STATISTICAL ANALYSIS PLAN

PROTOCOL: LDX0122
A phase II randomized, placebo-controlled, double-blinded, 2 parallel arm, clinical trial evaluating ladarixin 400 mg twice a day as adjunctive therapy to improve glycemic control in overweight insulin-resistant patients with type 1 diabetes.

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

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The Statistical Analysis Plan has been completed and reviewed and the contents are approved for use for the analysis.

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Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BDRM	Blinded Data Review Meeting
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGDR	Estimated Glucose Disposal Rate
ENR	Enrolled set
FAS	Full Analysis Set
HbA1c	Glycated hemoglobin
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IR	Insulin Resistant
ITT	Intent to Treat
MAGE	Mean Amplitude Glycemic Excursion
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MI-RD	Multiple Imputation using Retrieved Dropouts
MODD	Mean Of the Daily Differences
MMRM	Mixed Model for Repeated Measurements
NCS	Not Clinically Significant
PP	Per Protocol
PT	Preferred Term
QTcF	corrected QT interval by Fredericia
RND	Randomized Set
SAE(s)	Serious Adverse Event(s)
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
T1D	Type 1 Diabetes
TAR	Time Above Range
TBR	Time Below Range

TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TIR	Time In Range

Revision History

Document Version	Changes Made	Document Date
Final 1.0	Final version 1.0, first release.	27 OCTOBER 2022

1. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of LDX0122 Clinical Trial. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol or Case Report Form (CRF) may necessitate updates to the Statistical Analysis Plan (SAP). In case of deviations from this updated SAP, explanations will be provided in the clinical study report.

This SAP is based on study protocol Version No. 1 final – CCI [redacted], Version No.2 final – CCI [redacted] (applicable to the Italian investigational sites only) and eCRF Version No. 3 – CCI [redacted].

2. Study Objectives

The primary objective of this trial is to determine whether oral ladarixin versus placebo adjunctive therapy improves glycemic control in overweight, insulin resistant (IR) adult subjects with type 1 diabetes (T1D).

The secondary objectives are:

- to ascertain the effect of ladarixin on glycemic variability as per Continuous Glucose Monitoring (CGM) derived parameters
- to determine the safety of oral ladarixin versus placebo adjunctive therapy in overweight, IR adult subjects with T1D.

Exploratory objectives (if site is able and deems appropriate to accommodate and conduct these objectives) are:

- CCI [redacted]

3. Study Design

3.1 General design and plan

This study will be a randomized, placebo-controlled, double-blinded, 2-parallel arm, phase II trial. It will enroll up to 86 patients across all genders, 21-65 years, inclusive, with established insulin - requiring T1D and IR, randomly assigned to receive (1:1) either oral ladarixin 400 mg b.i.d. for 7 cycles of 14 days on/14 days off (treatment group) or matched placebo (control group).
Each patient will be involved in the study for up to 30 weeks. This period consists of 4 site visits for informed consent acquisition and screening, randomization, and 2 post-randomization study visits during a maximum of 28 weeks from the first Investigational Medical product (IMP) dose.

Recruitment will be competitive among the study sites, until the planned number of patients is randomized.

3.2 Study day

The study day describes the day of the event or assessment date, relative to the reference start date which is the date of Randomization (Day 1 – Baseline).
The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date, etc.) – reference start date + 1 if event is on or after the reference start date.
- The date of the event (visit date, onset date of an event, assessment date, etc.) – reference start date if event precedes the reference start date.

There is no 'Day 0'.

3.3 Visit Schedule and Visit Windows

Please refer to Table 1: Study Flow Chart Study Flow Chart for full details on the schedule of suggested assessments.

For all measurements, the actual date and time of assessment, including date of sampling, will be recorded in the eCRF.

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits for all parameters. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1, as defined in Section 3.2. If a subject has two or more actual visits in a visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The additional unscheduled visit(s) will not be used in the summaries or analyses by visit, but they are used for determination of clinically important endpoints as described in this document. If two actual visits are equidistant from the target day within a visit window, the later visit is used. If more than one value falls on the same day then the worst value will always be used (higher or lower value, depending on the parameter).
All assessments corresponding to both scheduled and unscheduled visits will be included in subject listings.

In Table 2 there are the visit windows and the target study days for each visit defined in the protocol; lower and upper limits associated to each visit are enlarged to cover all possible days from randomization to allow for mapping all assessments to the visits.
Unless otherwise specified, time points considered for analyses will be baseline, Week 4 (for Italian subjects only), Week 11/12 and Week 27/28.

Table 1: Study Flow Chart

Activity	PRESCREENING* (Identify and reach out to potential participants and offer ICF)	Screening Visit 1 (Within week -2)	Treatment phase (week 1 to 26)			End of study Visit 4 (week 27/28)
			Randomization Visit 2 (Day 1)	Visit 2b (week 4) **	Visit 3 (week 11/12)	
PRESCREENING* (Identify and reach out to Potential participants and offer ICF)	x	x				
Informed Consent Form (ICF) signed		x				
Medical history and pre-existing conditions		x				
Auto-antibodies evaluation[1]		x				
Fasting C-peptide		x				
Measurement of body weight, height, waist, and waist/hip circumference		x	x		x	x
eGDR and BMI assessment		x	x		x	x
Average (previous 3 days) Insulin requirement		x	x		x	x
HbA1c		x	x		x	x
CGM download for assessment of glycemic variability (previous 7 days)[2]			x		x	x
Vital signs		x	x		x	x
Serum Pregnancy Test (blood/urine)		x			x[3]	
Safety laboratory tests (hematology, biochemistry)		x		x	x	x
CCI [redacted]			[redacted]		[redacted]	[redacted]
ECG (QTcF)		x		x	x	x**
eGFR		x			x	x**
Randomization			x			
IMP dispensation			x		x	
Patient Diary delivery/check			x		x	x
Treatment			x----------		x	
Patient Phone call[5]			x----------x			
AE/SAE recording			x----------x			
Prior and Concomitant Medication			x----------x			

* Prescreening procedures can be performed during screening visit if applicable as per site practice
1. To include new testing should past data not be available.
2. Secondary CCI [redacted].
3. Urine dipstick.
CCI [redacted]
CCI [redacted]
5. Telephone calls at least every 30-45 days.
** For Italian subjects only

Table 2: Scheduled Visit Window and Mapping of Assessments for Analysis

Scheduled Visit Number	Scheduled Time point	Label on output	Target Study Day*	Time Interval Lower Limit (Day*)	Time Interval Upper Limit (Day*)
Baseline / Visit 2	Day 1	Baseline	1	−14	1
Visit 2b**	Week 4	Week 4	29	15	43
Visit 3	Week 11/12	Week 11/12	81	64	99
Visit 4	Week 27/28	Week 27/28	193	176	211

*Relative to Study Day 1
**For Italian subjects only

3.4 Sample size justification

Sample size calculation was based on results obtained in the phase 2 trial with ladarixin in T1D onset. Considering the following assumptions:

- randomization ratio 1:1 (ladarixin: placebo),
- one-side type I error of 0.05
- expected difference in favor of ladarixin in terms of responders: ~22.5%
- power of 80% to detect the expected treatment effect

a total of 76 evaluable patients are required; to account for a possible 10% of patients not evaluable for the primary variable (section 3.6.1) after enrollment, up to 86 patients will be enrolled.

3.5 Randomization and blinding

3.5.1 Randomization

A CRO independent statistician not involved in the conduct of the study will generate with a computer procedure the randomization list that will be provided to Dompé in a sealed envelope to prevent unblinding.
The facility responsible of IMP packaging/labelling will also receive appropriate randomization codes for the purpose of IMP preparation.
Randomization will be stratified by site to ensure balanced assignment across treatment groups.
A master randomization list will be generated, randomizing an excess of patients to allow competitive recruitment within each center.
The treatment assignment information will be kept confidential and will not be disclosed to any other person. The investigator and Dompé Pharmacovigilance will have access to the randomization code for a specific patient in case of a medical emergency or for safety reasons.
The randomization codes will be accessible to the independent statistician(s) who will generate the reports for the Data Monitoring Committee (DMC) evaluation.
Once the study has been completed and the database has been locked, the treatment assignment information will be accessible to the study biostatistician(s) who will perform the statistical analyses and will generate reports.

3.5.2 Unblinding

Appearance, including packaging and labelling, of the IMP (capsules, packaging) will not allow to recognize actual treatment (either ladarixin or placebo).
During the trial, blinding will be broken by the Investigator for emergency purposes only, where knowledge of the blinded treatment could influence further patient care. In addition, safety reports will be unblinded, as per regulatory requirements.
Only in case of a medical emergency for which the knowledge of patient is required to provide the patient with appropriate care, access to individual patient treatment code will be allowed.
Unblinding events will be recorded and reported in the Clinical Study Report (CSR).
Study blind will be broken after database lock.

3.6 Efficacy endpoints

3.6.1 Primary endpoint

- The proportion of responders, defined as "proportion of patients with an HbA1c reduction from baseline of ≥0.50% (absolute difference) without episodes of severe hypoglycemia [timeframe: week 27/28 (visit 4)].

3.6.2 Secondary efficacy endpoints

The following secondary endpoints will be considered:

1. The proportion of responders [Timeframe: week 11/12 (visit 3)]
2. The mean difference from baseline in HbA1c [Timeframe: week 11/12 (visit 3) and 27/28 (visit 4)]
3. Average (previous 3 days) daily insulin requirements (IU/kg/day) [Timeframe: week 11/12 (visit 3) and 27/28 (visit 4)]
4. Glycemic Variability by CGM (previous 7 days before the visit): time in range (TIR), time above range (TAR) time below range (TBR), standard deviation and coefficient of variation [Timeframe: week 11/12 (visit 3) and 27/28 (visit 4)]

3.6.3 Exploratory efficacy endpoints

The following exploratory endpoints will be considered:

- CCI [redacted]
- CCI [redacted] [Timeframe: CCI [redacted]
- CCI [redacted]

- CCI [redacted]
- [redacted] CCI [redacted]

3.7 Safety endpoints

- Vital signs (blood pressure and heart rate) [Timeframe: baseline, week 11/12 (visit 3), 27/28 (visit 4)]
- Laboratory tests [haematology (total WBC, neutrophils / lymphocytes / monocytes / basophils / eosinophils (% and absolute number), total RBC, MCV, hematocrit, platelet count) and clinical chemistry (sodium, potassium, serum creatinine, serum albumin, total bilirubin, ALT, AST)] [Timeframe: baseline, week 11/12 (visit 3) and 27/28 (visit 4)]
- Incidence of Treatment Emergent Adverse Events (TEAEs), Adverse Drug Reaction (ADR) and Treatment Emergent Serious Adverse Events (TESAEs) [Timeframe: from the beginning of IMP administration up to the end of study participation].

4. Statistical Analysis

4.1 General

Appropriate summary statistics will be produced separately by treatment arms according to the nature of the variable.

- For continuous data, number of observations, mean, standard deviation, median, first (Q1) and third (Q3) quartiles, and range (minimum and maximum) will be presented.
- For qualitative data, frequency distributions and percentages per category will be presented. If appropriate, confidence intervals around the mean or the proportions will be presented.

