School of Medicine

Center for Diabetes Technology

An Exploratory 16-Week Pilot Study Of The Effect And Safety Of A Novel CGM-Based Titration Algorithm For Basal Insulin, With Or Without Non-Insulin Antidiabetic Drugs, In T2DM Participants Treated With Basal Insulin

RUNNING TITLE: CGM-DTx Degludec

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Version Number: v.3.3

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KEY ROLES

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PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	Mary Oliveri, Ralf Nass Marc Breton	Ralf Nass	08/29/2023	Original Protocol
2.0	Mary Oliveri, Ralf Nass	Ralf Nass	08/31/2023	Removed redundancies, added Statistical Consideration Section
2.1	Mary Oliveri, Ralf Nass Marc Breton	Marc Breton	09/11/2023	Final read through, streamline language, and update outcomes
3.0	Mary Oliveri Ralf Nass Marc Breton	Marc Breton, Ralf Nass	09/12/2023	FDA submission
3.1	Mary Oliveri	Ralf Nass	09/24/2023	FDA edits: • Added Exclusion criteria (section 3.2) • Fasting SMBGs collected each day in both EXP & CTR Groups (section 4.4) • Weekly dose recommendations will be confirmed within 24 hours of receipt (sections 6.1 and 6.2) • Added CTR Safety Assessment (section 6.4) • Modified Participant Stopping Criteria (section 11.8.1)
3.2	Mary Oliveri	Ralf Nass	11/03/2023	Clarification of protocol discrepancies: • replace a narrative description of study events to a bulleted description throughout document • clarified study endpoints (section 1.8 and 13.3)
3.3	Mary Oliveri	Ralf Nass	02/19/2024	Study Team modifications: • Increased screen failure rate • Clarified that CGM Run-In phase may be extended, not just repeated, at MD discretion (section 5.2)

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: An Exploratory 16-Week Pilot Study of the Effect and Safety of a Novel CGM-Based Titration Algorithm for Basal Insulin, With or Without Non-Insulin Antidiabetic Drugs, in T2DM Participants Treated with Basal Insulin

Running Title: CGM-DTx Degludec

Protocol Version/Date: v.3.3 19-Feb-2024

I have read the protocol specified above. In my formal capacity as a Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____Date: _____ / _____ / _____

Investigator's Name: _____

Site Name: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AP	Artificial Pancreas
BG	Blood Glucose
CDCES	Certified Diabetes Care and Education Specialist
CDT	Center for Diabetes Technology
CGM	Continuous Glucose Monitoring
CIQ	Control-IQ AP system, Tandem Diabetes Care, San Diego, CA
CSII	Continuous Subcutaneous Insulin Injection
DCCT	Diabetes Control and Complications Trial
DiAs	Diabetes Assistant – the UVA algorithm prototyping system
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HHS	Hyperosmolar Hyperglycaemic State
iDCL	International Diabetes Closed-Loop trial
IDE	Investigational Device Exemption
IRB	Institutional Review Board
NIDDK	National Institute for Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
PI	Principal Investigator
POC	Point-of-Care
SAE	Serious Adverse Event
S.C.	Subcutaneous
SMBG	Self-Monitoring Blood Glucose
T1D	Type 1 Diabetes
TAE	Treatment Emergent Adverse Event
TAR	Time above range, above 180 mg/dL
TBR	Time below range, below 70 mg/dL
TGL	Titration Glucose Level
TIR	Time within the range 70-180 mg/dL
UADE	Unanticipated Adverse Device Effect
UVA	University of Virginia

PROTOCOL SUMMARY

Protocol section	Description
Title	An Exploratory 16-Week Pilot Study of the Effect and Safety of a Novel CGM-Based Titration Algorithm for Basal Insulin, With or Without Non-Insulin Antidiabetic Drugs, in T2DM Participants Treated with Basal Insulin
Investigational Devices	CGM-based titration of basal insulin module as implemented in DiAs Cloud platform and partner applications
Study Medication	FDA approved insulin degludec (Tresiba) (used according to labelling)
Objectives	The primary objective of the study is to compare the effect of a CGM (Dexcom G6) based once weekly titration algorithm versus a standard titration by self-monitoring blood glucose (SMBG) on glycemic control in T2 DM participants.
Study Design	Multicenter, randomized, parallel group, active-comparator clinical trial of CGM based titration of insulin degludec vs. standard titration by SMBG. The study includes: • Screening Visit • 2-week blinded CGM Run-In Phase • 16-week Intervention Phase • 3 Check-In Visits • Study End Visit • Follow-up Visit about 48 hours after Intervention Phase
Number of Sites	Two clinical sites
Endpoint	The primary objective of the pilot study is to compare CGM-based titration versus standard SMBG-based titration of insulin degludec, both treatment arms with or without non-insulin anti-diabetic drugs, in terms of glycemic control measured by change in time in range (70-180 mg/dL) from baseline (-2 to 0 weeks) to week 14-16 in insulin experienced participants with T2DM. The secondary objective of the study is to explore other parameters of safety, efficacy and feasibility when using CGM-based titration of insulin degludec in insulin-experienced participants with T2DM.
Population	Type 2 Diabetes Mellitus (T2DM)
Sample Size	Up to 60 enrolled participants may sign consent with the enrollment goal of completing 30 participants at 2 centers
Treatment Groups	• Experimental (EXP) Arm: CGM based titration algorithm group • Control (CTR) Arm: SMBG titration algorithm group
Participant Duration	Approximately 18 weeks (2-week CGM Run-In Phase + 16-week Intervention Phase)
Protocol Overview/Synopsis	This is a ~18-week study designed to investigate the effect of a CGM based titration algorithm versus a standard titration by SMBG on glycemic control in T2DM participants using the insulin degludec. After 2 weeks of blinded CGM baseline observation, participants are randomized 2:1 to CGM-based titration or standard titration by SMBG for 16 weeks; all titrated doses will be reviewed by a study physician. All participants (both study groups) will be supplied with insulin degludec 100 units/ml, s.c, solution for injection, 3 mL prefilled pen-injector. After completion of the 16-week titration participants are followed up for 2 days. Participants in the standard SMBG based titration group will wear a blinded CGM during the whole study. Participants will be stratified related to use of sulfonylureas or glinides with a maximum cap of 9 participants being treated with sulfonylureas or glinides to complete the study.

STUDY VISITS AND PROCEDURES SCHEDULE

	Consent	Screening	Training	CGM Run-In Phase	Randomization		Check-In Visit		Check-In Visit		Check-In Visit		Study End Visit	Post-Study Check-In
Location (VC=video conference)	Clinic or VC	Clinic or VC	Clinic or VC	Home x 2 weeks	Clinic/ Phone/ VC		Clinic/ Phone/ VC		Clinic/ Phone/ VC		Clinic/ Phone/ VC		Clinic/ Phone/ VC	Clinic/ Phone/ VC
Visit	1	2	3	4	5		6		7		8		9	10
Intervention Phase (week)				-2 - 0	0	1-3	4	5-7	8	9-11	12	13-15	16	Post Day 2-7
Informed Consent	X													
Eligibility Assessment		X												
Medical History		X												
HbA1c – Central Lab					X				X				X	
HbA1c – Local Lab		X												
Laboratory testing (CMP & TSH) if needed		X												
Pregnancy Test (if applicable)		X												
Physical Exam		X												
Vital Signs (height/weight)		X												
Demographic Survey		X												
CGM Training			X		X									
Randomization					X									
DiAs Training					X									

Insulin Degludec (Tresiba) Pen Training					X		X		X		X			
Review of CGM data (EXP only) & SMBG data for hypo-and hyperglycemic events & AEs (EXP/CTR)						X	X	X	X	X	X	X	X	
Insulin dosing changes once per week at Day 7 in both groups						X	X	X	X	X	X	X	X	

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Chapter 1 Background and Synopsis

1.1 Introduction

Many people with Type 2 Diabetes Mellitus (T2DM) fail to reach glycemic control target even after the initiation of basal insulin [1]. Achieving tight glycemic control early following the diagnosis of T2DM is key to optimizing clinical outcomes, yet many patients and clinicians are reluctant to initiate and intensify insulin therapy. This arises primarily from a lack of healthcare provider (HCP) resources, clinical expertise, and participant understanding [2]. Furthermore, the literature indicates that self- titration of insulin could lead to faster glycemic control than physician led insulin titration [3].

Insulin degludec (degludec) is a daily administered basal insulin with a long duration of action (half-life of approximately 25 hours) and a stable profile. Degludec showed improved glycemic control with lower frequency of hypoglycemic events when compared to other long-acting insulins such as glargine [4].

