removal of the need to have access to a computer for data transfer outside clinic • Removal of references to examples of diabetes specialists • Clarifying definition --- using weight loss medications as an exclusion criterion	Sponsor discretion & clarification
5.	12. Study Design	8	Adding a space between "study" and "will"	Sponsor discretion & clarification
6.	Duration of Study Participation	9	Added "the"	Grammar
7.	22.2 Serious Adverse Event (SAE)	32	Removal of a "."	Sponsor discretion & clarification
8.	31 References	38	Moved to next page	Sponsor discretion & clarification

Continuous Glucose MOnitoring in T2D Basal InsuLin UsErs
The MOBILE Study

Statistical Analysis Plan

Version: 1.0

Version Date: 05/25/2018

Author: Tonya Riddlesworth

Protocol Version: 3.0

Note: The table shells are included in a separate document.

Revision History

The following table outlines changes made to the Statistical Analysis Plan.

Version Number	Author	Approver	Effective Date	Study Stage	Revision Description
1.0	Tonya Riddlesworth	Craig Kollman	05/25/2018	Enrollment Not Yet Started	Original Version

Signatures:

Role	Affiliation	Signature
Author	Jaeb Center for Health Research	
Senior Statistician	Jaeb Center for Health Research	
Chief Investigator/ Clinical Lead	DexCom, Inc.	

There are two phases to this protocol. Most of the details in this Statistical Analysis Plan apply to both phases but some sections give separate details for each phase.

1. Introduction

Use of real-time continuous glucose monitoring (RT-CGM) has been shown to improve glycemic control with a reduced risk of hypoglycemia in patients with Type 1 Diabetes Mellitus (T1DM) and patients with Type 2 Diabetes Mellitus (T2DM) on intensive insulin therapy. Only a few studies have studied RT-CGM's impact on glycemic control in T2DM with use of basal insulin, prandial insulin and oral anti-diabetic medications. Because once-daily basal insulin is the first step in initiating insulin therapy in T2DM, the need to evaluate the utility of RT-CGM with less intensive insulin regimens is warranted.

The study population consists of adult (>30 years of age) T2DM patients followed by a primary care physician for their diabetes, who are currently on basal insulin therapy with or without oral anti-diabetic therapy and/or GLP-1 analogue injections, sub-optimally controlled.

This is a prospective, randomized clinical trial with 2 phases and parallel arms in each phase.
Phase 1 will use a 2:1 randomization scheme to either the CGM Group (using CGM to inform diabetes management decisions) or the SMBG Group (using a blood glucose meter to inform diabetes management decisions).
For Phase 2, participants from the Phase 1 CGM Group will be re-randomized 1:1 to continue CGM use (Continue CGM Group) or to use SMBG (Discontinue CGM Group).

1.1 Randomization

Phase 1: N=207
For Phase 1, a 2:1 randomization scheme will be utilized (CGM:SMBG). Randomization will be stratified by site using a permuted blocks design. Randomization to group assignment will be obtained from a study website after all enrollment data have been entered and eligibility verified.

Phase 2: N= approximately 74
For Phase 2, a 1:1 randomization scheme will be utilized to re-randomize the Phase 1 CGM Group (Continue CGM:Discontinue CGM). All subjects from the Phase 1 SMBG group will continue in the study without re-randomization. The goal is for up to 92 participants from the Phase 1 CGM Group to enter Phase 2 (with approximately 74 completing Phase 2). There are no stratification factors for the Phase 2 randomization.

1.2 Timing of Final Analyses:

The Phase 1 outcomes will be analyzed after the last subject completes the Month 8 visit and all available data for the Phase 1 endpoints have been collected and cleaned (anticipated May 2019). The Phase 2 outcomes will be analyzed after the last Phase 2 subject completes the Month 14 visit (which is 6 months after the 2nd randomization) and all available data for the Phase 2 endpoints have been collected and cleaned (anticipated November 2019).

2. Statistical Hypotheses

Phase 1 Hypotheses

- Null hypothesis: There is no difference in the mean change in central lab-measured hemoglobin A1c (HbA1c) over 8 months between patients making CGM based decisions about their diabetes and patients making blood glucose monitoring based decisions
- Alternate hypothesis: Patients making CGM based decisions about their diabetes have a different mean change in central lab-measured HbA1c over patients making blood glucose monitoring based decisions

Phase 2 Hypotheses

- Null hypothesis: There is no difference in the mean change in CGM-measured time in the target range (70-180 mg/dL) over 6 months between patients who continue making CGM based decisions about their diabetes (after the initial 8 months) and patients who switch from making CGM based decisions to making blood glucose monitoring based decisions
- Alternate hypothesis: Patients who switch from making CGM based decisions to making blood glucose monitoring based decisions about their diabetes have a different mean CGM-measured time in the target range over patients who continue making CGM based decisions (after the initial 8 months)

3. Sample Size

The Phase 1 sample size is formally powered and the Phase 2 sample size is dependent on the number in the Phase 1 CGM Group who continue into Phase 2.

For Phase 1, the DIaMonD T2D RCT data were used to estimate the mean and standard deviation for HbA1c at baseline and 6 months. Data were taken from 121 participants with T2D who met the current protocol's eligibility criteria for HbA1c (8.0-11.5%). Based on an effective standard deviation of 0.80% (adjusting for baseline HbA1c as a covariate) and a true treatment effect of 0.4%, the total sample size for this study is estimated to be 165 to have at least 85% power with alpha=0.05 and 2:1 randomization. However, in order to account for a 20% dropout rate, a total sample size of 207 was selected (138 for the CGM Group and 69 for the SMBG Group) with up to 300 enrolled into screening.

For Phase 2, the DIaMonD Phase 2 RCT data (which included only T1D participants) were used to estimate the mean and standard deviation for the percent time in the target range (70-180 mg/dL) at 6 and 12 months. Data were taken from 38 participants in the CGM+MDI Group. Assuming 138 subjects were randomized to the current protocol's Phase 1 CGM Group and a 20% dropout rate, we expect at least 74 participants to enter and complete Phase 2. Based on an effective standard deviation at 12 months of 7% (adjusting for 6-month time in range as a covariate) and a treatment effect of 5%, there will be 85% power to detect a difference in the time in range between the Continue CGM and the Discontinue CGM groups with alpha=0.05 and 1:1 randomization.

4. Outcome Measures

4.1 Primary Efficacy Endpoints

4.1.1 Phase 1 Primary Endpoint

Change in central lab-measured HbA1c from baseline to Month 8

4.1.2 Phase 2 Primary Endpoint

Change in time in target range (70-180 mg/dL) from Month 8 to Month 14

Calculation of Time in Target Range at Months 8 and 14

The time in target range will be calculated over 24 hours at Month 8 (baseline for Phase 2) and Month 14 as follows:

- Baseline (Month 8): The time in target range will be calculated based on CGM data obtained in the 10 days prior to the Month 8 visit. If a subject has <96 hours of data available in the 10 days prior to the Month 8 visit, then an additional day will be added (up to 2 weeks) to try to obtain at least 96 hours of data.
- Followup (Month 14):
  - Discontinue CGM Group: For approximately 10 days prior to the Month 14 visit, each subject in the Discontinue CGM Group will wear a blinded CGM to obtain data to calculate glycemic variables. All blinded CGM data for this group will be used to calculate time in the target range.
  - Continue CGM Group: To get a comparable sample of data from the Continue CGM Group (who are being asked to wear CGM continually during the study), 10 days of data immediately prior to the Month 14 visit will also be used. If a subject misses the Month 14 visit then the 10 days of data immediately prior to their last visit will be used instead. If a subject has <96 hours of CGM data available in the 10 days used in the calculation, then an additional day will be added (up to 2 weeks) to try to obtain at least 96 hours of data.

4.2 Secondary Efficacy Endpoints

4.2.1 Phase 1 Secondary Endpoints

Between group differences (CGM and SMBG) from baseline to Month 8

- Change in CGM time in target range 70-180 mg/dL
- Percent decreasing HbA1c by ≥0.5% (absolute)
- Percent adding or removing diabetes medications (starting or stopping medication)
- Change in HbA1c based on their baseline HbA1c (restricted to participants with baseline HbA1c ≥8.5%, ≥9.0%, ≥9.5%, ≥10.0%)*
- Change in CGM time-hyperglycemic, defined as >250 mg/dL
- Change in CGM glucose variability measured by the coefficient of variation
- Change in CGM time-hypoglycemic, defined as <70 mg/dL

*Only performed if primary analysis is significant and each nested group is only tested if the superset is significant.