For primary analysis, the threshold for claiming statistical significance will be 0.05 one-sided. For secondary, exploratory and other analysis, unless otherwise specified, hypothesis testing will be carried out at the alpha = 0.05 level (two-sided) when comparing treatments.
In case data transformation is needed to meet normality assumptions, data will be presented both in the original and transformed scales and a specific focus will be added in CSR for interpreting the fact that the comparison between treatments is based on a transformed scale. Similarly, in case of use of non-parametric tests, it will be clarified which parameters are compared allowing for a fair and correct interpretation.

Additional post-hoc analysis may be produced to further allow comparison between ladarixin and placebo, according to the results obtained.
Any deviations from the original statistical plan (including unplanned analyses) will be clearly documented in the CSR.

All patient data collected and derived in the study will be listed by patient.

4.2 Analysis sets

4.2.1 Screened set

The Screened set will consist of all patients with signed written informed consent and have a subject identification number.

4.2.2 Enrolled set (ENR)

The ENR set will consist of all patients with signed written informed consent and fulfillment of eligibility criteria (i.e., not reported as screening failure).

4.2.3 Randomized set (RND)

The RND set will consist of all patients in the ENR set who are randomized to the study, regardless of whether they receive the IMP or not.

4.2.4 Full analysis set (FAS)

The FAS population will consist of all randomized patients who received at least one dose of the investigational product. FAS population will be analyzed according to the intention-to-treat (ITT) principle, i.e., by treatment allocation. The FAS population will be used to analyze results on efficacy data.

4.2.5 Safety set (SAF)

The SAF population will consist of all randomized patients who received at least one dose of the investigational product. Safety population will be analyzed according to the actual treatment received. The SAF population will be used to present results on safety data.

4.2.6 Per Protocol set (PP)

The PP set will consist of all patients in the FAS population who do not have Major Protocol Deviations. The PP population will be used for sensitivity supplemental analyses.

4.3 Usage of analysis sets

The usage of the analysis sets (see previous section) for the creation of tables and figures are illustrated in Table 3. Unless otherwise specified, all listings will be done for RND set. All listings will have planned and actual treatment names included, as well as the flag(s) of the analysis set(s) used to analyses the information of the listing (according to the Table 3).

Table 3: Usage of analysis set

Analysis	SCR	ENR	RND	FAS	SAF	PP
Subject enrolment and disposition	X					
Protocol violations			X			
Study discontinuations			X			

Analysis	SCR	ENR	RND	FAS	SAF	PP
Demographics and baseline characteristics				X		
Medical or surgical history and/or Concomitant Diseases				X		
Prior and concomitant medications				X		
Other baseline characteristics				X		
Compliance to IMP					X	
Exposure to IMP					X	
Analysis of primary efficacy endpoints				X		
Sensitivity analysis				X		X
Analysis of secondary efficacy endpoints				X		
CCI [redacted]				X		
Adverse events					X	
Clinical laboratory evaluation					X	
Vital signs, [redacted] and BMI				X	X	
ECGs					X	
Pregnancy test over the study					X	
Permanent treatment discontinuation criteria					X	
Patient phone calls					X	

4.4 Estimands

4.4.1 Primary estimand

The primary estimand is defined by the following:

- Population: Subjects in the Full Analysis Set population.
- Variable: HbA1c reduction from baseline of ≥0.50% (absolute difference) without episodes of severe hypoglycemia [timeframe: week 27/28 (visit 4)].
- Intercurrent event: In case of death before week 27/28 (Visit 4) a "composite strategy" will be used: the subject will be considered not reduced. Instead, the occurrence of other intercurrent events is irrelevant (the treatment policy will be used): all observed values will be used regardless of occurrence of these intercurrent events.
- Population-level summary: Proportion of Patients with an HbA1c reduction from baseline of ≥0.50% (absolute difference) without episodes of severe hypoglycemia [timeframe: week 27/28 (visit 4)].

4.4.2 Secondary estimands

Secondary endpoint #1 (section 3.6.2) will be analyzed according to the following estimand:

- Population: Subjects in the Full Analysis Set population.

- Variable: HbA1c reduction from baseline of ≥0.50% (absolute difference) without episodes of severe hypoglycemia [timeframe: week 11/12 (visit 3)].
- Intercurrent event: In case of death before week 11/12 (Visit 3), a "composite strategy" will be used: the subject will be considered not reduced Instead, the occurrence of other intercurrent events is irrelevant (the treatment policy will be used): all observed values will be used regardless of occurrence of these intercurrent.
- Population-level summary: Treatment difference in the proportion of Patients with an HbA1c reduction from baseline of ≥0.50% (absolute difference) without episodes of severe hypoglycemia [timeframe: week 11/12 (visit 3)].

Secondary endpoint #2 (section 3.6.2) will be analyzed according to the following estimand:

- Population: Subjects in the Full Analysis Set population.
- Variable: Difference from baseline in HbA1c [Timeframe: week 11/12 (visit 3) and week 27/28 (visit 4)].
- Intercurrent event: In case of death before week 11/12 (Visit 3), a "composite strategy" will be used: the 95th percentile change from baseline distribution within treatment and visit will be imputed to this secondary endpoint (95th worst value percentile). Instead, the occurrence of other intercurrent events is irrelevant (the treatment policy will be used): all observed values will be used regardless of occurrence of these intercurrent events. The same is applied for the other timeframe: week 27/28 (visit 4).
- Population-level summary: Treatment difference in the mean difference from baseline in HbA1c [Timeframe: week 11/12 (visit 3) and week 27/28 (visit 4)].

Secondary endpoint #3 (section 3.6.2) will be analyzed according to the following estimand:

- Population: Subjects in the Full Analysis Set population.
- Variable: Average (previous 3 days) daily insulin requirements (IU/kg/day) [Timeframe: week 11/12 (visit 3) and 27/28 (visit 4)].
- Intercurrent event: the occurrence of intercurrent events is irrelevant, the treatment policy will be used.
- Population-level summary: Treatment difference in the average (previous 3 days) daily insulin requirements (IU/kg/day) [Timeframe: week 11/12 (visit 3) and 27/28 (visit 4)].

Secondary endpoint #4 (section 3.6.2) will be analyzed according to the following estimand:

- Population: Subjects in the Full Analysis Set population.
- Variable: Glycemic Variability by CGM (previous 7 days before the visit): time in range (TIR), time above range (TAR), time below range (TBR) [Timeframe: week 11/12 (visit 3) and 27/28 (visit 4)].
- Intercurrent event: In case of death before week 11/12 (Visit 3), a "composite strategy" will be used: the 95th percentile of variable distribution within treatment and visit will be imputed to this secondary endpoint (95th worst value percentile). Instead, the occurrence of other intercurrent events is irrelevant (the treatment policy will be used): all observed values will be used regardless of occurrence of these intercurrent events. The same is applied for the other timeframe: week 27/28 (visit 4).

- Population-level summary: Treatment difference in the variability by CGM (previous 7 days before the visit): time in range (TIR), time above range (TAR) time below range (TBR) [Timeframe: week 11/12 (visit 3) and 27/28 (visit 4)]

4.5 Sub-group analyses

Subgroup analyses will be performed on the following subgroups of baseline characteristics:

- Age class (≤Median, >Median of the FAS),
- Sex,
- Race,
- Ethnicity,

Within each subgroup level, descriptive in nature analyses will be performed on:

- The proportion of responders
- The mean difference from baseline in HbA1c
- Average (previous 3 days) daily insulin requirements (IU/kg/day)
- Glycemic Variability by CGM (previous 7 days before the visit): time in range (TIR), time above range (TAR) time below range (TBR), standard deviation and coefficient of variation

at each available timepoints by means of descriptive statistics.

In case of continuous measures, analyses will be provided for baseline visit, each post-baseline visit, and their change from baseline.
In case of categorical variables, the means of a Chi-square test or, if more appropriate, a Fisher's Exact be provided in addition to summary description.

Additional sub-group analyses will be performed ad hoc according to the results obtained in the whole population. Statistical details on subgroup analysis will be reported in the CSR.

4.6 Interim analyses

No formal Interim analysis is planned for the study.

4.7 Handling of missing and incomplete data

The number of patients with missing data will be presented under the "Missing" category, if present. Missing values will not be included in the denominator count when computing percentages. Similarly, only the non-missing values will be evaluated for computing summary statistics for continuous endpoint. Any exception will be clarified as a note.

Since patients who discontinue the treatment with the IMP will not be withdrawn from the study but will be asked to complete safety and efficacy assessments as per the protocol, for the primary analyses missing data will be addressed by modeling patients with missing data after retrieved dropouts (see section 7.1.1). This approach is based on the assumption that missing data would have been like retrieved dropouts if they were assessed. If the MI-RD regression model doesn't converge

due to not enough retrieved dropouts, for assuring the convergence of the MI-RD regression model, the same multiple imputation model will be fitted using data from subjects of control group, washing-out the effect of treatment. This approach does not assume benefits for ladarixin in case of discontinuation and limits a post discontinuation clinical effect to that of placebo. When death prevents the collection of the endpoint and, in the variable derivation is included the "composite strategy" method to handle death, the MI will be done on data still missing after having considered the death.

4.8 Changes in the planned analysis

Analysis on exploratory endpoint CCI [redacted] will be done for all subjects although this endpoint is only mentioned in protocol CCI [redacted] – CCI [redacted] (applicable to the Italian investigational sites only).

4.9 Data Review Meeting

A Blinded Data Review Meeting (BDRM) will be held before the DB lock and the unblinding of the data. Any other details will be provided in the BDRM Report.

4.10 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.4) on a Windows 10 operating system. CGM data at patient level will be processed using cgmanalysis package 2 in R version 3.6.1 (or later) before performing statistical analysis.

5. Evaluation of Demographic and Baseline Characteristics

5.1 Subject enrolment and disposition

All presentations for subject disposition will be by treatment group, and overall. The table will be presented by country and site as well.

For describing the subject disposition, the following populations will be summarized:

- Subjects screened overall (N).
- Subjects with ongoing screening (N), not applicable for CSR.
- Subjects enrolled overall (N, 100%)
- Subjects enrolled but not randomized and reasons for non-allocation overall (N, %); percentage denominator will be the number of enrolled subjects.

- Subjects randomized by treatment group and overall (N, %); the percentage denominator will be the number of randomized subjects within each arm.
- Subjects randomized but not treated by treatment group, and overall (N, %); the percentage denominator will be the number of randomized subjects within each arm and overall.
- Subjects in each analysis set (FAS, SAF, PP) and reasons for exclusion by treatment group and overall (N, %); the percentage denominator will be the number of randomized subjects within each arm and overall.
- Number of subjects who completed each planned visit.

Listings will be provided based on ENR set.

5.2 Protocol violations

All the protocol deviations will be discussed case by case before unblinding of the treatment code with the clinical team during the BDRM and described in the BDRM Report. Any deviation from these protocol procedures will be reported in the study-specific Protocol Deviation form.