Current safe and effective titration of basal insulins commonly recommends stepwise dose adjustments towards an individualized glycemic target (e.g., ADA/EASD recommends a fasting blood glucose target of 80-130 mg/dl for many adult participants with diabetes) based on fasting blood glucose values measured by Self-Monitoring Blood Glucose (SMBG) or individual Continuous Glucose Monitor (CGM) values from CGMs approved for non-adjunctive use [5]. Currently a stepwise algorithm using SMBG has been recommended for degludec using a starting dose of 10 units once daily for insulin naive participants or a 1:1 conversion for participants with T2DM who are already taking basal insulin.

Since the initial introduction of CGM into clinical practice in 2000, the accuracy and sophistication of these devices has progressively increased, resulting in more widespread use of CGM systems [6]. This requires availability of a CGM based titration algorithm for long-acting insulins. The expectation is that the automatic processing of CGM data, which is more robust and collected continuously, would result in improved titration with potentially more effective and safe dose recommendations, compared to standard titration by SMBG.

1.2 Device Description

The titration algorithms (both CGM and SMBG based versions) will run on the Diabetes Assistant AWS platform (DiAs-Cloud) – an established prototyping platform that was introduced by UVA in 2011 and has been maintained since. DiAs-Cloud enables the seamless integration of a smart phone application and AWS server architecture to enable data capture, dose computation, review by the clinical team, and communication to study participants. DiAs-Cloud has been used in over 25 clinical trials to date.

The CGM titration module comprises the three following components demonstrated in Figure 1:

- **Titration glucose level (TGL):** The TGL is a daily value derived from CGM data. For a given day, the TGL value is the minimum moving average (MA) with a 4-hour window across the day. Weekly TGL values (average or minimum) are used to get a dose adjustment.
- **Personalized target:** The personalization evaluates the risk of hypoglycemia by measuring the TGL variability. It personalizes the TGL target range accordingly by setting a lower glycemic target for participants with a low TGL variability, and a safer glycemic target for participants with a high TGL variability. The TGL variability is based on the coefficient of variation (CV) of the latest 14 TGL values.
- **Safety hypoglycemia feature:** This module adds a supplementary safety layer by ensuring a decrease in insulin dose if in a given week, a daily TGL value is under 80 mg/dL, or if any hypoglycemic event has been self-reported by the user or if the percent time of CGM below range reaches predetermined thresholds. In the case where hypoglycemia has been reported, this feature will overrule the TGL-based titration by suggesting a decrease in dose.

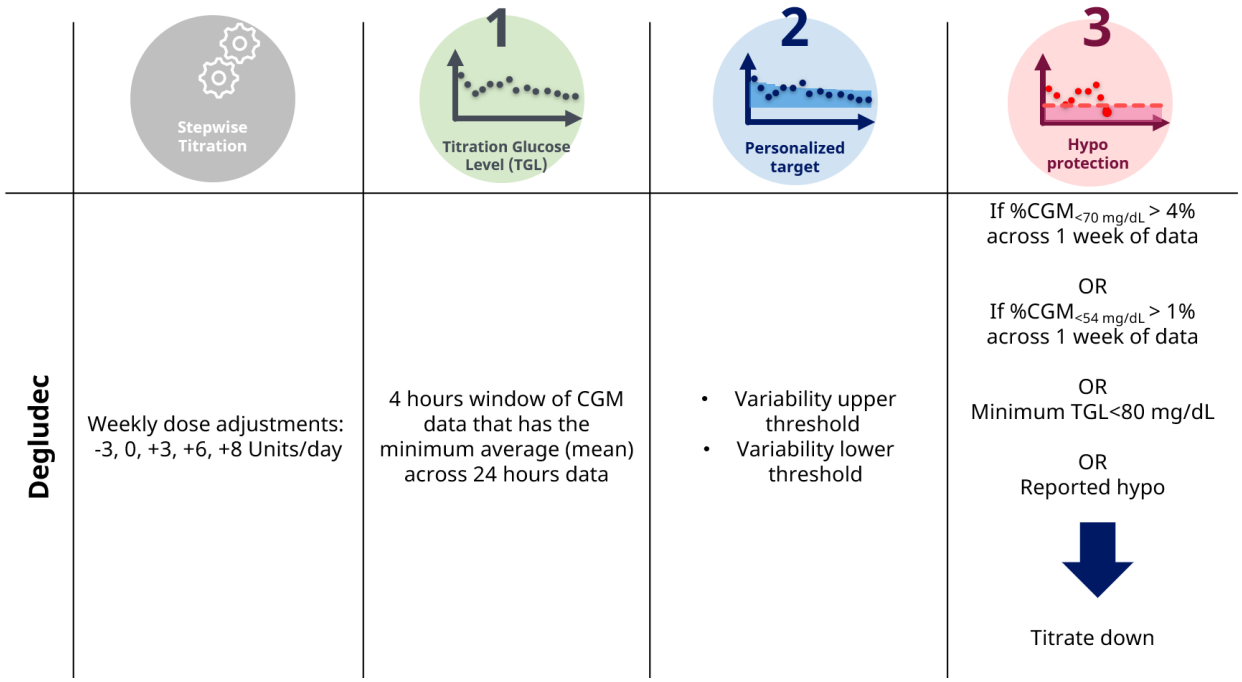

Figure 1: CGM-Based titration module review

1.3 Study Objective

The primary objective of the pilot study is to compare CGM-based titration versus standard SMBG-based titration of insulin degludec, both treatment arms with or without non-insulin anti-diabetic drugs, in terms of glycemic control measured by change in time in range (70-180 mg/dL) from baseline (-2 to 0 weeks) to week 14-16 in insulin experienced participants with T2DM. The secondary objective of the study is to explore other parameters of safety, efficacy

and feasibility when using CGM-based titration of insulin degludec in insulin-experienced participants with T2DM.

1.4 Study Design

This is a randomized, parallel group, multi-center trial. After two weeks of blinded CGM baseline observation, participants are randomized to CGM-based titration or standard titration by SMBG for 16 weeks. Participants in the standard SMBG based titration group will wear a blinded CGM during the whole study. The total daily basal insulin dose will be converted 1:1 to degludec. Dose changes will be made once weekly. Participants will be stratified related to use of sulfonylureas or glinides (either alone or in combination with other OADs) with a maximum cap of 9 participants (3 in the control arm and 6 in the experimental arm) being treated with sulfonylureas or glinides to complete the study.

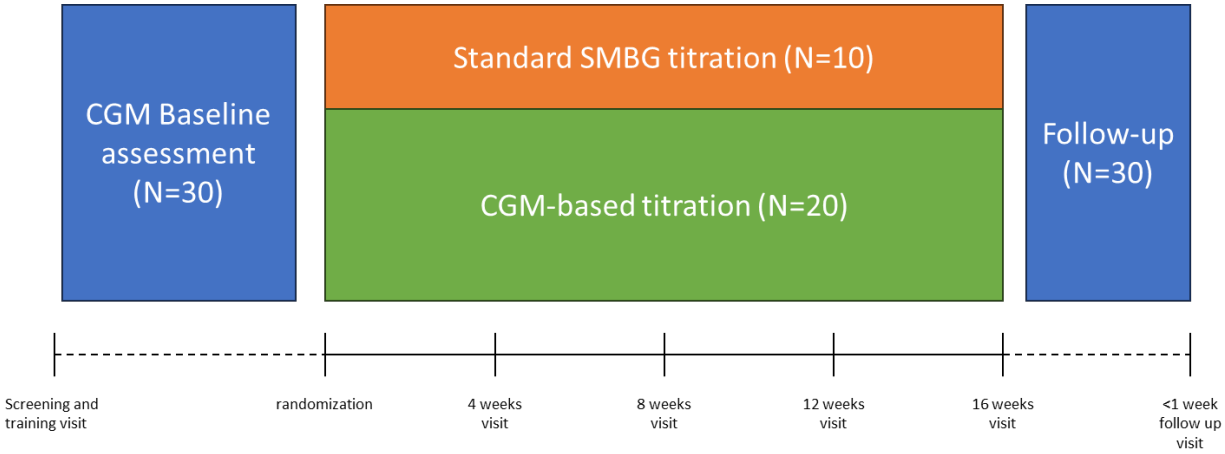

Figure 2: Study Diagram

1.5 Study Enrollment

Approximately 60 participants will be screened to complete 30 participants. This enrollment includes an estimated 50% for screen failures, dropouts, and withdrawal.

1.6 Clinical Sites

The study will be performed at the following clinical sites:

- University of Virginia (Charlottesville, VA)
- Mt. Sinai (New York, NY)

1.7 Study Visits

Clinic visits, videoconferences, or phone calls will be the preferred method of communication with study participants, but email and text communication will be used as needed. Additional clinic visits may occur as needed. The study physician may require participants to attend onsite visits as needed.