4.2.2 Phase 2 Secondary Endpoints

Between group differences for the Discontinue CGM Group (use SMBG only) and the Continue CGM Group from Month 8 to Month 14

Between group differences for the Continue CGM and the Continue SMBG groups from baseline to Month 14

- Change in HbA1c (central lab)
- Change in CGM time-hyperglycemic, defined as >250 mg/dL

- Percent decreasing HbA1c by ≥0.5% (absolute)
- Percent adding or removing diabetes medications (starting or stopping medication)
- Change in CGM glucose variability measured by the coefficient of variation
- Change in CGM time-hypoglycemic, defined as <70 mg/dL

4.3 Other Endpoints

Exploratory analyses will be performed on the endpoints listed below to better understand the effect of CGM on this population. The endpoints are the same for Phase 1 and Phase 2 and will only be listed once.

For Phase 1, the endpoints will be evaluated for between group differences in the CGM and SMBG groups from baseline to Month 8.

For Phase 2, the endpoints will be evaluated for between group differences for the Discontinue CGM Group (use SMBG only) and the Continue CGM Group from Month 8 to Month 14 as well as for the Continue CGM and the Continue SMBG groups from baseline to Month 14.

4.3.1 Other HbA1c Endpoints

- Percent reaching target HbA1c (<7.0%)
- Percent with HbA1c <7.5%
- Percent decreasing HbA1c by ≥1.0% (absolute) *
- Percent decreasing HbA1c by ≥1.0% (absolute) OR reaching target HbA1c (<7.0%) *
- Percent decreasing HbA1c by ≥10% (relative) *

* For Phase 2, these endpoints will only be evaluated for the Continue CGM and the Continue SMBG groups from baseline to Month 14.

4.3.2 Other CGM Endpoints

- Change in time <54 mg/dL
- Change in the rate of CGM-measured hypoglycemic events
    - A CGM-measured hypoglycemic event is defined as at least 2 sensor values <54 mg/dL that are 15 or more minutes apart plus no intervening values >54 mg/dL; at least 2 sensor values >70 mg/dL that are 30 or more minutes apart with no intervening values ≤70 mg/dL, are required to define the end of an event, at which point the study participant becomes eligible for a new event.
- Change in time >180 mg/dL
- Change in time >300 mg/dL
- Area under curve 180 mg/dL
- Change in mean glucose from CGM

4.3.3 CGM Endpoints by Time of Day

4.3.4 Questionnaires/Surveys

- Diabetes Distress Scale (DDS) – Change in mean score and 4 subscales
- Glucose Monitoring Satisfaction Survey (GMSS) – Change in mean score and 4 subscales
- Modified Hill-Bone Medication Adherence Scale – Change in total score

- Clinician Communication Rating Scale – Change in mean score on 1 subscale
- Modified Toobert's Scale – Change in mean score
- Fear of Hypoglycemia Survey – Change in mean score
- SF12 Health Survey – Change in Physical Health Composite score and Mental Health Composite score
- WHO-5 Well-Being Index – Change in total score
- CGM Satisfaction Survey (given only to the CGM groups at followup so no comparison between groups)
- Perceived Benefit Questionnaire (given at followup only) – Each item will be summarized individually; no total or mean score
- Subjective Numeracy Scale (given at study entry only so no comparison between groups)

4.3.5 Miscellaneous

- Change in SMBG frequency (self-reported and download)
- Number of visits to primary care physician for glucose management (self-reported)
- Change in total daily insulin units per kg
- Change in basal units per kg
- Addition of at least one prandial insulin
- Addition of at least one GLP-1 analog or SGLT2 inhibitor
- Change in body weight
- Change in BMI
- Change in blood pressure
- Change in non-HDL cholesterol

4.4 Calculation of CGM Metrics

Each of the CGM metrics will be calculated over 24 hours. For the Time of Day analysis, all CGM metrics will be calculated separately for sensor values during the daytime (6:00 AM – <midnight) and for nighttime (midnight – <6:00 AM).

For Phase 2, calculation of the CGM metrics will be similar to what was described for the Phase 2 primary analysis in Section 4.1.2.

For Phase 1, CGM metrics will be calculated separately at baseline and Month 8 as follows:

- Baseline: CGM metrics will be calculated based on all CGM data obtained prior to randomization. Note that only subjects who used CGM on at least 7 of the previous 10 days are eligible to be randomized.
- Month 8:
  - SMBG Group: For approximately 10 days after the Month 3 visit and prior to the Month 8 visit, each subject in the SMBG Group will wear a blinded CGM to obtain data to calculate glycemic variables. All blinded CGM data for this group will be used in the analysis for Phase 1 CGM metrics.
  - CGM Group: To get a comparable sample of data from the CGM Group (who are being asked to wear CGM continually during the study), 10 days of data immediately after the

Month 3 visit and prior to the Month 8 visit will also be used. If a subject misses the Month 3 visit but continues in the study then their Month 3 target date will be used in place of the Month 3 visit date. If they miss the Month 3 visit due to being dropped from the study prior to that visit then the last 10 days of data will be used instead and no additional data for Month 8 will be added. If a subject misses the Month 8 visit then the last 10 days of data will be used instead. If a subject has <96 hours of CGM data available in the 10 days used in the calculation, then an additional day will be added (up to 2 weeks) to try to obtain at least 96 hours of data. For both groups, the data will be pooled across Months 3 and 8 to calculate the glycemic metrics.

4.5 Timing of Outcome Assessments and Out of Window Visits:

The schedule of study visits is given in the protocol. The following table summarizes the expected timing of the 3-, 8-, and 14-month visits as well as when a visit will be considered "missed" and outcomes from that visit will be excluded from the analysis. Note that the analysis windows below apply to all outcomes other than CGM and SMBG metrics from downloaded data.

	Target Date (# days post-randomization)	Window Specified in the Protocol	Window to be Included in Analysis
3-month visit	90 days	+/- 5 days	+/- 30 days
8-month visit	240 days	+/- 5 days	+/- 30 days
14-month visit	520 days	+/- 5 days	+/- 30 days

5. Analysis Cohorts

- All randomized participants will be analyzed for the Intention-to-Treat (ITT) Analysis.
- Safety outcomes will be reported for all enrolled participants, irrespective of whether the study was completed.
- A per-protocol analysis of the primary outcome will be conducted in each phase separately. This analysis will be restricted to participants who satisfy the following criteria (assuming this results in at least 10% of the subjects being excluded):
    - Adherence: Subjects in the SMBG Group performing SMBG on average a minimum of 1 time per day based on self-report over the full 8 months (6 months for Phase 2) and subjects in the CGM Group using CGM on at least 70% of days over the full 8 months (6 months for Phase 2)
    - Final visit: Subjects who complete the final study visit (Month 8 for Phase 1 and Month 14 for Phase 2) within ±30 days of the target date
    - Exclusion: Subjects in the SMBG Group who used an unblinded CGM at any point during the study phase will be excluded
    - Exclusion: Subjects in either group whose last CGM reading is more than 30 days before the final study visit (Month 8 for Phase 1 and Month 14 for Phase 2) will be excluded

6. Statistical Methods

6.1 General Approach

All covariates obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that the covariate does not have a linear relationship with the dependent variable. In such a case, categorization and/or transformations will be explored. All p-values will be two-sided and all confidence intervals will be two-sided.

6.2 Analysis of the Primary Efficacy Endpoint for Phase 1

Summary statistics for HbA1c (from central lab) appropriate to the distribution will be calculated separately by treatment group. The method of direct likelihood[1] will be used by fitting a longitudinal mixed effects linear regression model including HbA1c values measured at baseline, 3 months and 8 months. All subjects will be included in this model even if the 3-month and/or 8-month HbA1c values are unavailable. The model will include a term for treatment arm, but the two arms will be forced to have the same predicted value at baseline (due to randomization). This is equivalent to adjusting for baseline as a covariate while allowing for missing values. The model will adjust for clinical site as a random effect and include the local HbA1c as an auxiliary variable in case any lab HbA1c values are missing. Separate treatment effects will be estimated at 3 and 8 months (treatment by time interaction) and inference will focus on the estimate at 8 months, which is the primary outcome. A risk-adjusted point-estimate, 95% confidence interval and p-value will reported for the treatment arm difference at 8 months.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation, robust regression or non-parametric methods will be used instead.