Number of occurrences and of subjects with at least one major and minor protocol violations will be summarized for each treatment and overall. Major and minor protocol deviations will be tabulated separately.

5.3 Permanent treatment discontinuation criteria

A summary table showing at each available timepoint (Section 3.3) the number and percentages of subjects who discontinued the study treatment along with the discontinuation criteria will be produced by treatment group. The number of patients still under treatment of discontinuing at the specific visit will be used as denominator for percentages.

5.4 Patient phone calls

A summary table showing at each available timepoint (Section 3.3) the number and percentages of subjects who were contacted by phone call and who needed/not needed an adjustment in the insulin regimen will be produced by treatment group. The number of all patients (including subjects that have discontinued IMP but still in the study) at the specific visit will be used as denominator for percentages.

5.5 Study discontinuations

The following information will be summarized for the randomized patients by treatment and overall:

- Trial completers;

- Trial ongoing (not applicable for the CSR);
- Subjects who discontinued the IMP"
  - Subjects who discontinued the IMP but complete the study
  - Subjects who discontinued the IMP and discontinued the trial prematurely
- Subjects who completed the IMP
- Subjects who are ongoing in the IMP (not applicable for the CSR);
- Subjects who discontinued the trial prematurely (and reason);
- Broken randomization code (and reason).

If more than 30% of randomized subjects discontinue the study prematurely, the distribution of the time from randomization to discontinuation (time to discontinuation, Section 9.1) will be summarized using time-to-event method (Kaplan-Meier estimates and plots will be provided with 95% confidence interval bounds calculated per Greenwood[3] method, the respective number of patients at risk, and the log-rank test p-value). Subjects who have not prematurely discontinued the trial will be censored at study termination or cut-off date.

5.6 Demographics and baseline characteristics

The baseline demographic characteristics will be summarized by treatment and overall, by means of descriptive statistics. No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and baseline characteristics will be reported for this study:

- Demography
  - Geographic region of the site
  - Age (years)
  - Sex (Male, Female)
  - If female, potential childbearing (Yes, No)
  - Race (White/Caucasian, Black or African American, Asian, Other)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Pregnancy test result (Positive or Negative), if appropriate
- BMI ($BMI \leq 25 kg/m^2$ vs $25 kg/m^2 < BMI \leq 30 kg/m^2$ vs $BMI > 30 kg/m^2$)

5.7 Medical and surgical history

A disease is defined:

- medical/surgical history if it is ended before screening visit.

- concomitant disease if it is ongoing at screening visit.

Medical history and concomitant diseases will be coded using Medical Dictionary for regulatory activities (MedDRA) dictionary and frequency distributions and percentages will be summarized by treatment, by System Organ Class (SOC), and Preferred Term (PT).

Medical history and concomitant diseases will be analyzed separately. Frequency distributions and percentages by treatment will be given for both SOC and PT by subject. Subjects experiencing more than one past/concomitant disease event will be counted only once within each SOC and PT.

5.8 Prior and concomitant medications

Medications will be coded using World Health Organization Drug Dictionary (WHO DD).

Based on the start/end medication date(s) reported in the eCRF (see Table 7 for derivation rules), a medication will be defined as follows:

- Prior medications are those which stop prior to the date of informed consent.
- Concomitant medications are those which:
    - start prior to, on or after the date of informed consent and start no later than date of study completion or discontinuation or cut-off date, and
    - end on or after the date of informed consent or are ongoing at the study completion or discontinuation or cut-off date.

In case of missing or incomplete dates/times not directly allowing allocation to any of the two categories of medications, a worst-case allocation will be done according to the available parts of the start and the end dates. The medication will be allocated to the first category allowed by the available data, according to the following order:

- concomitant medication
- prior medication.

Prior and concomitant medications will be summarized separately. Frequency distributions and percentages by treatment will be given by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

Subjects experiencing more than one medication classified in the same category (prior medications or concomitant medications) within the same anatomical main group, chemical subgroup and preferred name will be counted only once.

5.9 Other baseline characteristics

5.9.1 Auto-Antibodies

Auto-antibodies (anti-GAD; Insulin autoantibodies (IAA); anti-IA2; Zinc Transporter 8 (ZnT8)) results to confirm T1D diagnosis will be descriptively summarized. The distribution of patients by the number of positive antibodies (0, 1, 2, 3, 4) will be reported.

5.9.2 T1D diagnosis

The following parameters will be descriptively summarized by treatment:

- Diagnosis of T1D confirmed (Yes, No)
- Time from T1D diagnosis to inform consent (days), Section 9.1.

5.9.3 Fasting C-Peptide

Summary statistics by treatment of fasting C-Peptide value (nmol/L) at baseline will be provided.

5.9.4 Glycemic control parameter HbA1c result

Summary statistics by treatment of HbA1c (%) at baseline will be provided.

5.9.5 Daily insulin requirement

Summary statistics by treatment of Daily insulin requirement (U/kg/day – expressed as the average of the last 3 days) at baseline will be provided.

5.9.6 Routine use of a self-owned CGM system

The following parameters will be descriptively summarized by treatment:

- Device positioned (Yes, No)
- CGM data recorded for at least 7 days (Yes, No)

6. Evaluation of Treatment Compliance and Exposure

6.1 Compliance to IMP

Descriptive analysis of the following parameters will be presented by treatment group for each cycle and during the entire treatment period:

- from IMP dispensation form
  - number of capsules dispensed (given by the number of dispensed kits considering that each kit contains 56 capsules)
- from IMP accountability form
  - number of returned blisters
  - number of capsules taken

- number of returned unused capsules
- compliance to the study treatment (Yes, No)

On a per patient basis, the evaluation of the compliance during the overall treatment period will be done using the following formula:

$$Compliance\ (\%) = \frac{total\ number\ of\ capsules\ taken\ during\ the\ treatment\ period}{total\ number\ of\ capsules\ dispensed\ during\ the\ treatment\ period} \times 100$$

where "*total number of capsules taken during the treatment period*" is the sum of number of capsules taken at each cycle (CRF IMP ACCOUNTABILITY form), while the "*total number of capsules dispensed during the treatment period*" is given by the number of dispensed kits (CRF IMP DISPENSATION form) considering that each kit contains 56 capsules. For DMC analysis, for subjects ongoing in IMP, the last dispensed kit will not be counted because the number of capsules returned will be known only in the next visit.

Compliance will be summarized by treatment by means of summary statistics. In addition, compliance to IMP will also be presented for the following categories: <80%, ≥80%.

6.2 Exposure to study drug

The extent of exposure to IMP in weeks will be summarized overall with descriptive statistics by treatment group. The extent of exposure (weeks) will be calculated using the formula:

Extent of exposure (weeks) = (Date of last IMP intake – Date of first IMP intake +1)/7.

7. Evaluation of Efficacy

7.1 Analysis of primary endpoint

The following null hypothesis is defined: the proportion of patients with an HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 (visit 4) in ladarixin group is lower or equal than control:

$$H_0: T_{LADARIXIN} \leq T_{CONTROL}$$
$$H_1: T_{LADARIXIN} > T_{CONTROL}$$

where $T_{LADARIXIN}$ and $T_{CONTROL}$ are the proportions of patients with an HbA1c reduction from baseline of ≥ 0.50% without episodes of severe hypoglycemia for ladarixin and control groups, respectively. The null hypothesis H_0 will be rejected, and superiority of ladarixin declared if primary analysis p-value will be lower than 0.05 one sided.

7.1.1 Analysis details

Primary endpoint will be analyzed by means of a logistic regression model, adjusting by predefined factors (treatment, HbA1c baseline value, gender, age class, BMI and country as fixed effect). A one-sided test will be used to test for differences between treatment groups.
Summary statistics of the primary variable will be calculated separately by treatment arm.

Primary endpoint at week 27/28 will be analyzed by means of Multiple Imputation using retrieve dropouts (MI-RD). Retrieved dropout patients are defined as patients who discontinue study treatment and decide to remain in the study by following the schedule of assessments and continuing to adhere to protocol requirements. Consequently, MI will be performed based on the subjects' allocated treatment arm and observed values as covariates in a MI regression model using data from retrieved dropout patients that have the primary endpoint assessment done. Only data up to 27/28 week will be used to impute primary endpoint missing data.
For the imputation of missing data, a logistic regression model will be created by including treatment, gender, HbA1c baseline value, age class, BMI and Country (for convenience we will refer to this method as "MI regression model"). One thousand data sets will be generated. The random seed number will be 465789. MI will be implemented in the following steps:

1. Missing primary endpoint data will be imputed using the specified MI regression model. According to MI-RD approach, only non-missing values from retrieve dropouts will be used to inform the MI regression model. A total of 1000 datasets will be created. These datasets will be utilized in Step #2.
2. Each of the 1000 datasets with observed and imputed data will be analyzed using the logistic regression model. Rubin's rule will be used for combining results to draw inference.

If there are not enough retrieved dropouts for convergence of the MI regression model, a reference-based MI approach will be adopted to consider a Missing Not at Random (MNAR) mechanism for missing data: imputation of values in the ladarixin arm (above step #1) will be done using the non-missing values from the control group (this approach will be referred as "Copy Reference"). This approach does not assume benefits for ladarixin in case of discontinuation and limits a post-discontinuation clinical effect to that of placebo. If the MI-RD model does not converge, then the Copy reference will be used as primary analysis and reported in the CSR. If the MI-RD strategy will be performed, then the Copy-Reference method will be computed as sensitivity analysis (section 7.1.2.3).
Whether for MI-RD or Copy-Reference approach, the adjusted estimated treatment odds ratio between ladarixin and placebo at week 27/28 will be displayed together with the corresponding two-sided 95% confidence intervals and p-value. This p-value will be compared to the threshold 0.05 to demonstrate the superiority of ladarixin. In addition to odds ratio, the absolute risk difference and its 95% confidence interval will be provided.

7.1.2 Sensitivity analyses

Sensitivity analyses are defined to assess the robustness of results on primary endpoint versus assumptions used in the statistical model for the main estimator.

7.1.2.1 Missing at Random assumption

The comparison between treatment and control will be performed by means of MI under Missing at Random (MAR) assumption instead of MNAR. MI will be implemented in the following steps. The random seed number will be 465789.

- Missing primary endpoint data will be imputed using the MI regression model (section 7.1). According to MAR approach, all patients with non-missing values will be used to inform the MI regression model. A total of 1000 datasets will be created. These datasets will be utilized in Step #2.
- Each of the 1000 datasets with observed and imputed data will be analyzed using the logistic regression model. Rubin's rule will be used for combining results to draw inference.

The adjusted estimated treatment odds ratio between ladarixin and placebo at week 27/28 will be displayed together with the corresponding two-sided 95% confidence intervals and p-value. In addition to odds ratio, the absolute risk difference and its 95% confidence interval will be provided.