1.8 Study Endpoints

1.8.1 Primary Endpoint

Change in CGM-measured time in range 3.9-10.0 mmol/L (70-180 mg/dL) from baseline (-2 to 0, 2 weeks) to weeks 14-16 (2 weeks), compared between CTR and EXP arm.

1.8.2 Secondary Endpoints

With the exception of Device Deficiencies (DD), and acceptance rates, the secondary endpoints will be compared between EXP and CTR arm with correction of multiple comparisons if applicable. Refer to Chapter 13for more details.

Title	Time frame	Unit
Change in HbA1c	From baseline (week 0) to week 16	Percentage point
Change in time in tight range 3.9-7.8 mmol/L (70-140 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
Change in Time spent > 10.0 mmol/L (180 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
Change in Time spent > 13.9 mmol/L (250 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
Change in Coefficient of variation (CV - CGM)	From baseline (week -2-0) to week 14-16	%
Change in Mean glucose level (CGM)	From baseline (week -2-0) to week 14-16	Mmol/L
Change in Time spent < 3.9 mmol/L (70 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
Change in Time spent < 3.0 mmol/L (54 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
Number of clinically significant hypoglycemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 16	Number of episodes
Number of serious adverse events (SAEs)	From baseline (week 0) to week 16	Number of events
Number of treatment emergent adverse events (TAEs)	From baseline (week 0) to week 16	Number of events
Number of device deficiencies (DDs)	From baseline (week 0) to week 16	Number of events

Mean basal daily insulin dose at the end of trial.	Week 16	Units of insulin
Investigator acceptance rate of weekly dose guidance – from CGM based titration (EXP arm only)	From baseline (week 0) to week 16	%
The investigator changes the dose from the recommended or the current dose (EXP arm only)	From baseline (week 0) to week 16	Number of events

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Chapter 2 Study Consent Visit

Visit 1

2.1 Participant Recruitment and Enrollment

Before consent has been obtained, participants will be asked inclusion/exclusion criteria questions during pre-screening to determine study eligibility. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. Potential eligibility may be assessed as part of a routine-care examination.

A participant is considered enrolled in the study when the informed consent form has been signed by the participant and a member of the study team.

Consenting procedures and documentation are defined in section 15.3.

2.2 Informed Consent

After the informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by licensed study personnel, laboratory values, and pregnancy testing (if applicable) to screen for exclusionary medical conditions.

Individuals who do not initially meet study eligibility requirements may be rescreened later per investigator discretion. The study physician will have the discretion to exclude or discontinue a participant's enrollment in the trial.

Chapter 3 Screening Visit

Visit 2

3.1 Participant Inclusion Criteria

The participants must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Age 18 years or older at signing of informed consent
2. Diagnosis of T2DM minimum 180 days before the day of screening
3. HBA1c between 7-9% and measured by local lab at screening
4. On daily basal insulin for at least 90 days before inclusion into the study
5. Stable dose of oral and injectable (other than insulin) antidiabetic medications for 90 days prior inclusion. Acceptable medications include:

    a. Metformin
    b. Sulfonylureas
    c. Meglitinides (glinides)
    d. DPP-4 inhibitors
    e. SGLT2 inhibitors
    f. Thiazolidinediones
    g. Alpha-glucosidase inhibitors
    h. Oral combination products (for the allowed individual oral anti-diabetic drugs)
    i. Oral or injectable GLP-1 Receptor Agonists (RAs)
    j. If on sulfonylureas or glinides, willingness to reduce dose by 50%

3.2 Participant Exclusion Criteria

The participant must not have any exclusion criteria in order to be eligible to participate in the study.

1. Hypersensitivity to Degludec
2. Use of an insulin pump
3. Use of a short-acting insulin
4. Participation or has participated in another trial within 90 days of the screening visit
5. Female who is pregnant or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method
6. Any disorder, except for conditions associated with T2D, which in the investigator's opinion might jeopardize participant's safety or compliance with the protocol.
7. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days of the screening visit
8. Known skin reactions to CGM adhesives
9. Current/prior use of CGM within 30 days of the screening visit

10. Any planned surgery or procedures where basal insulin would be decreased or held in anticipation

3.3 Screening Procedures

Screening procedures will last approximately 1-2 hours. The visit may occur in-person or by telecommunication. The following procedures may be performed/data collected/eligibility criteria checked and documented:

1. Inclusion and Exclusion criteria assessed.

    1. Demographics, including:

        a. Date of birth
        b. Gender
        c. Race
        d. Ethnicity

    2. Medical History, including diabetes history

        a. Date of onset if known or duration of disease
        b. History of CGM use
        c. Severe hypoglycemia history
        d. Severe hyperglycemia history
        e. History of seizures
        f. Loss of consciousness
        g. Surgical history
        h. Allergies

    3. Daily sum (24 hour) of previous 7 days of basal insulin: amount and timing of injections
    4. Allergies
    5. Concomitant medications
    6. Physical Examination – A historical history and physical report within 12 months of screening appointments may be used but is not required for eligibility. If vitals are not available, may include self-reported values.

        a. Weight (may be self-reported)
        b. Height (may be self-reported)
        c. Blood pressure
        d. Temperature (if available)
        e. Heart Rate

    7. Screening Labs

a. Hemoglobin A1c (serum) at screening
b. Comprehensive Metabolic Panel (defined in Section 8.2) and Thyroid Stimulating Hormone within 14 days of screening
c. Urine or serum pregnancy test for all women of childbearing potential (this test can be done remotely with results sent to the study team)

Any labs required may be obtained at a laboratory (e.g., LabCorp) convenient to the participant. The study physician or physician designee will have the discretion to repeat screening tests.

This study is not meant to find out if the participant has any other disease or problem. The study leaders will alert the participant if any of the research results are important to his/her health during the study. The participant may have a copy of the screening tests to discuss with the personal physician. When the blood tests are completed, any blood left over will be thrown away. It will not be stored for any future testing.

The study physician or physician designee will have the discretion to repeat screening tests. The repeat screening tests may be conducted locally (e.g., LabCorp). The participant may request a copy of any of the results from the screening evaluation to review with their primary care provider.

Participants may be re-screened at another time if their clinical situation changes as determined by the study physician.

3.4 Demographic Data Survey

The study team has expanded the demographic questionnaire to include additional questions regarding race/ethnicity and socio-economic status (SES). This is in response to the growing body of research in diabetes treatment and technology revealing significant disparities in minoritized population's representation in clinical trials and access to devices/treatments that improve diabetes outcomes. Researchers are being asked by NIH and other funding institutions to make attempts to reduce this under-representation in clinical trial representation. For this reason, collection of detailed demographic data regarding participants in technology trials has become essential. This includes data on race/ethnicity, income levels and insurance status, as well as education and other variables that describe the study population. However, it is important to note that individuals completing demographic questionnaires are clearly instructed that responses to these items are not mandatory and will not affect their ability to participate in the study.

The Demographic Data Survey will be electronically administered once eligibility has been met.

a. Gender
b. Race
c. Ethnicity
d. Marital status
e. Level of education

344 f. Employment status
345 g. Household income
346 h. Health insurance status

Chapter 4 Training Visit

Visit 3

4.1 Algorithm Description

Two algorithms designed to aid basal insulin titration will be tested in this study:

- An SMBG-based weekly titration algorithm derived from current standard of care
- An investigational CGM-based, personalized titration algorithm developed in collaboration between the University of Virginia Center for Diabetes Technology and Novo Nordisk

The CGM-based titration algorithm will be tested for effectiveness and safety against the standard of care SMBG titration algorithm. The SMBG-based algorithm will be used by participants in the Control (CTR) arm and the CGM-based algorithm will be used by participants in the Experimental (EXP) arm as further defined in Chapter 6.

The SMBG-based algorithm is a simple look-up table algorithm advising to maintain, increase, or decrease the current basal dose by 3, 6, or 8 Units of insulin based on three (3) fasting SMBG taken on the two (2) days prior and the day of titration, see details in Chapter 6.

All dose computation will be run on the DiAs-Cloud AWS architecture, approved by the clinical team, and delivered to the participants via the study app.

4.2 Study App

All participants will use the investigational study app during the Intervention Period (visit 5-9). This app may be placed on the participants personal smartphones, or a study phone as needed. A study Dexcom Clarity account will be created for participants in the EXP arm. Participants in the CTR arm will use the same sensor technology, but “blinded”, i.e., they will use an app or sensor receiver to start and end sensor sessions but will not have access to any CGM measurements or alarms. All participants will receive weekly insulin dose recommendations based on the algorithm corresponding to their randomization and reviewed (CTR arm) or pre-approved (EXP arm) by their site study physician. Dose, date, and time of the dose change will be available via the study app. Study participants in the CTR arm will also record self-measured fasting blood glucose as measured by SMBGs through the study app. The study physician will be able to monitor only the EXP Group CGM data. The CGM data for the CTR Group is blinded to both the participant and the study team. The study physician will be able to monitor the insulin dose changes of both study groups during the entire study period via the Web portal of the DiAs-Cloud architecture.

