Study 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

Study Short title: CGM-DTx Degludec

Primary Study Phase

Statistical Analysis Plan

Version v2.0

Corresponds to Version 3.3 of the Protocol

Version History

SAP Version	Author	Approver	Effective Date	Revision Description	Study Stage	Protocol Version
1.0	Marc Breton	Marc Breton	11/29/2023	Initial draft	Before FPFV	V3.2
2.0	Marc Breton	Marc Breton	09/06/2024	Final version	Before LPLV	V3.3

Principal Investigator: _____

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1. Study Overview

The following table provides an overview of the CGM-Dtx Degludec trial.

Table 1. Study Overview

PARTICIPANT AREA	DESCRIPTION
Title	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.
Précis	Type 2 Diabetes Mellitus (T2DM)
Investigational Device	Enrollment goal of completing 30 participants at 2 centers
Objectives	Experimental (EXP) Arm: CGM based titration algorithm group. Control (CTR) Arm: SMBG titration algorithm group
Study Design	Approximately 18 weeks (2-week CGM Run-In Phase + 16-week Intervention Phase)
Number of Clinical Centers	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 subjects (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.
Endpoints	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)

PARTICIPANT AREA	DESCRIPTION
Sample Size	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 subjects (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.

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75 The following table provides an overview of the schedule of study visits, phone contacts, and key procedures.

76 Table 2. Schedule of Study Visits and Procedures

	Consent	Screening	Training	Randomization	Titration visit	Titration visit	Titration visit	Check-In Visit	Titration visit	Titration visit	Titration visit	Check-In Visit	Titration visit	Titration visit	Titration visit	Check-In Visit	Titration visit	Titration visit	Titration visit	Study End Visit	Post-Study Check-In
Visit (V), Video-conference (VC), or Phone (P)	**VC/V**	**VC/V**	**VC/V**	**P**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**VC/V**	**P**
Weeks			**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**16**
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	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	X	X	X	X	X	X	X	

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78 Table 3. List of Abbreviations

Abbreviation	Definition
SAP	Statistical Analysis Plan
FPFV	First Patient First Visit
T2DM	Type 2 Diabetes Mellitus
CGM	Continuous Glucose Monitoring
EXP Arm	Experimental Arm
CTR Arm	Control Arm
SMBG	Self-Monitoring Blood Glucose
DDs	Device Deficiencies
BH	Benjamini Hochberg
TAE	Treatment Emergent Adverse Event
SD	Standard Deviation
IQR	Inter Quartile Range
DKA	Diabetic Ketoacidosis
CMP	Comprehensive Metabolic Panel
TSH	Thyroid Stimulating Hormone

RCT	Randomized Control Trial
CV	Coefficient of Variation
BMI	Body Mass Index
TIR	Time within the range 70-180 mg/dL
DiAs	Diabetes Assistant – the UVA algorithm prototyping system
CI	Confidence Interval

2. Comparison with the Protocol

This SAP is consistent with version 3.3 of the protocol.

3. Primary Statistical Hypotheses

The primary outcome for this study is the change of CGM-measured % in range 70-180 mg/dL from baseline (weeks -1 and 0) to end of study (weeks 15 and 16). The intervention will be considered effective if the change in TIR is non-inferior between the CGM-driven titration arm (EXP) and the standard SMBG titration arm (CTR) using a statistical significance of $\alpha=0.05$. a non-inferiority margin of 5 percentage points, and the model specified below in Section 6.

The null/alternative hypotheses are:

a. *Null Hypothesis*: the difference between EXP and CTR changes in mean CGM-measured % in range 70-180 mg/dL between baseline and end of study is greater or equal to 5%

b. *Alternative Hypothesis*: the difference between EXP and CTR changes in mean CGM-measured % in range 70-180 mg/dL between baseline and end of study is less than 5%

4. Sample size

No a priori power computation were performed to determine the sample size. Instead, a predetermined sample of N=30 was chosen as representative of the feasibility of the intervention in this narrow population (see protocol for inclusion/exclusion criteria).

5. Outcome Measures

5.1. Primary Efficacy Outcome

The primary outcome for this study is the change of CGM-measured % in range 70-180 mg/dL from baseline (weeks -1 and 0) to end of study (weeks 15 and 16).