7.1.2.2 Tipping point

If superiority of ladarixin is shown, tipping point analysis will assess how departures from MI under MNAR assumptions must be to overturn conclusions from the primary superiority analysis. Tipping point will be based on iterative application of MI. In the first iteration, MI-RD method or Copy Reference is assumed as described in section 7.1. In successive iterations, the imputed values for the ladarixin arm are shifted by a constant to represent a worse effect in each iteration. This can be achieved by using the N completed datasets obtained under MI-RD (or Copy Reference) and shift the imputed values. The tipping point is the shift at which the p-value becomes non-significant. Outline of tipping point:

- Use MI-RD (or Copy Reference) to impute missing values.
- Assuming that the tipping point is between 0 and 20, the following actions will be performed for $\Delta = 0, 0.5, 1, 1.5$, etc., 20:
  - Add Δ to the imputed values at the ladarixin arm
  - Analyze the completed data sets using the same method outlined in section 7.1
- the plot of all p-values for Δ will be created
- based on the plot, the approximate value of the tipping point $Tp_{approx.}$ is identified considering a threshold for the p-values of 0.05.
- after identification of $Tp_{approx.}$, finest research of the tipping point will be performed in the range $Tp_{approx.} \pm 1$ by incrementing Δ of 0.01 and following the usual steps:
  - Add Δ to the imputed values at the ladarixin arm
  - Analyze the completed data sets using the same method outlined in section 7.1.
- The tipping point is the smallest Δ at which p-value ≥ 0.05.

7.1.2.3 Copy reference

In case the Copy-Reference approach will not be used for the primary analysis (instead of MI-RD), it will we performed for sensitivity purposes. See details in 7.1.1.

7.1.3 Supportive analyses

Per Protocol Set; this analysis will assess the robustness of results to protocol deviations.

7.1.3.1 Complete cases

The analysis of primary endpoint will be performed by fitting the logistic regression model described in section 7.1.1 on complete cases only i.e., without considering patients with missing primary endpoint, without implementing the MI and without use the "composite strategy".

7.2 Analysis of secondary efficacy endpoints

Analyses on secondary endpoints (section 3.6.2) will be performed at each available timepoint by means of descriptive statistics (section 4.1). In case of continuous measures, analyses will be provided for:

- baseline visit,
- each post-baseline visit, and
- the change from baseline measurements to each visit.

The following results will be displayed graphically:

- The proportion at each timepoint by treatment of patients with HbA1c reduction from baseline of ≥0.50% (absolute difference) without episodes of severe hypoglycemia;
- Boxplots at each timepoint by treatment of the HbA1c and its change from baseline;
- Waterfall plot by treatment of the proportion of patients with an HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 (visit 4) – complete cases;
- Boxplots at each timepoint by treatment of the Time in range (TIR), time above range (TAR) and time below range (TBR) and its change from baseline;
- Boxplots at each timepoint by treatment of the daily insulin requirement (IU/kg/day);

In each graph, where possible, significant p-values from the below analyses (sections 7.2.1 – 7.2.4) will be reported in the plot area, in correspondence of the associated timepoint.

7.2.1 Proportion of responders at week 11/12

The proportion of responders at week 11/12 (visit 3) will be analyzed with the same MI approach and the same logistic regression model described in section 7.1 for the primary efficacy endpoint.

Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of responders during treatment will be calculated for Week 11/12. The comparison between the two study treatment arms will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point.

Severe hypoglycemic events will be listed.

7.2.2 Mean difference from baseline in HbA1c

Mean difference in HbA1c from baseline [Timeframe: week 11/12 (visit 3) and 27/28 (visit 4)] will be analyzed by means of an ANOVA adjusting by pre-defined factors (treatment, HbA1c baseline value, gender, age class, BMI and Country as fixed effect) and a one-sided test will be used to test for differences between treatment groups. If assumption of normality is not confirmed (by a visual inspection of distribution) a log-transformation will be used. Before the log-transformation, the minimum change+0.001 will be computed and added to the original scale values. In this case negative and zero values will be avoided.
For the imputation of missing data, a MI regression model will be created by including treatment, HbA1c baseline value, gender ,age class, BMI and Country as covariates. One thousand data sets will be generated. MI will be implemented in the following steps. The random seed number will be 476534:

1. Missing HbA1c data will be imputed using the specified MI regression model. According to MI-RD approach, only non-missing values from retrieve dropouts will be used to inform the MI regression model. A total of 1000 datasets will be created. These datasets will be utilized in Step #2.
2. Each of the 1000 datasets with observed and imputed data will be analyzed using the ANOVA model. Rubin's rule will be used for combining results to draw inference.

If there are not enough retrieved dropouts for convergence of MI regression model, the Copy Reference approach will be used. The final decision on the use of the MI-RD vs Copy-Reference will be done at the time of the analysis and reported in the CSR.
Whether for MI-RD or Copy-Reference approach, the adjusted estimated treatment differences between ladarixin and placebo will be displayed together with the corresponding two-sided 95% confidence intervals and p-value.

7.2.3 Average (previous 3 days) daily insulin requirement

Average (previous 3 days) daily insulin requirement analysis at week 11/12 (visit 3) and 27/28 (visit 4) will be carried out using a mixed model for repeated measurements (MMRM) with treatment group, visit, treatment by visit interaction, age class, gender, BMI and County as fixed factors of the model and patient as random effect. An unstructured covariance matrix for each patient is considered and the Kenward-Roger adjustment is used for the degrees of freedom. In the case where the model does not converge, different covariance structures will be used, following the below order:

1. a heterogeneous Toeplitz covariance structure, or
2. a Toeplitz covariance structure, or
3. A compound symmetry structure (CS).

The adjusted estimated treatment differences between ladarixin and placebo at each timepoint will be displayed together with the corresponding 95% confidence intervals and p-values. The tests of the fixed effects (treatment, age class, gender, BMI and Country) will be presented, together with the estimated least squares means with the corresponding 95% confidence interval.

Assumption of normal distribution of this endpoint will be assessed by visual inspection. If required, a log transformation will be applied and specified in the notes.

7.2.4 Glycemic Variability by CGM (previous 7 days):

Time in range (TIR), time above range (TAR) and time below range (TBR) will be analyzed using the MI-RD modeling or, if not feasible, the model based on placebo completers (Copy Reference), as detailed in Section 7.2.2. The adjusted estimated treatment differences between ladarixin and placebo at each timepoint will be displayed together with the corresponding 95% confidence intervals and p-values. The tests of the fixed effects (treatment, baseline value of the variable, age class, gender, CGM device,BMI and County) will be presented, together with the estimated least squares means with the corresponding 95% confidence interval.

Assumption of normal distribution of Glycemic Variability by CGM will be assessed by visual inspection. If required, a log transformation will be applied and specified in the notes.

7.3 Analysis of exploratory efficacy endpoints

7.3.1 CCI [redacted]

CCI [redacted]

7.3.2 CCI [redacted]

CCI [redacted] will be performed by means of two-sample t-test or, if assumptions of normality are not confirmed (by visual inspection), two-sample Mann–Whitney U test.

7.3.3 CCI [redacted]

CCI [redacted]

[redacted] CCI [redacted]

CCI [redacted]

CCI [redacted] CCI [redacted]

CCI [redacted]

[redacted] CCI [redacted]

[redacted]

8. Evaluation of Safety

8.1 Adverse events

Adverse Events (AEs) started before administration of study treatment will be considered as pre-treatment. Any AE which starts at or after the first administration of study treatment will be considered a Treatment Emergent Adverse Event (TEAE). Pre-treatment AEs and TEAEs will be presented separately. Pre-treatment AEs will be presented in the listings only. In case of missing or incomplete dates not allowing a direct allocation to any of the two categories of AEs, a worst-case allocation will be done according to the available parts of the onset and the end dates. The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE (defined in Section 9.3);
- Pre-treatment AE (Not TEAE, with start date< IMP start date).

In case a pre-treatment AE change severity (became worst) occurs on or after treatment start date, then the date of change in severity will be considered as start date of a treatment-emergent AE.

In case of TEAE, the event can be classified as (Section 9.3):

- On Treatment Period, or
- On Follow-up period

according to the available parts of the onset and the end dates.

All AEs will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus. In addition, each AE will be graded according to severity definitions as “Mild”, “Moderate” or “Severe”.

TEAEs will be reported on a per-patient basis, i.e. if a patient reported the same event repeatedly (i.e. events mapped to the preferred term) the event will be counted only once.

For summaries, the drug-event relationship will be assessed as “None”, “Unlikely”, “Possible” “Probable” or “Highly probable”. Any TEAE reported in the study having a possible, probable, or highly probable relationship to IMP or missing relationships will be defined as “Adverse Drug Reaction” (ADR).

The following tables and listings will be presented by treatment group:

- An overview of TEAEs including the number of patients who exhibited at least one TEAE, at least one severe TEAE, at least one TESAE, at least one non-serious TEAE, at least one ADR, at least one serious ADR, at least one hypoglycemic episode, number of TEAEs, number of non-serious TEAEs, number of TESAEs, number of ADRs, number of serious

ADRs, number of deaths, number of patients who discontinued IMP due to a TEAE, number of hypoglycemic episodes;

- Summary of TEAEs by primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of TEAEs by primary System Organ Class, Preferred Term and Severity;
- Summary of Serious TEAEs by Primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of ADRs by Primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of ADRs by Primary System Organ Class and Preferred Term and Severity;
- Summary of TEAEs leading to IMP Discontinuation by Primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of TEAEs leading to Death by Primary System Organ Class and Preferred Term and by study period (on treatment/follow-up and overall);
- Summary of Hypoglycemic Episodes by ADA Criteria by study period (on treatment/follow-up and overall);
- Listing of all Aes by Patient;
- Listing of SAEs by Patient;
- Listing of ADR by Patient;
- Listing of Deaths.

In addition, time-to-event methods will be used to summarize the time to onset of hypoglycemic episodes from first dose of treatment. Kaplan-Meier estimates and plots will be provided with:

- the 95% confidence interval bounds calculated per the method proposed by Greenwood[3];
- the respective number of patients at risk and Kaplan-Meier estimates at different time points;
- the median and its 95% confidence interval;
- the log-rank test p-value.

Subjects ongoing and who are free from event at the analysis cut-off date will be censored at that date. A table footnote will clarify the analysis cut-off date. Subjects who have discontinued the study without an event will be censored at the date of discontinuation.

8.2 Clinical laboratory evaluation

Analysis of clinical laboratories data will be performed by treatment for Hematology and Biochemistry tests. In case of different units of measure considered for the same laboratory

parameter, all values will be converted into Standard International (SI) units (if applicable) or to the same unit.

The following summaries will be provided:

- A summary table showing for all laboratory tests the values and changes from baseline to each subsequent visit;
- A summary table showing for all laboratory tests the frequency of patients reporting an abnormal (clinically or not clinically significant) laboratory value at baseline , at subsequent visits and at least one at any visit
- Shift tables presenting the number and the percentage of patients in each bivariate category (baseline versus each post-baseline visit) with regards to investigator's interpretation.