6.2.1 Missing HbA1c Data for the Primary Efficacy Endpoint for Phase 1

It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. Our goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used. Different techniques (summarized below) will therefore be utilized to determine whether they reach similar conclusions:

- Primary Analysis: Missing HbA1c values will be handled using direct likelihood as described above.
- Sensitivity Analyses: Analyses will also be conducted using the following methods to handle missing HbA1c values:
  - Rubin's multiple imputation[2]
  - Available cases only

For the sensitivity analyses, a mixed effects linear regression model will be used with the 8-month central lab HbA1c as the outcome and will include fixed effects for the baseline central lab and random effects for the clinical site.

6.2.2 Sensitivity Analysis on Data-Driven Covariates for Phase 1

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. The presence of confounding will be evaluated as a sensitivity analysis by adjusting for covariates potentially associated with HbA1c for which there is an imbalance between groups. Whether a factor is imbalanced for the treatment arms will be determined by clinical judgment and will not be based on a p-value.

6.3 Analysis of the Primary Efficacy Endpoint for Phase 2

Summary statistics for the time in target range appropriate to the distribution will be calculated separately by treatment group. A mixed effects linear regression model will be used to compare the change in time in target range among the two treatment groups. All subjects randomized to Phase 2 will be included in this model regardless of if they dropped out of the study. The model will adjust for baseline time in target range as fixed effects and include random effects for clinical site. A risk adjusted difference and 95% confidence interval will be reported based on the least squares mean from this model.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead.

6.3.1 Missing CGM Data for the Primary Efficacy Endpoint for Phase 2

There will be no minimum requirement of CGM data to be included in the analyses and no imputation of CGM data.

6.3.2 Sensitivity Analysis on Data-Driven Covariates for Phase 2

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. The presence of confounding will be evaluated as a sensitivity analysis by adjusting for covariates potentially associated with time in target range for which there is an imbalance between groups. Whether a factor is imbalanced for the treatment arms will be determined by clinical judgment and will not be based on a p-value.

6.4 Analysis of the Secondary Efficacy Endpoints and Other Endpoints

For continuous variables, summary statistics appropriate to the distribution will be calculated separately by treatment group. For discrete variables, number and % will be calculated separately by treatment group.

All the binary measures will be compared between treatment groups using a logistic regression model and all the continuous measures will be compared using a linear regression model. Any model with some form of HbA1c as the dependent variable will adjust for baseline HbA1c as a fixed effect and include random effects for clinical site. All other models will adjust for the baseline value as a fixed effect and include random effects for clinical site. In addition to these factors, the model for body weight will also adjust for age and gender and the models for blood pressure and HDL cholesterol will adjust for age, gender and baseline BMI.

For the continuous measures, residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead. If the distribution is approximately normal then the adjusted mean difference and confidence interval will be reported.

For the binary measures, the risk-adjusted difference in percentages and the confidence interval will be reported. The adjusted difference in percentages will be calculated as in Kleinman and Norton[3] and the confidence interval will be calculated using a bootstrap.

6.4.1 CGM Analysis by Time of Day

For the CGM endpoints, the analysis will parallel what was described for the 24h analysis with the inclusion of a treatment by time of day interaction. The p-value for the interaction term will be reported. These analyses will be conducted to determine whether a similar trend to the overall treatment effect is seen in the different times of day.

The study is not expected to have sufficient statistical power for definitive conclusions in the CGM analyses by time of day, and statistical power will be low to formally assess a treatment by time-of-day interaction. Interpretation of the analyses by time of day will depend on whether the overall analysis demonstrates a significant treatment effect. In the absence of any significant treatment effects in the overall analyses, assessment of secondary analyses by time of day will be considered exploratory and used to suggest hypotheses for further investigation in future studies.

6.4.2 Missing Data for Secondary Efficacy Endpoints and Other Endpoints

Only participants with outcome data at baseline and follow-up will be included in the analysis (i.e. available cases only). For the CGM metrics and SMBG according to download, there will be no minimum requirement of data to be included in the analyses and no imputation of data. For the questionnaire outcomes, mean scores will be considered missing if <75% of the questions are answered and total scores will be considered missing if at least one question is left unanswered.

6.4.3 Details for Questionnaire Scoring

Mean scores will be calculated for the following questionnaires:

- Diabetes Distress Scale
  - Emotional Burden Subscale
  - Physician-related Distress Subscale
  - Regimen-related Distress Subscale
  - Interpersonal Distress Subscale
- Glucose Monitoring Satisfaction Survey
  - Openness Subscale
  - Emotional Burden Subscale
  - Behavioral Subscale
  - Worthwhileness Subscale
- Fear of Hypoglycemia Survey
- Modified Toobert's Scale
- CGM Satisfaction Survey
  - Benefits Subscale
  - Lack of Hassles Subscale
- Subjective Numeracy Scale
  - Ability Subscale
  - Preference Subscale

Total scores will be calculated for the following questionnaires:

- Hill-Bone Medication Adherence Scale
- WHO-5 Well-Being Index

Two composite scores (Physical Health and Mental Health) will be calculated for the SF-12 Survey based on the survey's scoring manual[6]. A mean score for the Overall Communication subscale will be calculated for the Clinician Communication Rating Scale[7]. No overall score will be given for the Perceived Benefit Questionnaire. This is an un-validated questionnaire and each question will be summarized individually.

Missing Data when Calculating Mean Scores

According to the Glucose Monitoring Satisfaction Survey scoring manual, if less than 75% of the data is available, the score for that scale or subscale should be counted as missing as it may not be a true reflection of the participants' behaviors and/or worries. The scoring manuals for the remaining questionnaires for calculating the mean score did not specify a minimum amount of data. However, we will apply the 75% rule to all the mean scales and subscales.

Missing Data when Calculating Total Scores

Total scores will only be calculated if all the questions are answered (i.e. no missing data). If any one of the questions is left blank, then the total score will be missing.

7. Safety Analyses

For both phases, all adverse events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. In addition, the following outcomes will be analyzed when the number of events is sufficient for a meaningful analysis and the analysis methods are described below:

1. Number of events per person (SH and DKA, separately)
2. Percentage of participants with at least one event (SH and DKA, separately)
3. Kaplan-Meier rate (SH and DKA, separately)
4. Incidence rate per 100 person-years (SH and DKA, separately)
5. Number of events (any event) per person thought by investigator to be related to study intervention

All of the safety outcomes will be tabulated for all subjects (including dropouts and withdrawals), regardless of whether CGM data are available.

Outcome #1 above will be compared between treatment groups using ordered logistic regression adjusting for the baseline value (whether or not the participant had an event in the previous year) as a fixed effect and clinical site as a random effect. Outcome #3 will be compared between treatment groups using a logrank test. Outcome #4 will be compared between treatment groups using Poisson regression adjusting for the baseline value (whether or not the participant had an event in the previous year) as a fixed effect and clinical site as a random effect. If there are outliers, then robust Poisson regression will be used.

7.1 SH and DKA Incidence Rate Calculation for Phase 1

The incidence rate per 100 person-years will be calculated by dividing the number of events in Phase 1 (this only includes events prior to the Month 8 visit for subjects who continue on to Phase 2 and includes

all events for subjects who do not continue on to Phase 2) by the number of follow-up years and multiplying by 100. The number of follow-up years will be calculated as follows:

- For subjects who continue on to Phase 2: equal to the number of years from randomization until the day of the Month 8 visit.
- For subjects who do not continue on to Phase 2: equal to the number of years from randomization until the latter of the Month 8 visit and the last adverse event.

7.2 SH and DKA Incidence Rate Calculation for Phase 2

The incidence rate per 100 person-years will be calculated by dividing the number of events in Phase 2 (this includes all events that occurred on or after the Month 8 visit, even if it was after the Month 14 visit) by the number of follow-up years and multiplying by 100. The number of follow-up years is equal to the number of years from the Month 8 visit until the latter of the Month 14 visit and the last adverse event.