Qualified study team members will train the participant in performing specific tasks when using the study app:

- How to view the CGM information including the most recent CGM value, trend arrow, and CGM graph (EXP arm only)
- Low and high threshold alerts will be set. The participant may choose the threshold alert values, but the low alert may not be set to less than 70 mg/dl and the high alert may not exceed 300 mg/dl (EXP arm only)
- How to read the insulin dose recommendations approved by the study physician
- How to record symptomatic hypoglycemic events and associated SMBG values
- How to record fasting SMBG values

4.3 Continuous Glucose Monitor

The study will use the Dexcom G6 CGM and/or Dexcom G6 Pro. All participants will be introduced to the CGM by a qualified member of the study team. Depending on the participant's prior experience, the study team will demonstrate the following CGM functionality:

- How to start a new CGM session.
- How to connect the CGM transmitter as well as troubleshooting techniques for reconnecting.
- For CGM-based titration arm participants: How to view the CGM information including the most recent CGM value, trend arrow, and CGM graph. Low and high threshold alerts will be set. The patient may choose the threshold alert values, but the low alert may not be set to less than 70 mg/dL and the high alert may not exceed 300 mg/dL.

With the guidance of the study team, the participant will then insert the sensor and begin wearing the CGM. The study team will confirm that the participant understood the training and all questions have been answered.

The participants in the EXP Group will wear a blinded CGM during the CGM Run-In Phase and will wear a commercial unblinded CGM during the intervention phase.

The participants in the CTR Group will wear a blinded CGM during the CGM Run-In Phase and during the intervention phase.

4.4 Blood Glucose Meter and Strips

All participants will be provided with a study glucometer before the start of the CGM Run-In Phase. All study blood glucose meters (BGM) will be QC tested with control solution(s) prior to issuing to the participant. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The BGM will be updated with correct local date and time before being provided to the participants

Study staff will demonstrate proper use of the meter as described in the user manual. The participant will be required to demonstrate proficiency in the use of the device. The study team will confirm that all questions have been answered and that the participant has understood the training.

Participants will be reminded to use the study blood glucose meter for all fingerstick BGs during the study. Participants will be instructed to perform an SMBG at the following timepoints:

- fasting, pre-breakfast each day with special importance on collecting the fasting, pre-breakfast SMBG on Day 5, 6 and 7 after an insulin dose change
- if experiencing symptoms of hypoglycemia (e.g., dizziness, light-headedness, sweating, shaking, trouble concentrating, etc.)
- if experiencing symptoms of hyperglycemia (e.g., extreme thirst, weakness, frequent urination, blurry vision, nausea, etc.)
- if the CGM alarms (EXP Group only)

Participants will be instructed to contact study staff for a replacement of the meter, test strips, and control solution, if necessary, if a meter fails QC testing at home.

Raw data from the BGM will be uploaded to the study database as a minimum at study end and checked for unreported hypoglycemia (BGM<70mg/dL).

At the end of trial, the participant BG reporting through the study app will be compared with a readout from the BGM.

4.5 Study Medication

All participants will be provided with the FDA approved Insulin Degludec (Tresiba) (Novo Nordisk) 100 units/ml, subcutaneous. (s.c,) solution for injection, 3 mL prefilled injector-pens after randomization for the duration of the Intervention Phase. Conversion with their prior basal insulin will follow the approved Tresiba label (1:1 conversion) at the start of the Intervention Phase which is in accordance with the drug labelling. Training on the use of the pen will be specific to the individual. Participants will receive an electronic copy of the package insert which includes Instructions for Use.

Insulin needles will also be provided for use during the study; however, participants may elect not to use this supply.

Insulin degludec is a daily administered basal insulin with a long duration of action with a half-life of approximately 25 hours and a stable profile. Degludec results in improved glycemic control with lower frequency of hypoglycemic events when compared to other long-acting insulins such as glargine [4].

Participants and the study physician will discuss missed dose and the proper dosage that should be administered. Missed doses will not be recorded as protocol deviations. Remaining degludec supplies will be returned to the study team at the conclusion of the study.

4.6 Additional Medication

The study team will be informed about any additional medication started during the study. All medication that can affect glycemic control must be kept unchanged throughout the trial. New such drugs or dose changes of should only be prescribed/ordered, if needed, after review by the clinical site PI of the participant.

4.7 Hemoglobin A1c Kit

The study team will review the contents of the HbA1c Capillary Kit with the participants. Instructions and the appropriate supplies are provided in each kit. The study team will review the proper collection techniques and mailing instructions. Participants will be provided with the option of collecting these samples at home or attending in-person clinic appointments.

4.8 Glycemic Treatment Guidelines

All participants will be instructed on hypoglycemia and hyperglycemia symptoms and will receive a handout on how to treat these symptoms.

4.9 Glucagon Emergency Kit

A home glucagon emergency kit will be required. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

4.10 Study Accountability Procedures

Device serial numbers will be recorded in a case report form (CRF) and use of equipment will be tracked. The pharmacy at each clinical site will oversee drug distribution and maintenance of drug accountability logs.

Chapter 5 Continuous Glucose Monitor Run-In Phase

Visit 4

5.1 CGM Run-In Phase

Once all screening procedures and all necessary training activities are completed, all participants will begin a two-week at home use of a blinded CGM. The Run-In Period starts when the CGM is activated by the participant. During this Run-In period, all participants will be asked to follow their usual care without any changes in their insulin parameters or glucose lowering drugs.

Participants will be advised that the CGM equipment will need to be promptly returned to the study team to facilitate downloading the data from this equipment. The participant will be informed that in order to be eligible for the study, the CGM must be used 10 out of 14 days CGM, a day must contain 70% measurements to be counted.

5.2 Successful Completion of Run-in Phase

The study team will review the CGM data to determine if 10 out of 14 days of data are available. If affirmed, the participant will be randomized into one of the two study arms. The investigator will have the discretion to extend or repeat this data collection period as needed.

Chapter 6 Randomization Visit

Visit 5

Upon the completion of the CGM Run-In Phase, study participants will be randomized 2:1 to one of two groups:

EXPERIMENTAL (EXP) Group – CGM Based Titration

- Participants will wear an unblinded CGM during the study.
- Participants will be supplied with Insulin Degludec (Tresiba) 100 units/ml, s.c, solution for injection, 3 mL prefilled pen-injector, by Novo Nordisk for the duration of the study.
- The total daily basal (long and intermediate-acting) insulin dose based on pretrial 24/h insulin dose will be converted 1:1 to Insulin Degludec (Tresiba) per FDA labelling.
- Participants will continue to use the study provided BGM meter (measuring daily fasting glucose and confirming symptomatic hypoglycemia).
- Study team will install the study app and the Dexcom Clarity app on the participant's compatible smartphone or on a study phone provided to participant per participant's request and compatibility of personal device. Study team will set the study app with the participant's study information (e.g., Participant ID)

CONTROL (CTR) GROUP – Standard SMBG Titration

- Participants will wear a blinded CGM during the study.
- Participants will be supplied with Insulin Degludec (Tresiba) 100 units/ml, s.c, solution for injection, 3 mL prefilled pen-injector, by Novo Nordisk for the duration of the study.
- The total daily basal (long and intermediate-acting) insulin dose based on pretrial 24/h insulin dose will be converted 1:1 to Insulin Degludec (Tresiba) per FDA labelling.
- Participants will continue to use the study provided BGM meter (measuring daily fasting glucose and confirming symptomatic hypoglycemia).
- Study team will install the study app on the participant's compatible smartphone or on a study phone provided to participant per participant's request and compatibility of personal device. Study team will set the study app with the participant's study information (e.g., Participant ID)

6.1 CGM Based Titration Algorithm

- The participant will measure fasting, pre-breakfast SMBG daily, but the insulin dose is adjusted based on the CGM.
- Participants in the CGM-based titration group will get a once weekly insulin dosing recommendation displayed on the study app. If the participant wants to deviate from the recommended insulin dose, they will be advised to contact the study physician prior to changing the dosing recommendation.