The following graphical representations will be provided for all laboratory parameters:

- Spaghetti plot of individuals' observed data and change from baseline (with x-axis marked by days relative to start of actual treatment);

8.3 Vital signs, Estimated Glucose Disposal Rate and BMI

Summary statistics by treatment will be provided along with summary of the change from baseline at each timepoint for:

- Vital signs:
  - Systolic Blood Pressure (mmHg),
  - Diastolic Blood Pressure (mmHg), and
  - Heart Rate (bpm));
- [redacted] BMI evaluations:
  - Weight (Kg) and Height (cm),
  - BMI (Kg/m^2) – derived from CRF,
  - Waist circumference (cm) and Waist-to-Hip Ratio,
  - Hypertension status (Yes, No)

The following graphical representations will be provided for all quantitative vital signs:

- Spaghetti plot of individuals' observed data and change from baseline (with x-axis marked by days relative to start of actual treatment);

8.4 ECGs

Summary statistics by treatment of QTcF Interval (msec) and ECG interpretation (Normal, Abnormal NCS, Abnormal CS, No Result) will be provided along with summary of the change/shift from baseline at each timepoint.

In case of repetition of ECG evaluation (according to protocol), the repeated QTcF value will be considered as the only evaluation value for that visit.

8.5 Pregnancy test over the study

A summary table showing test results (Negative/Positive) over the study will be produced by treatment group, where applicable.

9. Derivations and date conventions

9.1 Variable derivation

Table 4: Variable derivation rules

Parameter	Calculation
Screened	A patient is considered screened if (s)he has "Date of written informed consent signature from patient (dd-MMM-yyyy)" filled.
Enrolled	A patient is considered enrolled if (s)he has signed written informed consent and fulfillment of eligibility criteria (i.e., not reported as screening failure).
Timepoint	Defined in Section 3.3
IMP start date	Start of treatment refers to the date of the first IMP administration.
End of treatment	End of treatment (EOT) refers to the date of the last IMP administration.
Baseline	Baseline is defined as the last visit prior to and including date of the randomization visit (Day 1). Unless otherwise specified, baseline values are defined as the measurements taken during this visit. In case of multiple measurements during baseline visit, the last assessment before start of treatment will be considered as baseline evaluation.
Visit completion	If the visit is available (present in the source datasets) the visit is completed
Trial completers	A patient is considered completer if the tick box "Did the patient complete the study?" is ticked "Yes" in the "STUDY TERMINATION" page. If box is not ticked, the subject is considered ongoing in the trial (not applicable for the CSR).
Subject discontinued	A patient is considered completer if the tick box "Did the patient complete the study treatment?" is ticked "No" in the "END OF TREATMENT" page. If box is not ticked, the subject is considered ongoing in the IMP (not applicable for the CSR).
Patient with concomitant disease	A patient is considered with concomitant disease if CRF term "Has the patient experienced any relevant past and/or concomitant diseases or past surgeries?" = YES and at least a medical history term has "Ongoing" flagged. Otherwise the patient is considered as with no concomitant disease.

Parameter	Calculation
Prior Medical and surgery history	A patient is considered having a prior medical/surgery history if CRF term "Has the patient experienced any relevant past and/or concomitant diseases or past surgeries?" = YES and no medical history term has "Ongoing" flagged. Otherwise the patient is considered having no prior medical and surgery history
Treatment period	Starts from randomization [timeframe: Day 1 (visit 2)] and ends on the day of the last dose of study treatment.
Change from baseline	Each change from baseline will be defined as difference between the value (minuend) at each post-baseline assessment and the baseline value (subtrahend).
Severe hypoglycemia	An adverse event is considered as "severe hypoglycemia" if the assessment has • Ticked "yes" in the "SELF REPORTED HYPOGLYCEMIA" page And • Has ticked "Level 3" in the "ADVERSE EVENTS" eCRF form.
Time from T1D diagnosis to inform consent	Time from T1D diagnosis to IC (days) = Date of IC signature – Date of T1D diagnosis +1. Missing/partial dates will not be imputed. Anyway, since these dates are crucial for enrolment, their complete presence in the final database is expected.
Time to discontinuation	Time to discontinuation (days)= Date of discontinuation - date of randomization+1 Missing/partial dates will not be imputed. Anyway, since these dates are crucial for enrolment, their complete presence in the final database is expected.
Extent of exposure	Extent of exposure (days) = Date of last IMP intake – Date of first IMP intake +1.
CGM parameters	See section 12.1.
Identification of hypoglycemic episodes	CRF – SELF REPORTED HYPOGLYCEMIA form: Did the patient experience any hypoglycemic episodes?
Time to hypoglycemic episode from first IMP intake	Time to hypoglycemic episode = Date of onset of hypoglycemic episode (CRF - ADVERSE EVENTS form) - Date of first IMP intake +1.

Parameter	Calculation
Time from randomization to study discontinuation	Time from randomization to study discontinuation (days) = Date of study discontinuation - Date of randomization +1.
Responder definition: patients with an HbA1c reduction from baseline of >= 0.50% (absolute difference) without episodes of severe hypoglycemia [timeframe: Week xx (Visit xx)]	A patient is considered as responder at Week XX (Visit XX) - if reduction of HbA1c from baseline of >=0.50% (absolute difference) at Week XX (Visit XX), AND - no episodes of severe hypoglycemia by Week XX (Visit XX)
Average (previous 3 days) insulin requirements (IU/kg/day)	CRF - DAILY INSULIN REQUIREMENT EVALUATION form: Average Insulin requirement (IU/kg/day)
Conversion of Time Intervals	If a time interval was calculated in minutes, hours or days and needs to be converted into months or years the following conversion factors will be used: • 1 month = 30.4375 days • 1 year = 365.25 days
Cut-off Date	For DMC only. The database snapshot date is the date of the raw data extraction to create the Study Data Tabulation Model (SDTM) datasets. The SDTM production date may be later. The cutoff date is used to exclude all subjects screened after that date, as well as all the assessments carried out after that date. For adverse events, the onset date is compared to the cutoff date. The events with onset date after the cutoff date are excluded from the analyses. In case of purpose of the analyses is the CSR, cut-off date will be not applied.

9.2 CGM value derivation

Different Continuous Glucose Monitoring System may be used to perform CGM during the study. Each of them uses proprietary algorithms to create fully customable reports and summary measures for patients and clinicians. These reports will not be used during the trail given the fully customizable features. Instead, in order to standardize the summary statistics from each patient, the *cgmanalysis* package[2] written entirely in the statistical programming language R (R Foundation for Statistical Computing, Vienna, Austria) will be used.

Gaps in glucose data shorter or equal than 30 minutes will be imputed using linear interpolation. The *cgmanalysis* package[2] `cleandata` function will be used.

After filling eventual gaps in the glucose data, the following requirements should be met for a visit in order to be considered eligible for analysis:

- a total of at least 7 days of valid CGM recordings will be required for a visit to be used for analysis:
  - *cgmanalysis*: num_days_good_data >= 7;
- the number of sensor readings as a percentage of the number of potential readings (given time worn) has to be greater than 80%:
  - *cgmanalysis*: percent_cgm_wear > 80%.

The *cgmanalysis* package[2] `cgmvariables` function will be used for the CGM parameters (sections 3.6.2 and 3.6.3). The package has been modified in order to perform additional simultaneous analyses (see Appendix XX for the entire R code). Table 5 reports the correspondence between required endpoint and `cgmvariables` outcomes.

For the calculation of 2h PPG, the raw data from Dexcom G6 System have to be filtered in order to keep only observations ≤ 120 minutes from meals, where the exact time of meals (breakfast, lunch and dinner) are taken from eDiary. If time of meal is missing, the adjacent CGM observations will not be considered.

Table 5: Variable in cgmanalysis

Endpoint	**Variable in *cgmanalysis***
TIR	percent_time_70_180
TAR	percent_time_over_180
TBR	percent_time_under_70

**raw data must be filtered with observations ≤ 180 minutes from meals (eDiary)*

9.3 Partial date conventions

Table 6: Algorithm for Treatment Emergence of Adverse Events

AE START DATE^	**AE STOP DATE**	**RULE for TEAE definition**	**RULE for "Treatment"/"Follow-up" study period definition for TEAE summaries**
Known	Known, Partial or Missing	If AE start date < IMP start date, then not TEAE If AE start date >= IMP start date, then TEAE	If End of treatment is not missing, AE start date > End of Treatment then "Follow-up", otherwise "Treatment" period.

AE START DATE^	AE STOP DATE	RULE for TEAE definition	RULE for "Treatment"/"Follow-up" study period definition for TEAE summaries
Partial, but known components show that it cannot be on or after IMP start date	Known, Partial or Missing	Not TEAE	Not Applicable
Partial, could be on or after IMP start date	Known	If AE stop date < IMP start date, then not TEAE If AE stop date >= IMP start date, then TEAE	If TEAE, then Treatment study period for TEAE occurrence.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date < IMP start date, then not TEAE If AE stop date >= IMP start date, then TEAE	
	Missing	Assumed TEAE	
Missing	Known	If AE stop date < IMP start date, then not TEAE If AE stop date >= IMP start date, then TEAE	If TEAE, then Treatment study period for TEAE occurrence.
	Partial	Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date < IMP start date, then not TEAE If AE stop date >= IMP start date, then TEAE	
	Missing	Assumed TEAE	

*NOTE: * Assignment to "Treatment" or "Follow-up"study period is applicable only for TEAEs.*

^For start date the cut-off date rule is used (Section 9.1)

Table 7: Algorithm for Prior/Concomitant medications

MEDICATION START DATE	MEDICATION STOP DATE	RULE for prior or concomitant categorization
Known	Known	If medication stop date < date of informed consent, assign as prior If medication stop date >= date of informed consent, assign as concomitant
	Partial	Impute medication stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < date of informed consent, assign as prior If medication stop date >= date of informed consent, assign as concomitant
	Missing	Assign as concomitant
Partial or Missing	Known	If medication stop date < date of informed consent, assign as prior If medication stop date >= date of informed consent, assign as concomitant
	Partial	Impute medication stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < date of informed consent, assign as prior If medication stop date >= date of informed consent, assign as concomitant
	Missing	Assign as concomitant

10. Tables, Figures and Listings

10.1 Output conventions

- Each Table, Listing and Figure (TLF) should be numbered, following the ICH E3 Guideline.
- All titles have to be sufficiently explanatory, i.e. the content of the outputs should be clear even when consulted independently from the SAP.
- For numeric variables, units will be presented enclosed in square brackets ([ ])., when appropriate.
- Each table and each figure should provide reference to the listing where the data on which the table/figure is based are shown.
- Listings should include raw data, i.e. data collected in CRF or other data collection tool, as well as derived data, i.e. data of variables that have been generated for statistical analysis. The derived data must be clearly identified.
- Every TLF should report the following information on the upper side of the output:
    - Left aligned:
        - Protocol number
    - Centered aligned:
        - "Confidential"
    - Right aligned:
        - Dompé Farmaceutici SpA
        - Draft/Final Run <date>
- Every TLF should report the following information on the bottom side of the output:
    - Left aligned:
        - the name of the SAS program which will generate the output
    - Centered aligned:
        - Draft/Final Version - Date <date>
    - Right aligned:
        - "Page n of N", where n is the page number and N is the total number of pages of the document.