8. Adherence and Retention Analysis

For both Phase 1 and Phase 2, the following analyses will be done:

- Tabulate summary statistics for the CGM use frequency for each visit and overall (CGM group)
- Tabulate summary statistics for the CGM Satisfaction Survey for the CGM group
- Tabulate diabetes medication changes for the participants who switched, added, or dropped a diabetes medication
- Tabulate the number of clinic visits and calls by treatment group
- Tabulate the number of and reasons for unscheduled visits by treatment group
- Construct a flowchart accounting for all subjects according to treatment group for each visit
- Tabulate the number of protocol and procedural deviations by treatment group
- A CONSORT flow diagram will be used to summarize the number of subjects who were:
  - assessed for eligibility at screening
  - eligible at screening
  - ineligible at screening*
  - eligible and randomized
  - eligible and not randomized*
  - received allocation intervention
  - did not receive the allocation intervention*
  - lost to follow-up*
  - discontinued intervention*
  - randomized and included in the primary analysis
  - randomized and excluded from the primary analysis*

  *reasons will be provided

8.1 Calculation of CGM Use Statistics

All available data will be used to calculate CGM use statistics.

9. Baseline Descriptive Statistics

For each phase, summary statistics appropriate to the distribution will be given for the following characteristics at randomization by treatment group:

- Age
- Diabetes duration
- Gender
- Race/ethnicity
- Central lab HbA1c
- Education
- BMI
- Self-reported SMBG
- History of CGM Use
- Current Insulin Modality
- Number of subjects using a non-insulin glucose lowering medication
- Number of daily basal insulin units per KG
- Local C-peptide
- Non-HDL Cholesterol
- Subjective Numeracy Scale and Subscales

10. Planned Sample Size Re-estimation

Details of the planned sample size re-estimation analysis are given in a separate document and are briefly summarized here. Re-estimation of the sample size for Phase 1 will be undertaken when approximately 75 participants have completed the Month 3 visit. The analysis will involve assessment of the Month 3 central lab-measured HbA1c variance and the revised sample size will be estimated using this value by computing an effective standard deviation for HbA1c and keeping all other pertinent parameters fixed at the values used for the original sample size calculation (see the Sample Size Re-estimation Plan for details on calculating the effective standard deviation). The current sample size is estimated to be 207 and the re-estimation analysis could lower it to a minimum of 150 or raise it to a maximum of 250. This analysis will be performed by the study statistician. No estimate of the treatment effect will be given in the sample size re-estimation report or used to determine the revised sample size. There will be no early stopping for efficacy or futility so that there is no substantial inflation of the type 1 error rate.

11. Subgroup Analyses

Subgroup analyses will be conducted to determine whether a similar trend to the overall treatment effect for the primary endpoint is seen in these subgroups. The study is not expected to have sufficient statistical power for definitive conclusions in subgroups and statistical power will be low to formally assess for the presence of interaction. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment effect. In the absence of any significant treatment effects in the primary analysis, assessment of subgroups will be considered exploratory and used to suggest hypotheses for further investigation in future studies.

The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the same model used for the primary analysis. For continuous factors, the interaction term will use the continuous version of the variable.

The planned subgroups defined by factors measured at baseline are listed below. These subgroups will be used in both Phase 1 and Phase 2:

- CGM time in target range (70-180) mg/dL
- Age
- Diabetes duration
- Education
- Use of GLP1 or SGLT2 medications

Note: subgroups above will only be analyzed if there are at least 10 subjects in each treatment group for each subgroup.

11.1 HbA1c Analysis According to Baseline HbA1c Subgroups

The primary analysis will be repeated including subjects according to baseline HbA1c subgroups (≥8.5%, ≥9.0%, ≥9.5%, ≥10.0%). Separate treatment arm comparisons will be conducted within the above subgroups without testing for interaction. Multiple comparisons will be accounted for as described in the next section.

12. Multiple Comparisons/Multiplicity

Primary Analysis

The primary endpoints for both phases each involve a single treatment arm comparison for a single outcome measure so no correction for multiple comparisons will be performed. Phase 1 and Phase 2 are considered separate studies and no correction will be made for multiple phases.

HbA1c Subgroups in Phase 1

The familywise error rate (FWER) will be controlled for these analyses using a hierarchical testing procedure. Formal statistical comparisons of the primary outcome within HbA1c subgroups will only be performed if the overall primary analysis has a statistically significant ($p < 0.05$) result. In that case, the largest subgroup (baseline HbA1c ≥8.5%) will be tested. Should that also yield $p < 0.05$, then the next largest subgroup (≥9.5%) will be tested and so forth. If any non-significant ($p \geq 0.05$) result is observed, then no further HbA1c subgroups will be tested.

Other Analyses

For the other endpoints, the false discovery rate (FDR) will be will be controlled using the adaptive Two Stage Group Benjamini-Hochberg (TST GBH) method[4,5] with the following categories:

- Secondary Endpoints (as listed in Section 4.2)
- Other HbA1c Endpoints (Section 4.3.1)
- Other CGM Endpoints (Section 4.3.2)
- CGM Endpoints by Time of Day (Section 4.3.3)
- Questionnaires (Section 4.3.4)
- Miscellaneous (Section 4.3.5)
- Subgroup Analysis (Section 11) *excluding HbA1c

FDR adjustments will be done separately for the two study phases. For Phase 2, the above groups will be further stratified by the pairwise comparisons Continue CGM vs Discontinue CGM and Continue CGM vs Continue SMBG.

The per-protocol analysis and the safety analyses will not be corrected for multiple comparisons.

13. Exploratory Analyses

No other exploratory analyses are planned.

14. References

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Continuous Glucose MOnitoring in T2D Basal InsuLin UsErs
The MOBILE Study

Statistical Analysis Plan

Version: 1.3

Version Date: 11/17/2020

Author: Ryan Bailey

Protocol Version: 5.0

Note: The table shells are included in a separate document.

Revision History

The following table outlines changes made to the Statistical Analysis Plan.

Version Number	Author	Approver	Effective Date	Study Stage
1.0	Tonya Riddlesworth	Craig Kollman	05/25/2018	Enrollment Not Yet Started
1.1	Nathan Cohen	Peter Calhoun	11/26/2019	Follow-up
1.2	Nathan Cohen	Peter Calhoun	02/14/2020	Follow-up. Baseline data analyzed and submitted to ADA. Follow-up data have not been analyzed yet.
1.3	Ryan Bailey	Peter Calhoun	11/17/2020	Phase 1 Complete. Analysis from version 1.2 completed and presented to study group.

Version Number	Revision Description
1.1	Added two additional binary secondary outcomes for improvement in time in range. Removed visits to a primary care physician from the list of secondary outcomes and removed a couple baseline characteristics because they are not being captured. Added a p-value calculation for the primary outcome at 3 months.
1.2	Distinguish between key secondary outcomes and other secondary outcomes. Added a hierarchical testing procedure for controlling for FWER for secondary endpoints in Phase 1. Added an exclusion criterion for patients deemed ineligible after randomization. Changed binary time in range endpoints to 10% and 15%. Added more details on how CGM use will be calculated.
1.3	Clarified the calculation of CGM use in Section 9.1. Clarified that point estimates and confidence intervals will be reported for change in HbA1c based on baseline HbA1c in Section 5.2.2. Added a listing of additional analyses to Section 14.

Signatures:

Role	Affiliation	Signature

Author	Jaeb Center for Health Research	
Senior Statistician	Jaeb Center for Health Research	
Chief Investigator/ Clinical Lead	DexCom, Inc.	

There are two phases to this protocol. Most of the details in this Statistical Analysis Plan apply to both phases but some sections give separate details for each phase.

1 Consistency of Statistical Analysis Plan with Protocol

This SAP is consistent with the study protocol stats chapter (Version 5.0) with the exception of the following changes:

- Distinguishes between "key secondary outcomes" and "other secondary outcomes" in Phase 1
- Controls for the family-wise error rate for the key secondary outcomes using a hierarchical approach
- Clarifies patients deemed ineligible after randomization will be excluded from the analysis.

2 Introduction

Use of real-time continuous glucose monitoring (RT-CGM) has been shown to improve glycemic control with a reduced risk of hypoglycemia in patients with Type 1 Diabetes Mellitus (T1DM) and patients with Type 2 Diabetes Mellitus (T2DM) on intensive insulin therapy. Only a few studies have studied RT-CGM's impact on glycemic control in T2DM with use of basal insulin, prandial insulin and oral anti-diabetic medications. Because once-daily basal insulin is the first step in initiating insulin therapy in T2DM, the need to evaluate the utility of RT-CGM with less intensive insulin regimens is warranted.