- The study physician will monitor and approve the dose recommendations each week prior to participants notification. The participant's unblinded CGM data is reviewed by the physician as a function of reviewing the insulin dosing recommendations.
- The physician approval will be completed using the DiAs-Cloud architecture where the study physician will access the data and recommendation via the study Web portal. Study physician will be instructed to only deviate from the provided dose if the safety of the participant is engaged.
- Modification of the dose recommendation should occur for safety purposes only. If modified, the study physician should document the revised dose and the rationale for the change of dose on a study CRF.
- Once approved, the participants will receive notification in their phone/study phone with the new dose.; the recommended dose taken will be confirmed once a week (and within 24h of receiving the new dose) by the participant into the study app. Dose, date, and time of the dose change will be available via the study app.

- At the end of each week, the participant will be asked to confirm the doses taken during the week on a study CRF.
- Only weekly dose adjustments/titration will be performed unless the insulin dose is changed during the week for safety purposes (at which point the participant will be asked to enter the new dose in the study app).

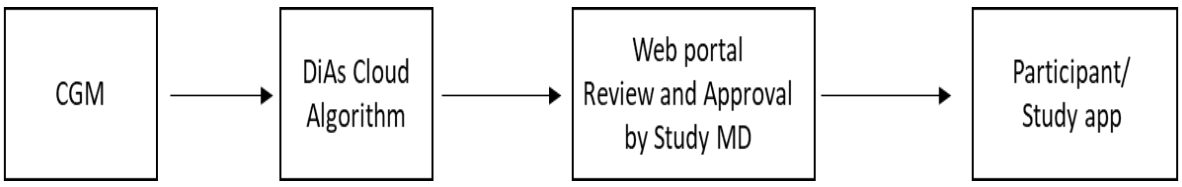

Figure 3: CGM-Based Titration Flow

Risk categories are based on the variance of the Titration Glucose Levels (TGL, a CGM-based glycemic index) (Table 1) over the past two (2) weeks; dose changes are as follow:

Low hypo risk	Avg risk	High risk	Dose change
Min TGL <80*	Min TGL <80*	Min TGL < 80* OR Avg TGL <98	-3IU
80 ≤ Avg TGL < 102	80 ≤ Avg TGL < 120	98≤ Avg TGL < 120	0 IU

102 ≤ Avg TGL < 144	120 ≤ Avg TGL < 144	120 ≤ Avg TGL < 144	+ 3IU
144 ≤ Avg TGL < 162	144 ≤ Avg TGL < 162	144 ≤ Avg TGL < 162	+ 6IU
Avg TGL ≥162	Avg TGL ≥162	Avg TGL ≥162	+8IU

* If one TGL is below 80 mg/dL the patient will be down titrated

Table 1: Titration Glucose Levels.

6.2 Safety Assessment

- Weekly insulin dose recommendations made by the CGM-based algorithm will be approved by the study physician each week.
- The acceptance of the recommended dose will be entered by the participant into the study app Failure to do so within 24h of receiving the titrated dose advice for the week will trigger an automated system notification to the study team who will follow up with the participant and document an out of cycle visit CRF.
- Hypoglycemic monitoring and reporting.
- Systematic collection of insulin dose history: while not available in real-time it can be made available to study physicians if necessary for safety
- Any revised recommended dose changes will be entered into the study app along with the date and time.

6.3 Standard Titration Algorithm

- The participant will measure fasting, pre-breakfast SMBG daily, but three (3) fasting, pre-breakfast SMBGs measured on Day 5, 6 and 7 will be used to titrate the insulin dose; if less than three SMBGs are provided, the previous week's dose will be re-recommended or titrated -3IU (if one SMBG is below 80 mg/dL).
- The dose recommendation will be based on the titration algorithm described in Table 2 below based on the three SMBGs. The participant will receive their weekly basal dose recommendation via their phone/study phone and will confirm acceptance/receipt of recommended dose in the study app. If the participant wants to deviate from the recommended insulin dose, they will be advised to contact the study physician prior to changing the dosing recommendation.

Value to be used	Pre-breakfast SMBG available (mg/dL)	Dose change
Lowest value	Pre-breakfast SMBG <80	-3IU
	80 ≤ Pre-breakfast SMBG ≤ 130	0 IU
	130 < Pre-breakfast SMBG < 144	+3IU
	144 ≤ Pre-breakfast SMBG < 162**	+6IU
Mean	Pre-breakfast SMBG ≥162**	+8IU

Table 2: Standard Algorithm Table

- Study physician will document review of each dose recommendation via the study web portal and document this review on a study case report form (CRF). Study physician will be instructed to only follow up with the participant if the safety of the participant is engaged.
- Modification of the dose recommendation by either the participant or study physician should occur for safety purposes only. If modified, the study physician should document the revised dose and the rationale for the change of dose on a study CRF.
- At the end of each week, the participant will be asked to confirm the dose taken during the week on a study CRF.
- The physician will contact the study participant in case of safety concerns.
- Only weekly dose adjustments/titration will be performed unless the insulin dose is changed during the week for safety purposes.

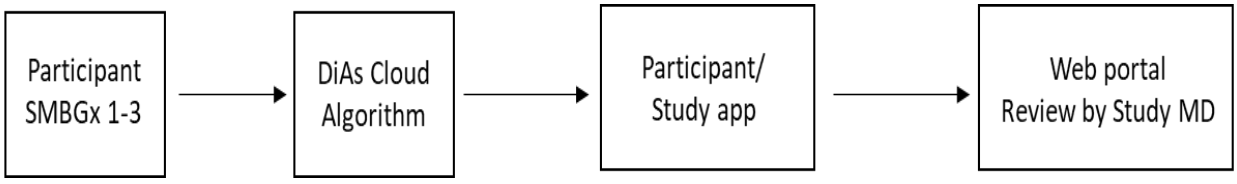

Figure 4: Standard SMBG Titration Flow

6.4 Safety Assessment

- Fasting, pre-breakfast each day with special importance on collecting a fasting, pre-breakfast SMBG on Day 5, 6 and 7 after an insulin dose change.
- Hypoglycemic monitoring and reporting.
- Systematic collection of insulin dose history: while not available in real-time it can be made available to study physicians if necessary for safety.

- Systematic collection of blinded CGM: while not available in real-time, the CGM data is automatically transmitted from the blinded CGM app to our study server, allowing for easy unblinding if necessary for safety.
- Study physician will review the dose that the participant has entered into the web portal within 24 hours.

6.5 Hemoglobin A1c Collection – Central Lab

All participants will collect a hemoglobin A1c capillary blood sample and will send the sample in a provided pre-labeled package to the central laboratory for analysis.

6.6 Internet Disconnection

If the participant is without internet service for more than 14 days, participant will be instructed to contact the study team to re-establish connectivity. The study team may provide a study phone with SIM card. CGM Based Titration Algorithm participants will be asked to maintain their current basal dosing until they contact study team or re-establish connectivity, whichever comes first. All participants will be instructed to follow Glycemic Treatment Guidelines (Chapter 9) regardless of connectivity status.

Chapter 7 Intervention Phase

7.1 4-Week Check-In Visits

Visit 6

The study team will contact the participant via telephone call or videoconferencing to assess adverse events, adverse device effects, and device issues approximately every 2 weeks (+/-3 days). If the participant chooses, this visit can occur at the clinical site. The study team will verify the following information:

- Inquire about any changes to the participant's medical history and medication changes
- Review of CGM data (EXP group only)
- Review of SMBG
- Review of hypoglycemic events & confirmation SMBG measurements
- Review of hyperglycemic events & confirmation SMBG measurements
- Review of insulin dosing
- Review proper insulin pen use and injection technique
- Address any concerns about the algorithm (Standardized Titration and CGM based)
- Review of any technical complaints expressed by the participant
- Verify that CGM alarms continue to be set at <70 mg/dL and >300 mg/dL (EXP Group only)

7.2 8-Week Check-In Visit

Visit 7

Participants will have a telephone call or videoconference call in Week 8 (+/-3 days). Procedures are described in section 7.1.

All participants will collect a hemoglobin A1c blood sample and will send the sample in a pre-labeled package to the central laboratory for analysis.

7.3 12-Week Check-In Visit

Visit 8

Participants will have a telephone call or videoconference call in Week 12 (+/-3 days). Procedures are described in section 7.1.

7.4 Study End Visit -16-Week

Visit 9

Participants will have clinic visit, a telephone call, or videoconference call in Week 16 (+/-3 days). Study participants will be instructed on how to transition back to the home insulins and the doses to be used. Participants will be informed that there may be a risk of severe hypoglycemia and/or severe hyperglycemia during the transition back to the participant's usual home basal insulin. The study physician will be available for consultation during this transition period.