10.2 Format requirements:

- All TLFs will be produced in landscape format on A4 paper size, unless otherwise specified.
- The titles are centered. The analysis sets are identified on the line following the title.
- it is preferable to use "Courier New" with minimal font size of 8, which is the smallest acceptable point size for the Regulatory Authorities.
- Output files will be delivered in Rich Text Format (RTF) that can be manipulated in Word.

10.3 Table Conventions

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table even in case of frequency equal to 0.

- If the categories are not ordered (e.g., Medical History), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and SDs.
- Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

10.4 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups, subject number, and visit.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000).
- In case listings will not fit the page, it will be splitted in two different parts.

11. Reference

1. Study protocol, A phase II randomized, placebo-controlled, double-blinded, 2-parallel arm, clinical trial evaluating ladarixin 400 mg twice a day as adjunctive therapy to improve glycemic control in overweight insulin-resistant patients with type 1 diabetes., Protocol Version - Date: Version No. 1 final – CCI [redacted].
2. Vigers T, Chan CL, Snell-Bergeon J, Bjornstad P, Zeitler PS, Forlenza G, et al. (2019) Cgmanalysis: An R package for descriptive analysis of continuous glucose monitor data. PLoS ONE 14 (10): e0216851. https://doi.org/10.1371/journal.pone.0216851
3. Kalbfleisch, J. D., and Prentice, R. L. (1980). The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons.
4. P. K. Andersen. R. D. Gill. "Cox's Regression Model for Counting Processes: A Large Sample Study." Ann. Statist. 10 (4) 1100 - 1120, December, 1982.

12. Appendices

12.1 R code for CGM

R code	Notes

```
Cgmvariables_mod <- function(inputdirectory,
                     outputdirectory = tempdir(),
                     outputname = "Dexcom",
                     customintervals = list(c(,)),
                     aboveexcursionlength = 35,
                     belowexcursionlength = 10,
                     magedef = "1sd",
                     daystart = 0,
                     dayend = 24,
                     id_filename = F,
                     format = "rows",
                     printname = F) {

  # Read in data, create results dataframe. The dataframe has one column for each
  # file in the input directory, and is desgined to be uploaded to REDCap.
  files <- base::list.files(path = inputdirectory,full.names = TRUE)
  cgmupload <-
    base::as.data.frame(base::matrix(nrow = 0,ncol = base::length(files)))
  base::colnames(cgmupload) <- base::rep("Record",base::length(files))
  # Define the order in which lubridate parses dates.
  dateparseorder <- c("mdy HM","mdy HMS","mdY HM","mdY HMS","dmy
HM","dmy HMS",
                      "dmY HM","dmY HMS","Ymd HM","Ymd HMS","ymd HM","ymd
HMS",
                      "Ydm HM","Ydm HMS","ydm HM","ydm HMS")
  allhours <- 0:23
  # Iterate through the input directory and calculate CGM variables for each file.
  # The cgmvariables() function only works on CSV files that have been cleaned by
  # cleandata(), or that have been manually edited and fit the format of
  # cleandata() output.
  for (f in 1:base::length(files)) {
    # Basic variables
    table <- utils::read.csv(files[f],stringsAsFactors = FALSE,na.strings = c("NA",""))
    # Remove duplicates
    if(id_filename == F) {
      table$subjectid <- table$subjectid[1]
    } else {
      table$subjectid[1] <- sub("*.csv","",basename(files[f]))
    }
    table <- unique(table)
    # Print name
    if(printname == T) {
      print(basename(files[f]))
    }
    # Column names to lower case
    colnames(table) = tolower(colnames(table))
    cgmupload["subject_id",f] <- table$subjectid[1]
    # Format columns.
```

R code	Notes

```
    table$timestamp <-
      base::as.POSIXct(lubridate::parse_date_time(table$timestamp,
                                          dateparseorder,tz = "UTC"))
    table$sensorglucose <- suppressWarnings(base::as.numeric(table$CCI [redacted]
    interval <- pracma::Mode(base::diff(base::as.numeric(table$timestamp)))
    interval <- base::abs(interval)
    cgmupload["date_cgm_placement", f] <-
      base::as.character(min(table$timestamp,na.rm = T))

    totaltime <-
      base::as.numeric(base::difftime(base::max(table$timestamp, na.rm = T),
                                base::min(table$timestamp,na.rm = T),
                                units = "secs"))
    cgmupload["percent_cgm_wear",f] <-

CCI [redacted]
    table <- table[!is.na(table$timestamp) & !is.na(table$CCI [redacted]

    cgmupload["total_sensor_readings",f] <-
      base::as.numeric(base::length(base::which(!is.na(table$CCI [redacted]
    cgmupload["average_sensor",f] <-
      base::mean(table$CCI [redacted] [base::which(!is.na(table$CCI [redacted],na.rm =
T)
    cgmupload["estimated_a1c",f] <-
      CCI [redacted]
      base::which(!is.na(table$CCI [redacted] digits = 1)
    cgmupload["q1_sensor",f] <-
      base::as.numeric(base::summary(table$CCI [redacted]
        base::which(!is.na(table$CCI [redacted] [2])
    cgmupload["median_sensor",f] <-
      base::as.numeric(base::summary(table$CCI [redacted]
        base::which(!is.na(table$CCI [redacted] [3])
    cgmupload["q3_sensor",f] <-
      base::as.numeric(base::summary(table$CCI [redacted]
        base::which(!is.na(table$CCI [redacted] [5])
    cgmupload["standard_deviation",f] <-
      stats::sd(table$CCI [redacted] [base::which(!is.na(table$CCI [redacted]
    cgmupload["cv",f] <-
      (stats::sd(table$CCI [redacted] [base::which(!is.na(table$CCI [redacted]
      base::mean(table$CCI [redacted] [base::which(!is.na(table$CCI [redacted]
    cgmupload["min_sensor",f] <-
      base::min(table$CCI [redacted] [base::which(!is.na(table$CCI [redacted]
    cgmupload["max_sensor",f] <-
      base::max(table$CCI [redacted] [base::which(!is.na(table$CCI [redacted]

    #CCI [redacted]
    [redacted] <-
      base::as.numeric(table$CCI [redacted] [base::which(!is.na(
```

R code	Notes
table$sensorglucose))],length = 1) CCI [redacted] base::CCI [redacted] cgmupload[CCI [redacted],f] <- base::length(base::which(CCI [redacted] > ((aboveexcursionlength * 60)/interval))) cgmupload["CCI [redacted]",f] <- base::sum(CCI [redacted]) * (interval/CCI cgmupload["pCCI [redacted]",f] <- ((base::sum(BGover120) * (interval/CCI (base::length(table$CCI [redacted] * (interval/CCI [redacted] * 100 # Over CCI CCI [redacted] <- base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],length = 1) CCI [redacted] base::as.CCI [redacted] cgmupload["excursions_CCI [redacted]",f] <- base::length(base::CCI [redacted]0 > ((aboveexcursionlength * CCI/interval))) cgmupload[CCI [redacted]] <- base::sum(CCI [redacted]) * (interval/CCI cgmupload["percent_time_over_140",f] <- ((base::sumCCI [redacted]) * (interval/CCI (base::length(table$CCI [redacted] * (interval/CCI [redacted] * 100 # Over CCI CCI [redacted] <- base::as.numeric(table$CCI [redacted][base::which(!is.na(table$sensorglucose))],length = 1) CCI [redacted] base::as.CCI [redacted] cgmupload["excursions_CCI _CCI ,f] <- base::length(base::CCI [redacted]> ((aboveexcursionlength * CCI/interval))) cgmupload["CCI [redacted]",f] <- base::sum(CCI [redacted] * (interval/CCI cgmupload[CCI [redacted]",f] <- ((base::sum(CCI [redacted]) * (interval/CCI (base::length(table$sensorglucose) * (interval/CCI [redacted] * 100 # Over CCI CCI [redacted] <- base::as.numeric(table$CCI [redacted][base::which(!is.na(	

R code	Notes
table$sensorglucose))],length = 1) CCI [redacted] base::as.CCI [redacted] (CCI [redacted] cgmupload["excursions_CCI [redacted],f] <- base::length(base::CCI [redacted] > ((aboveexcursionlength * CCI [redacted]/interval))) cgmupload["CCI [redacted]",f] <- base::sum(CCI [redacted]) * (CCI [redacted]/60) cgmupload["CCI [redacted]",f] <- ((base::sumCCI [redacted]) * (interval/CCI [redacted] (base::length(table$sensorglucose) * (interval/CCI [redacted] * 100 cgmupload["CCI [redacted]",f] <- as.numeric(cgmupload["eCCI [redacted]",f])/ as.numeric(cgmupload["num_days_good_data",f]) cgmupload["avg_CCI [redacted]] <- as.numeric(cgmupload[CCI [redacted]",f])/ as.numeric(cgmupload["num_days_good_data",f]) #CCI [redacted] [redacted] <- base::as.numeric(table$CCI [redacted][base::which(!is.na(table$sensorglucose))],length = 1) CCI [redacted] [redacted] <- base::CCI [redacted] cgmupload["CCI [redacted]",f] <- base::length(base::which(CCI [redacted]0 > ((aboveexcursionlength * CCI [redacted]/interval))) cgmupload["CCI [redacted]0",f] <- base::sum(CCI [redacted]) * (interval/CCI cgmupload["CCI [redacted]0",f] <- ((base::sum(CCI [redacted]) * (interval/CCI [redacted] (base::length(table$sensorglucose) * (interval/CCI [redacted] * 100 #CCI [redacted] [redacted]4 <- base::as.numeric(table$CCI [redacted][base::which(!is.na(table$sensorglucose))],length = 1) CCI [redacted] [redacted] base::as.numeric(BG54.rle$lengths[base::which(BG54.rle$values == 1)]) cgmupload["eCCI [redacted]] <- base::length(base::which(CCI [redacted] > ((belowexcursionlength * CCI [redacted]/interval))) cgmupload["CCI [redacted]",f] <- base::sum(CCI [redacted]) * (interval/6[redacted])	

R code	Notes
cgmupload[CCI [redacted]",f] <- ((base::sum(CCI [redacted]) * (interval CCI))/ (base::length(table$CCI [redacted] * (interval/CCI * 100 #CCI [redacted] [redacted] <- base::as.numeric(table$CCI [redacted][base::which(!is.na(table$CCI [redacted],length = 1) CCI [redacted] base::as.numeric(BG60.rle$lengths[base::which(BG60.rle$values == 1)]) cgmupload["CCI [redacted],f] <- base::length(base::which CCI [redacted] > ((belowexcursionlength * CCI /interval))) cgmupload["CCI [redacted]",f] <- base::sum CCI [redacted] * (interval/CCI cgmupload["percent_time_under_CCI ,f] <- ((base::sum(BGunder60) * (interval/CCI (base::length(table$CCI [redacted] * (interval CCI))) * 100 #CCI [redacted] [redacted] <- base::as.numeric(table$CCI [redacted][base::which(!is.na(table$CCI [redacted] length = 1) CCI [redacted] base::CCI [redacted] cgmupload[CCI [redacted] <- base::length(base::which(CCI [redacted] ((belowexcursionlength * CCI /interval))) CCI [redacted] # Time in range. BGinrange <- base::as.numeric(table$CCI [redacted][base::which(!is.na(table$CCI [redacted] length = 1) CCI [redacted] #CCI [redacted]	