The study population consists of adult (>30 years of age) T2DM patients followed by a primary care physician for their diabetes, who are currently on basal insulin therapy with or without oral anti-diabetic therapy and/or GLP-1 analogue injections, sub-optimally controlled.

This is a prospective, randomized clinical trial with 2 phases and parallel arms in each phase.

Phase 1 will use a 2:1 randomization scheme to either the CGM Group (using CGM to inform diabetes management decisions) or the SMBG Group (using a blood glucose meter to inform diabetes management decisions).

For Phase 2, participants from the Phase 1 CGM Group will be re-randomized 1:1 to continue CGM use (Continue CGM Group) or to use SMBG (Discontinue CGM Group).

2.1 Randomization

Phase 1: N=207

For Phase 1, a 2:1 randomization scheme will be utilized (CGM:SMBG). Randomization will be stratified by site using a permuted blocks design. Randomization to group assignment will be obtained from a study website after all enrollment data have been entered and eligibility verified.

2.2 Phase 2: N= approximately 74

For Phase 2, a 1:1 randomization scheme will be utilized to re-randomize the Phase 1 CGM Group (Continue CGM:Discontinue CGM). All subjects from the Phase 1 SMBG group will continue in the study without re-randomization. The goal is for up to 92 participants from the Phase 1 CGM Group to

enter Phase 2 (with approximately 74 completing Phase 2). There are no stratification factors for the Phase 2 randomization.

2.3 Timing of Final Analyses:

The Phase 1 outcomes will be analyzed after the last subject completes the Month 8 visit and all available data for the Phase 1 endpoints have been collected and cleaned (anticipated May 2019). The Phase 2 outcomes will be analyzed after the last Phase 2 subject completes the Month 14 visit (which is 6 months after the 2nd randomization) and all available data for the Phase 2 endpoints have been collected and cleaned (anticipated November 2019).

3 Statistical Hypotheses

Phase 1 Hypotheses

- Null hypothesis: There is no difference in the mean change in central lab-measured hemoglobin A1c (HbA1c) over 8 months between patients making CGM based decisions about their diabetes and patients making blood glucose monitoring based decisions
- Alternative hypothesis: Patients making CGM based decisions about their diabetes have a different mean change in central lab-measured HbA1c over patients making blood glucose monitoring based decisions

Phase 2 Hypotheses

- Null hypothesis: There is no difference in the mean change in CGM-measured time in the target range (70-180 mg/dL) over 6 months between patients who continue making CGM based decisions about their diabetes (after the initial 8 months) and patients who switch from making CGM based decisions to making blood glucose monitoring based decisions
- Alternative hypothesis: Patients who switch from making CGM based decisions to making blood glucose monitoring based decisions about their diabetes have a different mean CGM-measured time in the target range over patients who continue making CGM based decisions (after the initial 8 months)

4 Sample Size

The Phase 1 sample size is formally powered and the Phase 2 sample size is dependent on the number in the Phase 1 CGM Group who continue into Phase 2.

For Phase 1, the DIaMonD T2D RCT data were used to estimate the mean and standard deviation for HbA1c at baseline and 6 months. Data were taken from 121 participants with T2D who met the current protocol's eligibility criteria for HbA1c (8.0-11.5%). Based on an effective standard deviation of 0.80% (adjusting for baseline HbA1c as a covariate) and a true treatment effect of 0.4%, the total sample size for this study is estimated to be 165 to have at least 85% power with alpha=0.05 and 2:1 randomization. However, in order to account for a 20% dropout rate, a total sample size of 207 was selected (138 for the CGM Group and 69 for the SMBG Group) with up to 300 enrolled into screening.

For Phase 2, the DIaMonD Phase 2 RCT data (which included only T1D participants) were used to estimate the mean and standard deviation for the percent time in the target range (70-180 mg/dL) at 6 and 12 months. Data were taken from 38 participants in the CGM+MDI Group. Assuming 138 subjects were

randomized to the current protocol's Phase 1 CGM Group and a 20% dropout rate, we expect at least 74 participants to enter and complete Phase 2. Based on an effective standard deviation at 12 months of 7% (adjusting for 6-month time in range as a covariate) and a treatment effect of 5%, there will be 85% power to detect a difference in the time in range between the Continue CGM and the Discontinue CGM groups with alpha=0.05 and 1:1 randomization.

5 Outcome Measures

5.1 Primary Efficacy Endpoints

5.1.1 Phase 1 Primary Endpoint

Change in central lab-measured HbA1c from baseline to Month 8

5.1.2 Phase 2 Primary Endpoint

Change in time in target range (70-180 mg/dL) from Month 8 to Month 14

Calculation of Time in Target Range at Months 8 and 14

The time in target range will be calculated over 24 hours at Month 8 (baseline for Phase 2) and Month 14 as follows:

- Baseline (Month 8): The time in target range will be calculated based on CGM data obtained in the 10 days prior to the Month 8 visit. If a subject has <96 hours of data available in the 10 days prior to the Month 8 visit, then an additional day will be added (up to 2 weeks) to try to obtain at least 96 hours of data.
- Followup (Month 14):
    - Discontinue CGM Group: For approximately 10 days prior to the Month 14 visit, each subject in the Discontinue CGM Group will wear a blinded CGM to obtain data to calculate glycemic variables. All blinded CGM data for this group will be used to calculate time in the target range.
    - Continue CGM Group: To get a comparable sample of data from the Continue CGM Group (who are being asked to wear CGM continually during the study), 10 days of data immediately prior to the Month 14 visit will also be used. If a subject misses the Month 14 visit then the 10 days of data immediately prior to their last visit will be used instead. If a subject has <96 hours of CGM data available in the 10 days used in the calculation, then an additional day will be added (up to 2 weeks) to try to obtain at least 96 hours of data.

5.2 Secondary Efficacy Endpoints

5.2.1 Phase 1 Key Secondary Endpoints Included in Hierarchical Analysis

Between group differences (CGM and SMBG) from baseline to Month 8

1. Change in CGM time in target range 70-180 mg/dL
2. Change in CGM time-hyperglycemic, defined as >250 mg/dL
3. Change in mean glucose from CGM

5.2.2 Phase 1 Other Secondary Endpoints

Between group differences (CGM and SMBG) from baseline to Month 8

- Percent decreasing HbA1c by ≥0.5% (absolute)
- Proportion increasing time in target range by ≥10% and ≥15% (absolute)
- Percent adding or removing diabetes medications (starting or stopping medication)
- Change in HbA1c based on their baseline HbA1c (restricted to participants with baseline HbA1c ≥8.5%, ≥9.0%, ≥9.5%, ≥10.0%)*
- Change in CGM glucose variability measured by the coefficient of variation
- Change in CGM time-hypoglycemic, defined as <70 mg/dL

*Only performed if primary analysis is significant and each nested group is only tested if the superset is significant. Adjusted mean differences and 95% confidence intervals will be reported for each nested group.

5.2.3 Phase 2 Secondary Endpoints

Between group differences for the Discontinue CGM Group (use SMBG only) and the Continue CGM Group from Month 8 to Month 14

Between group differences for the Continue CGM and the Continue SMBG groups from baseline to Month 14

- Change in HbA1c (central lab)
- Change in CGM time-hyperglycemic, defined as >250 mg/dL
- Percent decreasing HbA1c by ≥0.5% (absolute)
- Proportion increasing time in target range by ≥10% and ≥15% (absolute)
- Percent adding or removing diabetes medications (starting or stopping medication)
- Change in CGM glucose variability measured by the coefficient of variation
- Change in CGM time-hypoglycemic, defined as <70 mg/dL

5.3 Other Endpoints

Exploratory analyses will be performed on the endpoints listed below to better understand the effect of CGM on this population. The endpoints are the same for Phase 1 and Phase 2 and will only be listed once.

For Phase 1, the endpoints will be evaluated for between group differences in the CGM and SMBG groups from baseline to Month 8.

For Phase 2, the endpoints will be evaluated for between group differences for the Discontinue CGM Group (use SMBG only) and the Continue CGM Group from Month 8 to Month 14 as well as for the Continue CGM and the Continue SMBG groups from baseline to Month 14.