5.2. Secondary Efficacy Outcomes

With the exception of Device Deficiencies (DD), acceptance rates of weekly doses, and the magnitude of changes in the dose by the investigator, 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.

	BH Group	Title	Time Frame	Unit
1.	1	Change in HbA1c	From week 0 to week 16	Percentage point
2.	1	Change in CGM time in tight range 3.9-7.8 mmol/L (70-140 mg/dL)	Weeks -1&0 vs 15&16	% of time
3.	1	Change in CGM Time spent > 10.0 mmol/L (180 mg/dL)	Weeks -1&0 vs 15&16	% of time
4.	1	Change in CGM Time spent > 13.9 mmol/L (250 mg/dL)	Weeks -1&0 vs 15&16	% of time
5.	1	Change in Coefficient of variation (CV - CGM)	Weeks -1&0 vs 15&16	%
6.	1	Change in CGM Mean glucose level (CGM)	Weeks -1&0 vs 15&16	Mmol/L
7.	1	Change in CGM Time spent < 3.9 mmol/L (70 mg/dL)	Weeks -1&0 vs 15&16	% of time
8.	1	Change in CGM Time spent < 3.0 mmol/L (54 mg/dL)	Weeks -1&0 vs 15&16	% of time
9.	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
10.	2	Number of serious adverse events (SAEs)	From week 0 to week 16	Number of events
11.	2	Number of treatment emergent adverse events (TAEs)	From week 0 to week 16	Number of events
12.	2	Mean basal daily insulin dose at the end of trial.	Week 16	Units of insulin
13.	NA	Number of device deficiencies (DDs)	From week 0 to week 16	Number of events
14.	NA	Investigator acceptance rate of weekly dose guidance – from CGM based titration (EXP arm only)	From baseline (week 0) to week 16	Percentage
15.	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

5.3. Calculation of CGM Metrics

- Baseline: CGM data to calculate baseline metrics will come from the run-in period: the last 2 weeks of CGM data prior to randomization will be used in the calculation of baseline CGM metrics. If <168 hours of CGM data are available for any reason (e.g., lost data or device failure), then the baseline metrics will not be calculated and will be set to missing.

- Follow-up:
    - CGM metrics will be calculated by pooling all CGM readings during weeks 15 & 16 starting midnight after the titration visit of week 14 (see Table 1) through the end of study visit (week 16, see table 1). If a participant drops out before completing the 16-week visit, all available data through the last visit date will be included for calculating CGM metrics. A minimum of 168 hours of CGM data will be required to calculate CGM metrics.
- CGM metrics 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.
- HIGH and LOW values from the sensor will be imputed as 401 and 39, respectively.

5.4. Calculation of Insulin Metrics

The total basal insulin dose will be computed as the average daily dose over the 7 days prior to the end of the study visit. Insulin data on 5 of 7 days will be required to calculate insulin metrics.

5.5. Analysis Windows

Analysis windows apply to the following outcomes measured at randomization and 16 week visit:

- HbA1c

This does not apply to the CGM metrics which are calculated as described above.

Data from the randomization visit occurring in the following window will be included in analysis:

Visit (Target Date)	From Day[a]	Thru Day[a]
0 weeks (0 days)	-14	+14

Data from the 13-week visit occurring in the following window will be included in analysis:

Visit (Target Date)	From Day[a]	Thru Day[a]

16 weeks (112 days)	98	126

a – Days from randomization, inclusive.

6. Analysis Datasets and Sensitivity Analyses

6.1. Analysis Datasets

All analyses comparing the EXP arm with CTR arm will follow intention-to-treatment approach, which means participants will be analyzed in the treatment arm assigned by randomization regardless of compliance. All randomized participants will be included in the primary and secondary analysis analyses of CGM metrics.

Safety outcomes will be reported for all enrolled participants, irrespective of whether the participants were randomized or the study was completed.

6.2. Per-Protocol Analyses

- No per protocol analysis are contemplated at this time

6.3. Other Sensitivity Analyses

The following sensitivity analyses will be conducted for the primary endpoint only.

Confounding:

A sensitivity analysis will also be conducted if potential confounding factors collected at baseline are detected. The baseline factors listed in Section 11 will be assessed for imbalance between treatment groups.