R code	Notes

CCI [redacted]
[redacted]
[redacted]-
base::as.numeric(table$CCI [redacted][base::which(!is.na(table$CCI [redacted]
length = 1)
CCI [redacted]
# Below 	
BGunder <-
base::as.numeric(table$CCI [redacted][base::which(!is.na(table$CCI [redacted]
length = 1)
CCI [redacted]
[redacted] 100
# Above 	
BGover <-
base::as.numeric(table$CCI [redacted][base::which(!is.na(
table$CCI [redacted],length = 1)
CCI [redacted]
[redacted]<-
base::as.CCI [redacted]
cgmupload[paste0(CCI [redacted]),f] <-
base::length(base::which(excursionsover >
CCI [redacted]))))
CCI [redacted]
(interval/60)
cgmupload[paste0("percent_time_over_",highs[r]),f] <-
((base::sum(BGover) * (CCI [redacted])/
(base::length(table$CCI [redacted] * CCI [redacted]
}
}
# Find daytime AUC. 	
if ("wake" %in% colnames(table)) {
daytime_indexes <-
base::which(table$wake == 1)	

R code	Notes

} else {
daytime_indexes <-
base::which(base::as.numeric(base::format(table$timestamp,"%H")) %in%
daystart:dayend)
}
daytime_sensor <- table$CCI [redacted][daytime_indexes]
xaxis <-
base::seq(from = 0, length.out = base::length(daytime_sensor),by =
(interval / 60))
 	
# Remove NAs if they are present. 	
xaxis[base::which(is.na(daytime_sensor))] <- NA
xaxis <- xaxis[!is.na(xaxis)]
daytime_sensor <- daytime_sensor[!is.na(daytime_sensor)]
aucs <- pracma::cumtrapz(xaxis,daytime_sensor)
cgmupload["daytime_auc",f] <- aucs[base::length(daytime_sensor)]
 	
# TIR variables for daytime 	
BGinrange <- ifelse(CCI [redacted])
c CCI [redacted] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
cgmupload[CCI [redacted]] <-
(base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(daytime_sensor) *
(interval/CCI * 100
 	
BGinrange <- ifelse(CCI [redacted])
cgmupload["CCI [redacted] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
cgmupload["p CCI [redacted] <-
(base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(daytime_sensor) *
(interval/CCI * 100
 	
BGinrange <- ifelse(CCI [redacted])
cgmupload[CCI [redacted]] <- base::sum(BGinrange,na.rm = T) *
(interval/60)
cgmupload["CCI [redacted]] <-
(base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(daytime_sensor) *
(interval/CCI * 100
 	
BGinrange <- ifelse(CCI [redacted])
cgmupload["CCI [redacted] f] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
cgmupload["CCI [redacted] <-
(base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(daytime_sensor) *
(interval/CCI * 100
 	
BGinrange <- ifelse(CCI [redacted])
cgmupload["CCI [redacted]] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
cgmupload["CCI [redacted]] <-
(base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(daytime_sensor) *
(interval/CCI * 100
 	
BGinrange <- ifelse(CCI [redacted])	

R code	Notes

```
   cgmupload["CCI [redacted] ] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
   cgmupload["CCI [redacted] ] <-
     (base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(daytime_sensor) *
(interval/CCI  * 100

   BGinrange <- ifelse(CCI [redacted] )
   cgmupload["CCI [redacted] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
   cgmupload["percent_time_over_250_day",f] <-
     (base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(daytime_sensor) *
(interval/CCI  * 100

   # CCI [redacted]
   [redacted]
    [redacted]
   [redacted]
   [redacted]
   [redacted]
   [redacted]

   # Nighttime AUC.
   if ("wake" %in% colnames(table)) {
     nighttime_indexes <- base::which(table$wake == 0)
   } else {
     nighttime_indexes <-
       base::which(base::as.numeric(base::format(table$timestamp,"%H")) %in%
                   allhours[base::which(!(0:23 %in% daystart:dayend))])
   }
   if (length(nighttime_indexes) > 0) {
     nighttime_sensor <- table$sensorglucose[nighttime_indexes]
     xaxis <-
       base::seq(from = 0, length.out = base::length(nighttime_indexes),by =
                 (interval / CCI

     # Day/night ratio.
     cgmupload["day_night_sensor_ratio",f] <-
       base::round(base::length(daytime_sensor)/base::length(nighttime_sensor),1)

     # Remove NAs if they are present.
     xaxis[base::which(is.na(nighttime_sensor))] <- NA
     xaxis <- xaxis[!is.na(xaxis)]
     nighttime_sensor <- nighttime_sensor[!is.na(nighttime_sensor)]
     aucs <- pracma::cumtrapz(xaxis,nighttime_sensor)
     cgmupload["nighttime_auc",f] <- aucs[base::length(nighttime_sensor)]

     # TIR variables for nighttime
     BGinrange <- ifelse(CCI [redacted]
     cgmupload["CCI [redacted] ] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
     cgmupload["CCI [redacted] ] <-
       (base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(nighttime_sensor)
* (interval/CCI  * 100

     BGinrange <- CCI [redacted]
```

R code	Notes

```
    cgmupload[CCI [redacted] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
    cgmupload[CCI [redacted] ] <-
      (base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(nighttime_sensor)
* (interval/CCI  * 100

    BGinrange <- CCI [redacted])
    cgmupload["CCI [redacted] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
    cgmupload["pCCI [redacted] <-
      (base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(nighttime_sensor)
* (interval/CCI  * 100

    BGinrange <- CCI [redacted])
    cgmupload[CCI [redacted] ] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
    cgmupload["CCI [redacted] ] <-
      (base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(nighttime_sensor)
* (interval/CCI  * 100

    BGinrange <- ifelse(nighttime_sensor > 180, 1,0)
    cgmupload[CCI [redacted] f] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
    cgmupload["CCI [redacted] <-
      (base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(nighttime_sensor)
* (interval/CCI  * 100

    BGinrange <-CCI [redacted])
    cgmupload[CCI [redacted] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
    cgmupload["pCCI [redacted] <-
      (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(nighttime_sensor)
* (interval/CCI  * 100

    BGinrange <- ifelse(CCI [redacted])
    cgmupload[CCI [redacted] ] <- base::sum(BGinrange,na.rm = T) *
(interval/CCI
    cgmupload["CCI [redacted] ] <-
      (base::sum(BGinrange,na.rm = T) * (interval/CCI (base::length(nighttime_sensor)
* (CCI  /60)) * 100

    # Other nighttime sensor glucose variables.
    cgmupload["nighttime_avg_sens_glucose",f] <-
      base::mean(stats::na.omit(nighttime_sensor))
    cgmupload["nighttime_min_sens_glucose",f] <- base::min(nighttime_sensor)
    cgmupload["nighttime_max_sens_glucose",f] <- base::max(nighttime_sensor)
    cgmupload["nighttime_sd",f] <- stats::sd(nighttime_sensor)
  }

  # Total AUC.
  sensorBG <- base::as.numeric(table$CCI [redacted],length = 1)
  xaxis <-
    CCI [redacted]
```

R code	Notes
# Remove NAs if they are present. xaxis[base::which(is.na(sensorBG))] <- NA xaxis <- xaxis[!is.na(xaxis)] sensorBG <- sensorBG[!is.na(sensorBG)] aucs <- pracma::cumtrapz(xaxis,sensorBG) cgmupload["total_auc",f] <- aucs[base::length(sensorBG)] cgmupload["average_auc_per_day",f] <- base::as.numeric(cgmupload["total_auc",f]) / base::as.numeric(cgmupload["num_days_good_data",f]) # CCI [redacted] # Calculate cumulative AUC, and subtract rectangle where length = CCI [redacted]	

# CCI [redacted] 	
 	
# Calculate cumulative CCI [redacted] and subtract recatangle where length = CCI [redacted] 	
.
if (base::length(CCI [redacted] {
aucs <- pracma::cumtrapz(xaxis,sensorlower70)
aucs <-
-(aucs[base::length CCI [redacted])]) + (xaxis[base::length(xaxis)] * CCI [redacted]
 	
cgmupload["CCI [redacted]] <- aucs
} else {
cgmupload["CCI [redacted]
}
cgmupload["CCI [redacted]
	This section has been modified in order to calculate the AUC between 70 (upper limit) and the glucose curve (lower limit).

R code	Notes
base::as.numeric(cgmupload["CCI [redacted]/ base::as.numeric(cgmupload["rCCI [redacted] cgmupload["interval (sec)",f] <- interval	

# Calculate CCI [redacted] 	
# Smooth data using an exponentially weighted moving average, calculate SD of 	
# unsmoothed data. 	
table$smoothed <-
base::as.numeric(zoo::rollapply(zoo::zoo(CCI [redacted]
table$smoothed[1:4] <- base::mean(stats::na.omit(table$CCI [redacted] [CCI))
table$smoothed[(base::length(table$smoothed)CCI):
base::length(table$smoothed)] <-
base::mean(table$sensorglucose[(base::lengthCCI CCI [redacted] -CCI
base::length(table$CCI [redacted]
 	
sd <- stats::sd(table$CCI [redacted]
# Identify turning points, peaks, and nadirs. 	
tpoints <- pastecs::turnpoints(table$smoothed)
peaks <- base::which(tpoints[["peaks"]] == TRUE)
pits <- base::which(tpoints[["pits"]] == TRUE)
#CCI [redacted]
if (tpoints[["firstispeak"]] == TRUE && base::length(peaks) !=
base::length(pits)) {
peaks <- peaks[2:base::length(peaks)]
} else if (tpoints[["firstispeak"]] == FALSE &&
base::length(peaks) != base::length(pits)) {
pits <- pits[1:(base::length(pits)-1)]
}
differences <- table$sensorglucose[peaks] - table$sensorglucose[pits]
 	
#CCI [redacted]
if (magedef == "1sd") {
cgmupload["r_mage",f] <-
base::mean(stats::na.omit(differences[base::which(differences > sd)]))
} else if (CCI [redacted]") {
cgmupload["r_mage",f] <-
base::mean(stats::na.omit(differences[base::which(differences >
(sd * 1.5))]))
} else if (magedef == "2sd") {
cgmupload[CCI [redacted]<-
base::mean(stats::na.omit(differences[base::which(differences >
(sd * 2))]))
} else {
cgmupload["CCI [redacted]<-
base::mean(stats::na.omit(differences[base::which(differences >
CCI [redacted]
}	

R code	Notes
CCI [redacted] cgmupload["j_index",f] <- 0.001 * (base::mean(table$CCI [redacted] na.rm = T) + stats::sd(table$CCI [redacted] na.rm = T))^2	

CCI [redacted].
CCI [redacted]
[redacted]
}
# Average the averages. 	
cgmupload["modd",f] <-
base::mean(stats::na.omit(moddtable$mean_differences))
 	
#CCI [redacted]
table$gluctransform <- y * ((base::log(CCI [redacted] ^a)-b)
table$rBG <- 10 * (table$gluctransform^2)
rl <- table$rBG[base::which(CCI [redacted]
rh <- table$rBG[base::CCI [redacted]
CCI [redacted]
}
 	
# Write file. 	
cgmupload <-
base::cbind("Variable / Field Name" = rownames(cgmupload),cgmupload)
if (format == "rows") {
cgmupload <- base::as.data.frame(base::t(cgmupload))
cgmupload <- cgmupload[-1,]
}
filename <- base::paste(outputdirectory,"/",outputname,".csv",sep = "")
utils::write.csv(cgmupload, file = filename,row.names = FALSE,na = "")
}	

library(cgmanalysis) library(stringi) library(base) cleandata(	Cleandata will fill in gaps shorter than 30 minutes but will not remove the 24-hour chunks containing larger gaps.