5.3.1 Other HbA1c Endpoints

- Percent reaching target HbA1c (<7.0%)
- Percent with HbA1c <7.5%
- Percent decreasing HbA1c by ≥1.0% (absolute) *****
- Percent decreasing HbA1c by ≥1.0% (absolute) OR reaching target HbA1c (<7.0%) *****
- Percent decreasing HbA1c by ≥10% (relative) *****

* For Phase 2, these endpoints will only be evaluated for the Continue CGM and the Continue SMBG groups from baseline to Month 14.

5.3.2 Other CGM Endpoints

- Change in time <54 mg/dL
- Proportion of participants with time in target range ≥70% at Month 8
- Change in the rate of CGM-measured hypoglycemic events
    - A CGM-measured hypoglycemic event is defined as at least 2 sensor values <54 mg/dL that are 15 or more minutes apart plus no intervening values >54 mg/dL; at least 2 sensor values >70 mg/dL that are 30 or more minutes apart with no intervening values ≤70 mg/dL, are required to define the end of an event, at which point the study participant becomes eligible for a new event.
- Change in time >180 mg/dL
- Change in time >300 mg/dL
- Area under curve 180 mg/dL

5.3.3 CGM Endpoints by Time of Day

5.3.4 Questionnaires/Surveys

- Diabetes Distress Scale (DDS) – Change in mean score and 4 subscales
- Glucose Monitoring Satisfaction Survey (GMSS) – Change in mean score and 4 subscales
- Modified Hill-Bone Medication Adherence Scale – Change in total score
- Clinician Communication Rating Scale – Change in mean score on 1 subscale
- Modified Toobert's Scale – Change in mean score
- Fear of Hypoglycemia Survey – Change in mean score
- SF12 Health Survey – Change in Physical Health Composite score and Mental Health Composite score
- WHO-5 Well-Being Index – Change in total score
- CGM Satisfaction Survey (given only to the CGM groups at followup so no comparison between groups)
- Perceived Benefit Questionnaire (given at followup only) – Each item will be summarized individually; no total or mean score
- Subjective Numeracy Scale (given at study entry only so no comparison between groups)

5.3.5 Miscellaneous

- Change in SMBG frequency (self-reported and download)
- Change in total daily insulin units per kg
- Change in basal units per kg
- Addition of at least one prandial insulin
- Addition of at least one GLP-1 analog or SGLT2 inhibitor
- Change in body weight
- Change in BMI
- Change in blood pressure
- Change in non-HDL cholesterol

5.4 Calculation of CGM Metrics

Each of the CGM metrics will be calculated over 24 hours. For the Time of Day analysis, all CGM metrics will be calculated separately for sensor values during the daytime (6:00 AM – <midnight) and for nighttime (midnight – <6:00 AM).

For Phase 2, calculation of the CGM metrics will be similar to what was described for the Phase 2 primary analysis in Section 5.1.2.

For Phase 1, CGM metrics will be calculated separately at baseline and Month 8 as follows:

- Baseline: CGM metrics will be calculated based on all CGM data obtained prior to randomization. Note that only subjects who used CGM on at least 7 of the previous 10 days are eligible to be randomized.
- Month 8:
  - SMBG Group: For approximately 10 days after the Month 3 visit and prior to the Month 8 visit, each subject in the SMBG Group will wear a blinded CGM to obtain data to calculate glycemic variables. All blinded CGM data for this group will be used in the analysis for Phase 1 CGM metrics.
  - CGM Group: To get a comparable sample of data from the CGM Group (who are being asked to wear CGM continually during the study), 10 days of data immediately after the Month 3 visit and prior to the Month 8 visit will also be used. If a subject misses the Month 3 visit but continues in the study then their Month 3 target date will be used in place of the Month 3 visit date. If they miss the Month 3 visit due to being dropped from the study prior to that visit then the last 10 days of data will be used instead and no additional data for Month 8 will be added. If a subject misses the Month 8 visit then the last 10 days of data will be used instead. If a subject has <96 hours of CGM data available in the 10 days used in the calculation, then an additional day will be added (up to 2 weeks) to try to obtain at least 96 hours of data. For both groups, the data will be pooled across Months 3 and 8 to calculate the glycemic metrics.

5.5 Timing of Outcome Assessments and Out of Window Visits:

The schedule of study visits is given in the protocol. The following table summarizes the expected timing of the 3-, 8-, and 14-month visits as well as when a visit will be considered "missed" and outcomes from that visit will be excluded from the analysis. Note that the analysis windows below apply to all outcomes other than CGM and SMBG metrics from downloaded data.

	Target Date (# days post-randomization)	**Window Specified in the Protocol**	**Window to be Included in Analysis**
3-month visit	90 days	+/- 5 days	+/- 30 days
8-month visit	240 days	+/- 5 days	+/- 30 days
14-month visit	520 days	+/- 5 days	+/- 30 days

6 Analysis Cohorts

- All randomized participants will be analyzed for the Intention-to-Treat (ITT) Analysis. Randomized participants who are deemed ineligible after randomization will be excluded from the analysis.
- Safety outcomes will be reported for all enrolled participants, irrespective of whether the study was completed.
- A per-protocol analysis of the primary outcome will be conducted in each phase separately. This analysis will be restricted to participants who satisfy the following criteria (assuming this results in at least 10% of the subjects being excluded):
    - Adherence: Subjects in the SMBG Group performing SMBG on average a minimum of 1 time per day based on self-report over the full 8 months (6 months for Phase 2) and subjects in the CGM Group using CGM on at least 70% of days over the full 8 months (6 months for Phase 2)
    - Final visit: Subjects who complete the final study visit (Month 8 for Phase 1 and Month 14 for Phase 2) within ±30 days of the target date
    - Exclusion: Subjects in the SMBG Group who used an unblinded CGM at any point during the study phase will be excluded
    - Exclusion: Subjects in either group whose last CGM reading is more than 30 days before the final study visit (Month 8 for Phase 1 and Month 14 for Phase 2) will be excluded

7 Statistical Methods

7.1 General Approach

All covariates obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that the covariate does not have a linear relationship with the dependent variable. In such a case, categorization and/or transformations will be explored. All p-values will be two-sided and all confidence intervals will be two-sided.

7.2 Analysis of the Primary Efficacy Endpoint for Phase 1

Summary statistics for HbA1c (from central lab) appropriate to the distribution will be calculated separately by treatment group. The method of direct likelihood[1] will be used by fitting a longitudinal mixed effects linear regression model including HbA1c values measured at baseline, 3 months and 8 months. All subjects will be included in this model even if the 3-month and/or 8-month HbA1c values are unavailable. The model will include a term for treatment arm, but the two arms will be forced to have the same predicted value at baseline (due to randomization). This is equivalent to adjusting for baseline as a covariate while allowing for missing values. The model will adjust for clinical site as a random effect and include the local HbA1c as an auxiliary variable in case any lab HbA1c values are missing. Separate treatment effects will be estimated at 3 and 8 months (treatment by time interaction) and inference will focus on the estimate at 8 months, which is the primary outcome. A risk-adjusted point-estimate, 95% confidence interval and p-value will reported for the treatment arm difference at 3 months and 8 months.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation, robust regression or non-parametric methods will be used instead.

7.2.1 Missing HbA1c Data for the Primary Efficacy Endpoint for Phase 1

It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. Our goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used. Different techniques (summarized below) will therefore be utilized to determine whether they reach similar conclusions:

- Primary Analysis: Missing HbA1c values will be handled using direct likelihood as described above.
- Sensitivity Analyses: Analyses will also be conducted using the following methods to handle missing HbA1c values:
  - Rubin's multiple imputation[2]
  - Available cases only

For the sensitivity analyses, a mixed effects linear regression model will be used with the 8-month central lab HbA1c as the outcome and will include fixed effects for the baseline central lab and random effects for the clinical site.

7.2.2 Sensitivity Analysis on Data-Driven Covariates for Phase 1

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. The presence of confounding will be evaluated as a sensitivity analysis by adjusting for covariates potentially associated with HbA1c for which there is an imbalance between groups. Whether a factor is imbalanced for the treatment arms will be determined by clinical judgment and will not be based on a p-value.