The study team will verify the following information:

a. Return of any remaining study supplies (i.e., CGM sensors, transmitter)
b. Return of unused degludec
c. Download of glucometer; equipment may be returned to the participant
d. Review of the CGM data and SMBG data (hypo- and hyperglycemic events)
e. The participant has collected a hemoglobin A1c blood sample and has sent the sample in the pre-labeled package to the central laboratory for analysis.
f. Assessment of adverse events, adverse device effects, and device issues
g. Obtain body weight measurement (measured on-site or self-reported)

7.5 Post-Study Check-In Visit

Visit 10

Participants will have a telephone call or videoconference call about 2-7 days after completing the study. Study participants will be asked about their glycemic control as well as hypo-and hyperglycemic events since completing the Intervention Phase (visit 9).

7.6 Early Termination Visit (If Applicable)

Participants will be asked to attend the Study End Visit (visit 9) in the event of withdrawal or early termination.

7.7 Unscheduled Visits

Participants may have unscheduled visits during the study period if required for additional device training or other unanticipated needs per the study investigator discretion.

Chapter 8 Testing Procedures

8.1 Hemoglobin A1c

8.1.1 Local Laboratory

A blood sample may be obtained to measure a hemoglobin A1c level at the screening visit. Labs may be obtained at the clinical site or a local laboratory (e.g., LabCorp) convenient to the participant.

8.1.2 Central Laboratory

The hemoglobin A1c level will be based on a capillary sample collected by the participant using a kit at home or at an in-person clinic visit if assistance is needed [8]. Collection points will be at Randomization (week 0), visit 7 (week 8), and visit 9 (week 16). The participant will collect this blood sample and will send the sample in a pre-labeled package to the central laboratory for analysis. The same collection kit (ARDL HBA1c collection kit) will be used at all sites.

8.2 Comprehensive Metabolic Panel

A blood sample will be obtained at screening to assess kidney and liver functioning. Labs may be obtained at the clinical site or a local laboratory (e.g., LabCorp) convenient to the participant. Blood test obtained within 14 days prior to enrollment may be used for eligibility purposes.

CMP Definition: Alanine aminotransferase (ALT/SGPT); albumin:globulin (A:G) ratio; albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase (AST/SGOT); bilirubin, total; BUN; BUN:creatinine ratio; calcium, serum; carbon dioxide, total; chloride, serum; creatinine, serum; eGFR calculation; globulin, total; glucose, serum; potassium, serum; protein, total, serum; sodium, serum.

8.3 Thyroid Stimulating Hormone

A blood sample will be obtained at screening to assess thyroid function. Labs may be obtained at the clinical site or a local laboratory (e.g., LabCorp) convenient to the participant. Blood test obtained within 14 days prior to enrollment may be used for eligibility purposes.

8.4 Pregnancy Test

A beta HCG or urine pregnancy test will be required for women of childbearing potential at the screening appointment. The test must be negative to continue participation in the study. Labs may be obtained at the clinical site or a local laboratory (e.g., LabCorp) convenient to the participant. A point of care test may also be used to assess pregnancy status. A photograph of the test result will serve as source documentation.

8.5 Demographic Data Survey

The Demographic Data Survey will be asked after study eligibility has been met (visit 2).

Chapter 9 Glycemic Treatment Guidelines

9.1 Hypoglycemia Protocol

Hypoglycemic events should be classified as per ADA guidelines and based on SMBG confirmatory measurements [5]. Study participants will follow the standard hypoglycemia protocol described in the appendix Glycemic Treatment Guidelines in case of a hypoglycemic event. Participants will be reminded to obtain a SMBG at the onset of hypoglycemic symptoms. All participants will be asked to report symptomatic hypoglycemic events and provide SMBG confirmation to the study team via the study app. Mild hypoglycemia (situation where study participant is able to treat her/himself) can be treated by oral administration of glucose of carbohydrate containing products.

In case a participant is not able to treat him/herself (level 3 hypoglycemia), treatment will escalate to glucagon or glucose given intravenously (see also section “reportable events”). The study coordinator and the study physician will be informed of the event by the study participant as soon as possible but not later than 12 hours after the event.

The study participant will record day and time of the hypoglycemic events in a pre-designed form via the study app in addition to reporting all relevant data in order to properly classify the event. Participant will be instructed to record a confirmation SMBG(s). Study coordinator and study physician will report the event if required per protocol.

9.2 Hyperglycemia Protocol

Study participants will follow the standard hyperglycemia protocol described in the appendix Glycemic Treatment Guidelines in case of a hyperglycemic event during both the CGM run-in phase and the intervention phase. Participants will be reminded to obtain a SMBG at the onset of hyperglycemic symptoms. All participants will be asked to report symptomatic hyperglycemic events and provide SMBG confirmation to the study team. The study coordinator and the study physician will be informed of the event by the study participant as soon as possible but not later than 12 hours after the event.

The study participant will record day and time of the hyperglycemic events in a pre-designed form via the study app in addition to reporting all relevant data in order to properly classify the event. Participant will be instructed to record a confirmation SMBG(s).

9.3 Study Support

Participants will receive study staff contact information to ask any questions they may have during the study. Additionally, participants will be provided with study contact information for technical support with the study app and the study CGM. The participant will be asked to call the study team at any time during the study for any health-related issues, including hypoglycemia <70 mg/dL or frequent highs >300 mg/dL, as confirmed by an SMBG value. The blood glucose value will be confirmed by fingerstick blood glucose measurement.

Chapter 10 Risks Associated with Clinical Trial

10.1 Potential Risks and Benefits

Risks and Benefits are detailed below. Hypoglycemia and hyperglycemia are a risk in participants with type 2 diabetes, and participants will be monitored for these symptoms.

10.1.1 Venipuncture Risks

A hollow needle will be placed in the arm for taking blood samples. Blood draws can cause common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

There is the risk of contamination from blood sampling techniques. Hand washing with either soap & water or waterless hand sanitizer will be used prior to caring for the study participant. Gloves will be worn during blood sample collection and processing. Medical personnel will continue to practice hygiene for the participant's protection (i.e., hand washing, changing gloves frequently, disposing needles properly). Gloves will be removed, and hands washed or sanitized prior to leaving and upon return to the participant's room. Soiled linen will be changed to minimize the transfer of pathogenic organisms.

10.1.2 Fingerstick Risks

About 2 drops of blood will be removed by fingerstick for measuring blood sugars and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as finger sticks are part of the usual care for people with diabetes.

10.1.3 CGM Sensor Needle Risks

Participants using the CGM will be at low risk for developing a local skin infection or skin reactions at the site of the sensor needle placement. Though approved for 10 days of use, if a catheter is left under the skin for more than 24 hours, it is possible to get an infection where it goes into the skin, with swelling, redness, and pain. There may be bleeding where the needle is inserted and bleeding under the skin causes a bruise (1 in 10 risk).

Study staff should verbally alert the participant that on rare occasions, the CGM may break and leave a small portion of the needle under the skin that may cause redness, swelling, or pain. The participants will be instructed to notify the study coordinator immediately if this occurs.

10.1.4 Risks of Hypoglycemia

As with any person having T2DM and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and subsequently for a few days the participant may not be as aware of symptoms of hypoglycemia. There is the risk of false hypoglycemia alarms based on sensor pressure, e.g., sleeping on the sensor

A poorly functioning CGM can periodically display falsely high glucose values, which could lead to inappropriate insulin recommendation.

10.1.5 Risks of Hyperglycemia

Hyperglycemia could occur if insulin dosage is too low. A poorly functioning CGM can periodically display falsely high glucose values, which could lead to inappropriate insulin recommendation.

10.1.6 Risks of Device Reuse or Exposure to Used Device

Participants will be informed that FDA or relevant national authorities have approved the CGM for single use and that by using them among multiple patients, bloodborne pathogens (i.e., Hepatitis B) may be spread through the use of multiple users. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter is attached to the sensor but does not enter the skin and the receiver, if used, is a handheld device.

CGM cleaning instructions are provided in the Dexcom G4 Platinum (Professional) Cleaning and Disinfection manual (current edition) and a similar approach will be applied for the G6 version used in this study.

The study-provided blood glucose meter will be returned to the study participant at the conclusion of the study after the study team has confirmed data collection. Cleaning procedures will be used if it is necessary to be in physical contact with the equipment to download the device.

10.1.7 Risk Related Use of the Algorithm

Use of the algorithm may result in hypoglycemia, hyperglycemia, and increased glucose variability.

10.1.8 Risk of Using Degludec

The study drug, degludec, may result in hypoglycemia or an allergic reaction.

10.1.9 Missing Insulin Doses

All participants will be asked to document missed insulin doses on the CRF completed at the end of each week. Study physician may review CRF and contact study participant as needed.

10.1.10 Internet Disconnection

An unplanned internet disconnection of >14 days will be considered a device deficiency.

10.1.11 Risk of Loss of Confidentiality

Loss of confidentiality is a potential risk. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits. The study team will assign a Participant ID number and a code word to each person who signs a consent form. Both are entered to record study data in eCRFs. Limited study team members have access to identified data. CGM and BGM data are de- stored in a cloud storage in a de-identified format.