The imbalance will be assessed based on clinical judgement reviewing the distributions in the two treatment arms, not on a p-value. The person making this judgement will be unaware of whether there is an association between baseline variables and study outcome. All variables 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.

7. Efficacy Analysis

7.1. Primary Analysis

This study's primary outcome is change in CGM-measured % time in range 70-180 mg/dL between baseline and end of study.

Summary statistics (mean ± SD or median (quartiles)) will be reported by treatment group for the CGM-measured % in range 70-180 mg/dL at baseline, 16 weeks intervention and change from baseline to follow-up.

Change in CGM-measured % in range 70-180 mg/dL between two treatment arms will be compared using a linear mixed effects regression model while adjusting for baseline TIR, age, prior CGM and pump use, and clinical center (random effect). A point estimate 95% one-sided confidence interval, and a one-sided p-value will be reported for the treatment effect based on the linear regression model and a 5% level will be used to declare statistical significance. Residual values will be examined for an approximate normal distribution. If values are highly skewed, then robust regression using M-estimation will be used instead. However, previous experience suggests that the residual values for % time glucose in target range will follow an approximately normal distribution.

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 sensitivity analyses by including factors potentially associated with the outcome for which there is an imbalance between groups (Section 6.3).

7.2. Analysis of Secondary Endpoints

Point estimates and confidence intervals for the treatment arm differences will be presented for all secondary metrics. Analyses will parallel those described above for the primary outcome.

Summary statistics (mean ± SD, median (IQR) or n (%)) appropriate to the distribution will be tabulated for participants at the timeframe listed in section 5.2

7.3. Formal Statistical Comparisons of Treatment Groups

all secondary outcomes noted in Section 5.2. will have formal statistical comparisons of treatment groups. To control for the risk of false discovery, the Benjamini-Hochberg procedure will be applied to the secondary outcomes by groups as listed in Section 5.2

8. Safety Analysis

All randomized participants will be included in these analyses and all their post-randomization safety events will be tabulated. Any pre-randomization adverse events will be tabulated separately and will include any participants who were never randomized. Any adverse events after the 16 week visit (or 112 days post-randomization if the 13 week visit is missed) will be excluded from this analysis of the RCT phase.

Safety analyses of the study will include events occurring on or after randomization until and including the 16-week visit date or randomization date + 112 days whichever is earlier.

The number of Severe Adverse Events and Treatment emergent events will be tabulated by treatment group. Formal statistical comparisons will be performed if there are enough events (at least 5 events combined between the two treatment groups):

9. Intervention Adherence

9.1. Titration System

For the experimental arm, the number of times a study investigator changed the recommended or current insulin dose will be computed per participants between randomization and week 16 visit. The overall rate of dose acceptance will be computed as the total number of dose advice minus the number of changed doses, divided by the total number of dose advice and reported per participant in percentage. Median (IQR) will be reported.

9.2. Sensor Use

The amount of CGM sensor use for both treatment groups will be calculated as the percent of maximum data collected per day, averaged overall and over 4-week periods from randomization to week 16 visit from downloaded data from the study portal software.

median (IQR) of percent time sensor use overall will be tabulated by treatment group.

10. 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. Descriptive statistics will be displayed by treatment group for the following:

- Age
- Gender
- Race/ethnicity
- income, education, and/or insurance status
- Diabetes duration
- HbA1c
- BMI %
- Participant-reported number of SH and DKA 12 months prior to the start of the study
- Baseline CGM metrics including:
    - % in range 70-180 mg/dL
    - % time >250 mg/dL
    - Mean glucose
    - % time <70 mg/dL
    - % time <54 mg/dL

11. Device Issues

The following tabulations and analyses will be performed by treatment group to assess device issues:

- Number of Device deficiencies from week 0 to week 16

12. Planned Interim Analyses

No formal interim efficacy analyses are planned. The analysis of the RCT will be performed on completion of the RCT prior to the completion of the extension phase.

13. Exploratory Analyses

1. To compare the stricter criteria used in larger studies, the primary analysis will be repeated but with a 95% two-sided CI, using a 2.5% one-sided test of non-inferiority, 3% non-inferiority margin, and only including participants with at least 70% CGM data in the run-in period.

2. The number of investigator-initiated dose changes from baseline (week 0) to week 16 that differ from the recommended or the current dose will be presented for EXP and CTR respectively.