7.3 Analysis of the Primary Efficacy Endpoint for Phase 2

Summary statistics for the time in target range appropriate to the distribution will be calculated separately by treatment group. A mixed effects linear regression model will be used to compare the change in time in target range among the two treatment groups. All subjects randomized to Phase 2 will be included in this model regardless of if they dropped out of the study. The model will adjust for baseline time in target range as fixed effects and include random effects for clinical site. A risk adjusted difference and 95% confidence interval will be reported based on the least squares mean from this model.

Residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead.

7.3.1 Missing CGM Data for the Primary Efficacy Endpoint for Phase 2

There will be no minimum requirement of CGM data to be included in the analyses and no imputation of CGM data.

7.3.2 Sensitivity Analysis on Data-Driven Covariates for Phase 2

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. The presence of confounding will be evaluated as a sensitivity analysis by adjusting for covariates potentially associated with time in target range for which there is an imbalance between groups. Whether a factor is imbalanced for the treatment arms will be determined by clinical judgment and will not be based on a p-value.

7.4 Analysis of the Secondary Efficacy Endpoints and Other Endpoints

For continuous variables, summary statistics appropriate to the distribution will be calculated separately by treatment group. For discrete variables, number and % will be calculated separately by treatment group.

All the binary measures will be compared between treatment groups using a logistic regression model and all the continuous measures will be compared using a linear regression model. Any model with some form of HbA1c as the dependent variable will adjust for baseline HbA1c as a fixed effect and include random effects for clinical site. All other models will adjust for the baseline value as a fixed effect and include random effects for clinical site. In addition to these factors, the model for body weight will also adjust for age and gender and the models for blood pressure and HDL cholesterol will adjust for age, gender and baseline BMI.

For the continuous measures, residual values will be examined for an approximate normal distribution. If values are highly skewed then an appropriate transformation or non-parametric methods will be used instead. If the distribution is approximately normal then the adjusted mean difference and confidence interval will be reported.

For the binary measures, the risk-adjusted difference in percentages and the confidence interval will be reported. The adjusted difference in percentages will be calculated as in Kleinman and Norton[3] and the confidence interval will be calculated using a bootstrap.

7.4.1 CGM Analysis by Time of Day

For the CGM endpoints, the analysis will parallel what was described for the 24h analysis with the inclusion of a treatment by time of day interaction. The p-value for the interaction term will be reported. These analyses will be conducted to determine whether a similar trend to the overall treatment effect is seen in the different times of day.

The study is not expected to have sufficient statistical power for definitive conclusions in the CGM analyses by time of day, and statistical power will be low to formally assess a treatment by time-of-day interaction. Interpretation of the analyses by time of day will depend on whether the overall analysis demonstrates a significant treatment effect. In the absence of any significant treatment effects in the overall analyses, assessment of secondary analyses by time of day will be considered exploratory and used to suggest hypotheses for further investigation in future studies.

7.4.2 Missing Data for Secondary Efficacy Endpoints and Other Endpoints

Only participants with outcome data at baseline and follow-up will be included in the analysis (i.e. available cases only). For the CGM metrics and SMBG according to download, there will be no minimum requirement of data to be included in the analyses and no imputation of data. For the questionnaire outcomes, mean scores will be considered missing if <75% of the questions are answered and total scores will be considered missing if at least one question is left unanswered.

7.4.3 Details for Questionnaire Scoring

Mean scores will be calculated for the following questionnaires:

- Diabetes Distress Scale
  - Emotional Burden Subscale
  - Physician-related Distress Subscale
  - Regimen-related Distress Subscale
  - Interpersonal Distress Subscale
- Glucose Monitoring Satisfaction Survey
  - Openness Subscale
  - Emotional Burden Subscale
  - Behavioral Subscale
  - Worthwhileness Subscale
- Fear of Hypoglycemia Survey
- Modified Toobert's Scale
- CGM Satisfaction Survey
  - Benefits Subscale
  - Lack of Hassles Subscale
- Subjective Numeracy Scale
  - Ability Subscale
  - Preference Subscale

Total scores will be calculated for the following questionnaires:

- Hill-Bone Medication Adherence Scale
- WHO-5 Well-Being Index

Two composite scores (Physical Health and Mental Health) will be calculated for the SF-12 Survey based on the survey's scoring manual[6]. A mean score for the Overall Communication subscale will be calculated for the Clinician Communication Rating Scale[7]. No overall score will be given for the Perceived Benefit Questionnaire. This is an un-validated questionnaire and each question will be summarized individually.

Missing Data when Calculating Mean Scores

According to the Glucose Monitoring Satisfaction Survey scoring manual, if less than 75% of the data is available, the score for that scale or subscale should be counted as missing as it may not be a true reflection of the participants' behaviors and/or worries. The scoring manuals for the remaining questionnaires for calculating the mean score did not specify a minimum amount of data. However, we will apply the 75% rule to all the mean scales and subscales.

Missing Data when Calculating Total Scores

Total scores will only be calculated if all the questions are answered (i.e. no missing data). If any one of the questions is left blank, then the total score will be missing.

8 Safety Analyses

For both phases, all adverse events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. In addition, the following outcomes will be analyzed when the number of events is sufficient for a meaningful analysis and the analysis methods are described below:

1. Number of events per person (SH and DKA, separately)
2. Percentage of participants with at least one event (SH and DKA, separately)
3. Kaplan-Meier rate (SH and DKA, separately)
4. Incidence rate per 100 person-years (SH and DKA, separately)
5. Number of events (any event) per person thought by investigator to be related to study intervention

All of the safety outcomes will be tabulated for all subjects (including dropouts and withdrawals), regardless of whether CGM data are available.

Outcome #1 above will be compared between treatment groups using ordered logistic regression adjusting for the baseline value (whether or not the participant had an event in the previous year) as a fixed effect and clinical site as a random effect. Outcome #3 will be compared between treatment groups using a logrank test. Outcome #4 will be compared between treatment groups using Poisson regression adjusting for the baseline value (whether or not the participant had an event in the previous year) as a fixed effect and clinical site as a random effect. If there are outliers, then robust Poisson regression will be used.

8.1 SH and DKA Incidence Rate Calculation for Phase 1

The incidence rate per 100 person-years will be calculated by dividing the number of events in Phase 1 (this only includes events prior to the Month 8 visit for subjects who continue on to Phase 2 and includes all events for subjects who do not continue on to Phase 2) by the number of follow-up years and multiplying by 100. The number of follow-up years will be calculated as follows:

- For subjects who continue on to Phase 2: equal to the number of years from randomization until the day of the Month 8 visit.
- For subjects who do not continue on to Phase 2: equal to the number of years from randomization until the latter of the Month 8 visit and the last adverse event.

8.2 SH and DKA Incidence Rate Calculation for Phase 2

The incidence rate per 100 person-years will be calculated by dividing the number of events in Phase 2 (this includes all events that occurred on or after the Month 8 visit, even if it was after the Month 14 visit) by the number of follow-up years and multiplying by 100. The number of follow-up years is equal to the number of years from the Month 8 visit until the latter of the Month 14 visit and the last adverse event.

9 Adherence and Retention Analysis

For both Phase 1 and Phase 2, the following analyses will be done:

- Tabulate summary statistics for the CGM use frequency for each visit and overall (CGM group)
- Tabulate summary statistics for the CGM Satisfaction Survey for the CGM group
- Tabulate diabetes medication changes for the participants who switched, added, or dropped a diabetes medication

- Tabulate the number of clinic visits and calls by treatment group
- Tabulate the number of and reasons for unscheduled visits by treatment group
- Construct a flowchart accounting for all subjects according to treatment group for each visit
- Tabulate the number of protocol and procedural deviations by treatment group
- A CONSORT flow diagram will be used to summarize the number of subjects who were:
  - assessed for eligibility at screening
  - eligible at screening
  - ineligible at screening*
  - eligible and randomized
  - eligible and not randomized*
  - received allocation intervention
  - did not receive the allocation intervention*
  - lost to follow-up*
  - discontinued intervention*
  - randomized and included in the primary analysis
  - randomized and excluded from the primary analysis*

  *reasons will be provided

9.1 Calculation of CGM Use Statistics

At each visit, all post-randomization CGM data occurring up to and including the date of the given visit will be used to calculate days per week of CGM use in the CGM arm. This will be done by calculating the total number of possible CGM hours from the time of randomization until 11:59 PM on the date prior to the visit. Days per week of CGM use will then be calculated by dividing the number of hours of available data during that period by the total number of possible hours and then multiplying by 7. This will only be calculated for participants in the CGM group. Participants who did not complete a visit will be excluded from the calculation of CGM use from baseline up until that visit.