10.1.12 Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM. If these reactions occur, different adhesives or “under-taping” (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Whenever the skin is broken there is the possibility of an infection. The CGM sites are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is indicated for use. Therefore, participants will be carefully instructed about proper use of the sensor.

Participants will be advised that acetaminophen (Tylenol) taken in high doses (e.g., > 1 gram every 6 hours in adults) may falsely raise sensor glucose readings.

10.1.13 Known Potential Benefits

It is expected that this protocol will yield increased knowledge about using a titration algorithm for insulin dosing suggestions. The access to a CGM can provide improvement in diabetic care. The individual participant may or may not benefit from study participation.

10.1.14 Risk Assessment

The risk to participants in this study is no higher than the risks associated with type 2 diabetes under normal outpatient conditions. This assessment is based on the following facts: (1) adults with insulin-treated diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) both study interventions involve feedback and advice for insulin dosing. Changes in dosing may result in hypoglycemia and hyperglycemia symptoms.

10.2 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and in compliance with CFR 21.

Whenever possible, data will be directly collected in electronic case report forms (eCRFs), which will be considered the source data.

The protocol is considered a significant risk device study since the algorithm used in this study is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

There is no restriction on the number of participants enrolled by each site towards the overall recruitment goal.

The study is supported by third party collaborators for the provision of study drugs, devices, and software. Current study collaborators are:

- Novo Nordisk (Bagsværd, Denmark)
- Dexcom Inc. (San Diego, CA)

Chapter 11 Adverse Events, Device Issues, and Stopping Rules

11.1 Definitions

11.1.1 Adverse Events (AE)

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures or occurring during the course of a study in which a device, biologic, or drug is used in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the device(s) under investigation).

For this protocol, an adverse event is considered any untoward medical occurrence, unintended disease or injury, or untoward clinically significant clinical sign in a study participant that manifests while in the study if it was not present before enrolling in the study, or if present prior to enrollment, it has increased in severity, frequency, or type. Adverse Event recording and reporting will occur at the onset of the CGM Run-In through post-study check-in visit (visit 4 – visit 10).

All reportable AEs—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on the Adverse Event Form. Adverse Events that are identified during the study and defined as related to the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect.

Skin reactions from sensor placement are only reportable if severe and/or required treatment.

A positive pregnancy test will not be considered an adverse event.

Treatment Emergent Adverse Event (TAE): An undesirable event that is not present prior to medical treatment, and an already present event that worsens either in intensity or frequency which occurs between the first dose and the end of follow up visits.

11.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that:

- results in death.
- is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- 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 (life threatening).

- is a congenital anomaly or birth defect.
- is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).
- Any serious psychological and emotional distress in study participation (suggesting need for professional counseling or intervention).

11.1.3 Unanticipated Problem (UP)

An unanticipated problem is any event, experience, issue, instance, problem or outcome that meets all 3 of the following criteria:

- Is unexpected in terms of the nature, severity or frequency given the research procedures that are described in the protocol –related documents AND in the characteristics of the population under study.
- Is related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research places the participant or others at greater risk of harm (physical, psychological, economic or social) than was previously known or recognized OR results in actual harm of the participant or others. An unanticipated problem generally required a change in policy or procedure , warrants consideration of substantive changes to the protocol/consent or other immediate corrective actions in order to reduce the risk or eliminate immediate hazard.

11.1.4 Adverse Reaction (AR)

An adverse reaction (AR) is an AE for which the causal relationship between the drug and the AE is suspected. The FDA-approved Prescribing Information (PI), also known as United States Prescribing Information (USPI), which reflects the FDA's finding regarding the safety and effectiveness of the human prescription drug under the labeled conditions of use, will be reviewed in the event of an adverse reaction. In this trial the review will be performed whenever an AE is considered related to Insulin Degludec (Tresiba).

11.1.5 Serious Adverse Reaction (SAR)

An adverse event which fulfils both the criteria for a serious adverse event and the criteria for an adverse reaction.

11.1.6 Suspected Unexpected Serious Adverse Reactions (SUSAR):

An SAR which is unexpected and regarded as possibly or probably related to the insulin degludec by the investigator.

11.1.7 Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

11.1.8 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device. Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed per the medical monitor's assessment, in collaboration with the investigator (section 11.7.1) .

11.1.9 Device Complaints and Malfunctions

A device complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise work as intended. Performance specifications include all claims made in the labelling for the device. The intended performance of a device refers to the intended use for which the device is labelled or marketed (21 CFR 803.3).

11.2 Reportable Events

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

11.2.1 Hypoglycemia Event

Hypoglycemia not associated with an ADE is only reportable as an AE when the following definition for severe hypoglycemia is met:

Level 1	Glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3 mmol/L)	SMBG	Not reportable event
Level 2	Glucose <54 mg/dL (3 mmol/L)	SMBG	Reportable event
Level 3	Characterized by altered mental and/or physical status requiring assistance	SMBG if available, or without SMBG but symptomatic	Reportable event

	for treatment of hypoglycemia		

11.2.2 Hyperglycemia Events (HHS)/Diabetes Ketoacidosis (9)

Hyperglycemia not associated with an ADE is only reportable as an AE when one of the following is met:

- The event involved DKA, as defined by the DCCT and described below evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia resulting in hyperglycemic hyperosmolar syndrome (HHS) or ketosis

Hyperglycemic events are classified as HHS if the following are present:

- Arterial pH >7.3
- Serum bicarbonate > 18mEq/L
- Serum beta-hydroxybutyrate < 3 mmol/L
- Urine or serum ketones normal or small

Hyperglycemic events are classified as DKA if the following are present:

- 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 <15mEq/L
- Treatment provided in a health care facility

An adverse event as defined in section above which leads to discontinuation of a study device for 2 or more hours will be considered a reportable event.

11.3 Relationship of Adverse Events to Study Device

The study investigator will assess whether any AE is related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is:

- Related: There is a plausible temporal relationship between the onset of the adverse event and the study device, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon rechallenge.

- Unrelated: Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

11.4 Intensity of Adverse Event

The intensity of an AE, coded per the UVA IRB website instructions, will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe AE is not necessarily serious. For example, itching for several days may be severe, but may not be clinically serious.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities but is ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

11.5 Outcome of Adverse Events

The outcome of each reportable AE will be classified by the investigator as follows:

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as SAE resulting in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing prior to death, however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
- An ongoing outcome will require follow-up by the site to determine the final outcome of the AE/SAE.
- The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine outcome (e.g., a participant lost to follow-up).

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation. If the adverse event has not been resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

11.6 Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an AE occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported but will be reported as an AE if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labelling
- CGM tape adherence issues
- Skin reactions from CGM sensor placement or pump infusion set placement do not meet criteria for AE reporting.

11.7 Timing of Event Reporting

- The University of Virginia IRB does not accept reports of adverse events and IND Safety Reports that do not meet the definition of an unanticipated problem or an unexpected and serious adverse event involving risks to participants or others. Internal, serious, and unexpected AEs must be reported to the IRB-HSR within 7 calendar days from the time that the study team received knowledge of the event. These events will be reported using the IRB Online found at http://irb.virginia.edu.
- SAEs possibly related to a study device, study drug, or study participation and UADEs and SUSARs must be reported by the investigator to the IDE Sponsor within 24 hours of the site becoming aware of the event. This can occur via phone or email. An Adverse Event Form CRF, and Device Deficiency Reportable Events form if applicable, should be completed. If the form is not initially completed, it should be completed as soon as possible after there is sufficient information to evaluate the event. All other reportable ADEs and other reportable AEs should be submitted by completion CRF within 7 days of the site becoming aware of the event.
- The IDE Sponsor will investigate the UADE and if indicated, report the results of the investigation to the IRBs, FDA, and Medical Monitor within 10 working days of the study team becoming aware of the UADE per 21CFR 812.46(b).
- The Medical Monitor will determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor will must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitor will makes this determination and no later than 15 working days after first receipt notice of the UADE.

- In the case of a device system component malfunction (e.g., CGM), information will be forwarded to the responsible manufacturer by the study personnel. At a minimum the following should be reported: Study name, Participant Identifier, Event (diagnosis), Trial drug, Reporter, Causality, Outcome.
- Other reportable adverse events, device malfunctions (with or without an adverse event) and device complaints must be reported in the yearly IDE progress report.

11.7.1 Data and Safety Monitoring

A Medical Monitor will review all HHS/DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. The Medical Monitor can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding the Medical Monitor review will be documented in a separate Medical Monitor document.

The Medical Monitor will review the investigator's assessment of causality of all SAEs (and derivatives) and may agree or disagree. Both the investigators and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect.

11.8 Stopping Criteria

11.8.1 Participant Discontinuation

Rules for discontinuing investigational device use are described below.

- The investigator believes it is unsafe for the participant to continue the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behaviors contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Two events of any kind (e.g., severe hypoglycemia or DKA/HHS events as defined above)

11.8.2 Suspending/Stopping Overall Study

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event, use of the study device system will be suspended while the problem is diagnosed.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g., product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

11.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practices (GCP), or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the site and implemented as appropriate. Major deviations will be reported to the IRB-HSR within 7 calendar days of when the study team becomes aware of the event.

11.10 Definition of a Data Breach

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Chapter 12 Miscellaneous Considerations

12.1 Prohibited Medications, Treatments, and Procedures

The study device (CGM) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the treatments above.

12.2 Participant Withdrawal

Participation in the study is voluntary. Participant may withdraw at any time. For participants who do withdraw from the study, the study team will determine if their data will be used in analysis.

12.3 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. De-identified participant information may also be provided to collaborators involved in the study after the appropriate research agreement has been executed.

Chapter 13 Statistical Consideration

13.1 Design and Randomization

This is an early study intended to pilot test the safety and feasibility of a CGM-based titration algorithm. The study will follow a multisite, unblinded, randomized, parallel arm design with 2:1 randomization to either the CTR arm (using a standardized SMBG-based titration) or the EXP arm (personalized CGM-based titration).

The primary hypothesis is that personalized CGM-based titration (with unblinded CGM) will lead to non-inferior improvement in time in the 70-180 mg/dL range during week 15 and 16 from baseline as compared to standardized SMBG-titration. A non-inferiority margin of 5% will be adopted per CGM outcomes consensus guidelines [9].

13.2 Sample Size

Published results on change in TIR from studies investigating glycaemic control in T2D participants titrating Degludec weekly showed an improvement of 7% with SD of 20% from baseline [8] after 16 weeks.

The current sample size is not computed based on a formal power analysis but chosen to provide sufficient system exposure to assess feasibility and estimate effect size.

13.3 Outcome Measures

13.3.1 Primary Endpoint

The primary endpoint is the change in CGM-measured time in range 3.9-10.0 mmol/L (70-180 mg/dL) from baseline (-2 to 0, 2 weeks) to weeks 14-16 (2 weeks), compared between CTR and EXP arm.

13.3.2 Secondary Endpoints

With the exception of Device Deficiencies (DD) and acceptance rates, the secondary endpoints will be compared between EXP and CTR arm with correction of multiple comparisons if applicable. Secondary endpoints 1 through 12 will be compared between EXP and CTR arm with Benjamini Hochberg correction to control the false discovery rate in the presence of multiple comparisons [10]. Outcomes will be grouped as noted in the table below, and corrected p-values will be reported.

Secondary outcomes are listed below:

BH Group	Title	Time Frame	Unit
1	Change in HbA1c	From week 0 to week 16	Percentage point
1	Change in CGM time in tight range 3.9-7.8 mmol/L (70-140 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
1	Change in CGM Time spent > 10.0 mmol/L (180 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
1	Change in CGM Time spent > 13.9 mmol/L (250 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
1	Change in Coefficient of variation (CV - CGM)	From baseline (week -2-0) to week 14-16	%
1	Change in CGM Mean glucose level (CGM)	From baseline (week -2-0) to week 14-16	Mmol/L
1	Change in CGM Time spent < 3.9 mmol/L (70 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
1	Change in CGM Time spent < 3.0 mmol/L (54 mg/dL)	From baseline (week -2-0) to week 14-16	% of time
2	Number of clinically significant hypoglycemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From week 0 to week 16	Number of episodes
2	Number of serious adverse events (SAEs)	From week 0 to week 16	Number of events
2	Number of treatment emergent adverse events (TAEs)	From week 0 to week 16	Number of events
2	Mean basal daily insulin dose at the end of trial.	Week 16	Units of insulin
NA	Number of device deficiencies (DDs)	From week 0 to week 16	Number of events
NA	Investigator acceptance rate of weekly dose guidance – from CGM based titration (EXP arm only)	From baseline (week 0) to week 16	%
NA	The investigator changes the dose from the recommended or the current dose (EXP arm only)	From baseline (week 0) to week 16	Number of events

13.4 Criteria for Success

Unpowered study. Not defined.

13.5 CGM data treatment

Raw CGM data from the study database will be downloaded for each participant. The approximately two weeks (14 days midnight to midnight) of data between each visit will be used to compute the CGM outcomes.

Low and High values in the CGM stream will be replaced by 39 and 401, respectively.

Any SMBG entered via the CGM collection app will be removed prior to analysis.

Consensus metric will be computed for each available day, if 70% or more of the maximum number of measurements are available (>201values per day), and then averaged over valid days for the period.

If more than 7 days have more than 30% of CGM measurements missing, the outcome will be labelled missing.

13.6 Safety Analyses and Participant Feedback

- Number of symptomatic hypoglycemic events
- Reported AEs will be used for safety analysis.
- Study physician override of automated insulin dose computation in the EXP arm

13.7 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. The following descriptive statistics will be displayed overall and by treatment group:

- Age
- HbA1c
- Gender
- Race/ethnicity
- Diabetes duration
- BMI
- Total Daily Insulin

Chapter 14 Data Collection and Monitoring

14.1 Case Report Forms and Device Data

Data is collected through a combination of case report forms (electronic and paper) and electronic device data files obtained from the software and individual hardware components. These electronic device files and electronic CRFs are considered the primary source documentation. For any data points for which the eCRF is not considered source, the original source documentation will be maintained in the participant's study chart or medical record.

Electronic reports (e.g., medical records), electronic results (e.g., LabCorp results), or electronic device data files (e.g., software and individual hardware components) will be considered the primary source documentation and stored in the participant study folder or on a highly sensitive UVA local secure drive.

HbA1c samples will be sent to the central laboratory for analysis. The results will be transmitted to the University of Virginia.

14.2 Study Records Retention

Study documents should be retained for a minimum of 6 years after the study completion, or until at least 2 years have elapsed since the formal discontinuation of development of the investigational product. Documents should be retained for a longer period, if required by local regulations. No records will be destroyed without the written consent of the IDE Sponsor. It is the responsibility of the IDE Sponsor to inform each clinical site if retention of these records will exceed these timelines.

Chapter 15 Ethics/Protection of Human Participants

15.1 Ethics Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

15.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

15.3 Informed Consent Process

15.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to an individual's agreement to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB approved, and the participant will be asked to read and review the document. The investigator or delegate will explain the study to the participant and answer any questions that may arise. All participants will receive verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Extensive discussion of risks and possible benefits of participation will be provided. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The potential participant will be provided with a short overview of the study including its study goals, study procedures, and study timeline. If the potential participant remains interested, they will be asked permission to review inclusion/exclusion criteria to assess if they are eligible to participate in the study. If permission is granted, the study team will review the Inclusion/Exclusion Questionnaire. If eligible, the study team member will provide a copy of the informed consent form (e.g., Clinic, email, fax, or mail) to the potential participant for their review. Potential participants may also elect to review the informed consent form prior to discussing pre-screening questions.

The consenting process will involve discussing the study at length in a phone call/HIPAA compliant telecommunication method for consenting that is not face to face. The potential participant will be given an opportunity to ask the study team questions or may speak directly with the study physician. The potential participant's understanding of the information presented in the process of consent will be assessed by asking open-ended questions.

The consent form may be signed electronically with the use of the Part 11 compliant version of DocuSign for both in-person and telecommunication screening visits. Note: For potential participants who are not able to use DocuSign, email, fax, or mail will be an option for receipt of the signed consent. A HIPAA compliant video conferencing tool will be utilized during the consenting process of the telecommunication screening visit to facilitate the FDA part 11 compliant process of verification of reviewing two forms of identification if signing electronically off site. A copy of the informed consent document will be given to the participant for their records. Study procedures may begin once the consent has been signed by the participant and a member of the study team.

The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.3.2 Participant and Data Confidentiality

The study monitor, representatives of the IRB, the pharmaceutical company, or the device company supplying study product may inspect documents and records required to be maintained by the investigator, for the participants in this study as detailed in the contractual agreements with these sponsors.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. The study team will assign a Participant ID number and a code word to each person who signs a consent form. Both are entered to record study data in eCRFs. Limited study team members have access to identified data. CGM and BGM data are stored in a cloud-based storage in a de-identified format. Data are anonymized by CDT personnel before being stored on UVA Office365 OneDrive or a highly sensitive UVA local secure drive. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Participants' research data, which is for the purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the UVA CDT. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases may be de-identified and archived at the UVA CDT.

Chapter 16 References

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