10 Baseline Descriptive Statistics

For each phase, summary statistics appropriate to the distribution will be given for the following characteristics at randomization by treatment group:

- Age
- Diabetes duration
- Gender
- Race/ethnicity
- Central lab HbA1c
- Education
- BMI
- Self-reported SMBG
- Number of subjects using a non-insulin glucose lowering medication
- Number of daily basal insulin units per KG
- Local C-peptide
- Non-HDL Cholesterol

- Subjective Numeracy Scale and Subscales

11 Planned Sample Size Re-estimation

Details of the planned sample size re-estimation analysis are given in a separate document and are briefly summarized here. Re-estimation of the sample size for Phase 1 will be undertaken when approximately 75 participants have completed the Month 3 visit. The analysis will involve assessment of the Month 3 central lab-measured HbA1c variance and the revised sample size will be estimated using this value by computing an effective standard deviation for HbA1c and keeping all other pertinent parameters fixed at the values used for the original sample size calculation (see the Sample Size Re-estimation Plan for details on calculating the effective standard deviation). The current sample size is estimated to be 207 and the re-estimation analysis could lower it to a minimum of 150 or raise it to a maximum of 250. This analysis will be performed by the study statistician. No estimate of the treatment effect will be given in the sample size re-estimation report or used to determine the revised sample size. There will be no early stopping for efficacy or futility so that there is no substantial inflation of the type 1 error rate.

12 Subgroup Analyses

Subgroup analyses will be conducted to determine whether a similar trend to the overall treatment effect for the primary endpoint is seen in these subgroups. The study is not expected to have sufficient statistical power for definitive conclusions in subgroups and statistical power will be low to formally assess for the presence of interaction. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment effect. In the absence of any significant treatment effects in the primary analysis, assessment of subgroups will be considered exploratory and used to suggest hypotheses for further investigation in future studies.

The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the same model used for the primary analysis. For continuous factors, the interaction term will use the continuous version of the variable.

The planned subgroups defined by factors measured at baseline are listed below. These subgroups will be used in both Phase 1 and Phase 2:

- CGM time in target range (70-180) mg/dL
- Age
- Diabetes duration
- Education
- Use of GLP1 or SGLT2 medications

Note: subgroups above will only be analyzed if there are at least 10 subjects in each treatment group for each subgroup.

12.1 HbA1c Analysis According to Baseline HbA1c Subgroups

The primary analysis will be repeated including subjects according to baseline HbA1c subgroups (≥8.5%, ≥9.0%, ≥9.5%, ≥10.0%). Separate treatment arm comparisons will be conducted within the above subgroups without testing for interaction. Multiple comparisons will be accounted for as described in the next section.

13 Multiple Comparisons/Multiplicity

Primary Analysis

The primary endpoints for both phases each involve a single treatment arm comparison for a single outcome measure so no correction for multiple comparisons will be performed. Phase 1 and Phase 2 are considered separate studies and no correction will be made for multiple phases.

Key Secondary Endpoints in Phase 1

In Phase 1, the key secondary endpoints will be tested hierarchically in the order in which they are listed in Section 5.2.1. This will control the familywise error rate (FWER). In these analyses, the cutoff value for testing the next endpoint will be $p < 0.05$.

HbA1c Subgroups in Phase 1

The FWER will be controlled for these analyses using a hierarchical testing procedure; this subgroup analysis will be considered as a second family of hypotheses. Formal statistical comparisons of the primary outcome within HbA1c subgroups will only be performed if the overall primary analysis has a statistically significant ($p < 0.05$) result. In that case, the largest subgroup (baseline HbA1c ≥8.5%) will be tested. Should that also yield $p < 0.05$, then the next largest subgroup (≥9.0%) will be tested and so forth. If any non-significant ($p \geq 0.05$) result is observed, then no further HbA1c subgroups will be tested.

Other Analyses

For the other endpoints, the false discovery rate (FDR) will be controlled using the adaptive Two Stage Group Benjamini-Hochberg (TST GBH) method[4,5] with the following categories:

- Other Secondary Endpoints (as listed in Section 5.2.2 and 5.2.3)
- Other HbA1c Endpoints (Section 5.3.1)
- Other CGM Endpoints (Section 5.3.2)
- CGM Endpoints by Time of Day (Section 5.3.3)
- Questionnaires (Section 5.3.4)
- Miscellaneous (Section 5.3.5)
- Subgroup Analysis (Section 12) *excluding HbA1c

FDR adjustments will be done separately for the two study phases. For Phase 2, the above groups will be further stratified by the pairwise comparisons Continue CGM vs Discontinue CGM and Continue CGM vs Continue SMBG.

The per-protocol analysis and the safety analyses will not be corrected for multiple comparisons.

14 Additional Analyses after Version 1.2

Following completion of Phase 1 and review of version 1.2 of this document, the following analyses are added to the SAP. These additional analyses apply to Phase 1 and Phase 2 analyses.

14.1 Additional Treatment Group Comparisons

Treatment group differences will be tested at 8 months (Phase 1) and 14 months (Phase 2) for the following metrics:

- Improvement of ≥5% in time in range 70-180 mg/dL
- Proportion with HbA1c <8%
- Proportion adding diabetes medications
- Proportion removing diabetes medications
- Proportion adding GLP1-Analogs
- Proportion adding SGLT2-Inhibitors

The statistical methods described in Section 7.4 will be used to test treatment group differences in the above outcomes.

14.2 Additional Subgroup Analyses

The primary endpoint will be compared within the subgroups listed below. Methods for analyzing subgroups have been described in Section 12

- Baseline HbA1c
- Race/Ethnicity
- Baseline Numeracy Scale Survey Score
- Insurance Status

14.3 Additional CGM Group Analyses

14.3.1 Calculation of Percent Time in Range 70-180 mg/dL by Month

The percentage of time in range will be calculated for each month of follow-up. CGM data from the date of randomization until 11:59 PM on the 30th day after randomization will be pooled to calculate time in range for the first month, data from 12:00 AM on the 31st day after randomization until 11:59 PM on 61st day after randomization will be pooled for the second month and so on. Time in range will also be calculated separately for each of the first 4 weeks after randomization and for the first 7 days after randomization.

14.3.2 CGM Use in Last Month

For Phase 1, CGM use will be calculated restricting to the 30 days prior to the month 8 visit date through 11:59 PM on the date prior to the month 8 visit date. Days per week of CGM use will be calculated by dividing the number of hours of available data by the total number of hours possible during that period and multiplying by 7. For Phase 2, CGM use will be calculated restricting to the 30 days prior to month 14 visit date.

15 References

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Revision History

The following table outlines changes made to the Statistical Analysis Plan.

Version Number	Author	Approver	Effective Date	Study Stage
1.0	Tonya Riddlesworth	Craig Kollman	05/25/2018	Enrollment Not Yet Started
1.1	Nathan Cohen	Peter Calhoun	11/26/2019	Follow-up
1.2	Nathan Cohen	Peter Calhoun	02/14/2020	Follow-up. Baseline data analyzed and submitted to ADA. Follow-up data have not been analyzed yet.
1.3	Ryan Bailey	Peter Calhoun	11/17/2020	Phase 1 Complete. Analysis from version 1.2 completed and presented to study group.

Version Number	Revision Description
1.1	Added two additional binary secondary outcomes for improvement in time in range. Removed visits to a primary care physician from the list of secondary outcomes and removed a couple baseline characteristics because they are not being captured. Added a p-value calculation for the primary outcome at 3 months.
1.2	Distinguish between key secondary outcomes and other secondary outcomes. Added a hierarchical testing procedure for controlling for FWER for secondary endpoints in Phase 1. Added an exclusion criterion for patients deemed ineligible after randomization. Changed binary time in range endpoints to 10% and 15%. Added more details on how CGM use will be calculated.
1.3	Clarified the calculation of CGM use in Section 9.1. Clarified that point estimates and confidence intervals will be reported for change in HbA1c based on baseline HbA1c in Section 5.2.2. Added a listing of additional analyses to Section 14.