R code	Notes
inputdirectory = "path\\to\\data", outputdirectory = "path\\to\\cleaned_data", removegaps = FALSE, gapfill = TRUE, maximumgap = 30) cgmvariables_mod(inputdirectory = "path\\to\\cleaned_data ", outputdirectory = "path\\to\\output", outputname = "Dexcom", customintervals = list(c(CCI [redacted]), aboveexcursionlength = CCI belowexcursionlength = CCI magedef = CCI [redacted], daystart = CCI [redacted], dayend = CCI id_filename = F, format = "rows", printname = F)	Parameters customintervals, aboveexcursionlength, belowexcursionlength, daystart, dayend will not be used.

12.2 List of TFLs

12.2.1 Tables

Title	Analysis Set	DMC*	Final Analysis
Table 14.1.1: Subject Enrolment and Disposition – overall and by country	Screened set	X	X
Table 14.1.2: Analysis Sets	Randomized Set		X
Table 14.1.3.1: Study Discontinuations	Randomized Set	X	X
Table 14.1.3.2: Time to Discontinuation	Randomized Set		X
Table 14.1.4: Permanent treatment discontinuation criteria	Safety Set		X
Table 14.1.5.1: Major protocol deviations	Randomized Set	X	X
Table 14.1.5.2: Minor protocol deviations	Randomized Set	X	X
Table 14.1.6: Patient phone calls	Safety Set		X
Table 14.1.7: Demographics and baseline characteristics	Full Analysis Set	X	X
Table 14.1.8.1: Medical or Surgical History	Full Analysis Set	X	X
Table 14.1.8.2: Concomitant Diseases	Full Analysis Set	X	X
Table 14.1.9.1: Prior Medications	Full Analysis Set	X	X
Table 14.1.9.2: Concomitant Medications	Full Analysis Set	X	X
Table 14.1.10: Other baseline characteristics	Full Analysis Set	X	X
Table 14.2.1.1: Compliance to IMP - dispensation and accountability by cycle	Safety Set	X	X
Table 14.2.1.2: Compliance to IMP – overall treatment period	Safety Set	X	X
Table 14.2.2.1.1: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 - Logistic regression model with Multiple Imputation under missing not at random	Full Analysis Set		X
Table 14.2.2.2.1: Sensitivity Analysis: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 - Logistic regression model with Multiple Imputation under missing at random	Full Analysis Set		X

Title	Analysis Set	DMC*	Final Analysis
Table 14.2.2.2.2: Sensitivity Analysis: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 - Tipping point analysis	Full Analysis Set		X
Table 14.2.2.2.3: Sensitivity Analysis: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 - Logistic regression model with Reference-based Multiple Imputation under missing not at random	Full Analysis Set		X
Table 14.2.2.3.1: Supportive Analysis: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 - Logistic regression model with Multiple Imputation under missing not at random	Per Protocol Set		X
Table 14.2.2.3.2: Supportive Analysis: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 - Logistic regression model considering complete cases only	Full Analysis Set		X
Table 14.2.3.1.1: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia	Full Analysis Set		X
Table 14.2.3.1.2: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 11/12 (visit 3) Logistic regression model with Multiple Imputation under missing not at random	Full Analysis Set		X
Table 14.2.3.2.1: Summary of HbA1c and changes from baseline	Full Analysis Set		X
Table 14.2.3.2.2: Mean difference from baseline in HbA1c at Week 11/12 Adjusted ANOVA model with Multiple Imputation using retrieve dropouts	Full Analysis Set		X
Table 14.2.3.2.3: Mean difference from baseline in HbA1c at Week 27/28 Adjusted ANOVA model with Multiple Imputation using retrieve dropouts	Full Analysis Set		X
Table 14.2.3.3.1: Summary of Average daily insulin requirement (IU/kg/day) and change from baseline	Full Analysis Set		X
Table 14.2.3.3.2: Average daily insulin requirement (IU/kg/day) Mixed model for repeated measurements	Full Analysis Set		X
Table 14.2.3.4.1: Summary of Time in range (TIR), Time above range (TAR), Time below range (TBR) by CGM and change from baseline	Full Analysis Set		X
Table 14.2.3.4.2: Time in range (TIR) by CGM at Week 11/12 Adjusted ANOVA model with Multiple Imputation using retrieve dropouts	Full Analysis Set		X

Title	Analysis Set	DMC*	Final Analysis
Table 14.2.3.4.3: Time in range (TIR) by CGM at Week 27/28 Adjusted ANOVA model with Multiple Imputation using retrieve dropouts	Full Analysis Set		X
Table 14.2.3.4.6: Time above range (TAR) by CGM at Week 11/12 Adjusted ANOVA model with Multiple Imputation using retrieve dropouts	Full Analysis Set		X
Table 14.2.3.4.7: Time above range (TAR) by CGM at Week 27/28 Adjusted ANOVA model with Multiple Imputation using retrieve dropouts	Full Analysis Set		X
Table 14.2.3.4.10: Time below range (TBR) by CGM at Week 11/12 Adjusted ANOVA model with Multiple Imputation using retrieve dropouts	Full Analysis Set		X
Table 14.2.3.4.11: Time below range (TBR) by CGM at Week 27/28 Adjusted ANOVA model with Multiple Imputation using retrieve dropouts	Full Analysis Set		X
Table 14.2.4.1.1: Summary of Additional Glucose Variability Indices and change from baseline	Full Analysis Set		X
Table 14.2.4.1.2:	Full Analysis Set		X
Table 14.2.4.1.3: CCI [redacted]	Full Analysis Set		X
Table 14.2.4.1.4: CCI [redacted]	Full Analysis Set		X
Table 14.2.4.1.5: CCI [redacted]	Full Analysis Set		X
Table 14.2.5.1.1: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia by Age class	Full Analysis Set		X
Table 14.2.5.1.2: Summary of HbA1c and changes from baseline by Age class	Full Analysis Set		X
Table 14.2.5.1.3: Summary of Average daily insulin requirement (IU/kg/day) and change from baseline by Age class	Full Analysis Set		X
Table 14.2.5.1.4: Summary of Time in range (TIR), Time above range (TAR), Time below range (TBR) by CGM and change from baseline by Age class	Full Analysis Set		X
Table 14.2.6.1.1: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia by Sex	Full Analysis Set		X
Table 14.2.6.1.2: Summary of HbA1c and changes from baseline by Sex	Full Analysis Set		X
Table 14.2.6.1.3: Summary of Average daily insulin requirement (IU/kg/day) and change from baseline by Sex	Full Analysis Set		X

Title	Analysis Set	DMC*	Final Analysis
Table 14.2.6.1.4: Summary of Time in range (TIR), Time above range (TAR), Time below range (TBR) by CGM and change from baseline by Sex	Full Analysis Set		X
Table 14.2.7.1.1: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia by Race	Full Analysis Set		X
Table 14.2.7.1.2: Summary of HbA1c and changes from baseline by Race	Full Analysis Set		X
Table 14.2.7.1.3: Summary of Average daily insulin requirement (IU/kg/day) and change from baseline by Race	Full Analysis Set		X
Table 14.2.7.1.4: Summary of Time in range (TIR), Time above range (TAR), Time below range (TBR) by CGM and change from baseline by Race	Full Analysis Set		X
Table 14.2.8.1.1: Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia by Ethnicity	Full Analysis Set		X
Table 14.2.8.1.2: Summary of HbA1c and changes from baseline by Ethnicity	Full Analysis Set		X
Table 14.2.8.1.3: Summary of Average daily insulin requirement (IU/kg/day) and change from baseline by Ethnicity	Full Analysis Set		X
Table 14.2.8.1.4: Summary of Time in range (TIR), Time above range (TAR), Time below range (TBR) by CGM and change from baseline by Ethnicity	Full Analysis Set		X
Table 14.3.1.1: Exposure to IMP	Safety Set	X	X
Table 14.3.1.2: Overview of Treatment Emergent Adverse Events	Safety Set	X	X
Table 14.3.1.3: Summary of Treatment Emergent Adverse Events by primary System Organ Class and Preferred Term	Safety Set	X	X
Table 14.3.1.4: Summary of Treatment Emergent Adverse Events by primary System Organ Class and Preferred Term and Severity	Safety Set	X	X
Table 14.3.1.5: Summary of Serious Treatment Emergent Adverse Events by primary System Organ Class and Preferred Term	Safety Set	X	X
Table 14.3.1.6: Summary of Adverse Drug Reaction by primary System Organ Class and Preferred Term	Safety Set	X	X
Table 14.3.1.7: Summary of Adverse Drug Reaction by primary System Organ Class and Preferred Term and Severity	Safety Set	X	X
Table 14.3.1.8: Summary of Treatment Emergent Adverse Events leading to IMP Discontinuation by primary System Organ Class and Preferred Term	Safety Set	X	X

Title	Analysis Set	DMC*	Final Analysis
Table 14.3.1.9: Summary of Treatment Emergent Adverse Events leading to Death by primary System Organ Class and Preferred Term	Safety Set	X	X
Table 14.3.1.10: Summary of Hypoglycemic Episodes by ADA Criteria	Safety Set	X	X
Table 14.3.2: Deaths, Listing	Safety Set	X	X
Table 14.3.3.1: Time to Onset of Hypoglycemic Episodes	Safety Set		X
Table 14.3.5.1.1: Summary of Hematology results and changes from baseline	Safety Set	X	X
Table 14.3.5.1.2: Proportion of patients reporting an abnormal laboratory value by visit - Hematology	Safety Set	X	X
Table 14.3.5.1.3: Hematology results: Shift from baseline to each post-baseline visit - investigator's interpretation	Safety Set	X	X
Table 14.3.5.2.1: Summary of Biochemistry results and changes from baseline	Safety Set	X	X
Table 14.3.5.2.2: Proportion of patients reporting an abnormal laboratory value by visit - Biochemistry	Safety Set	X	X
Table 14.3.5.2.3: Biochemistry results: Shift from baseline to each post-baseline visit - investigator's interpretation	Safety Set	X	X
Table 14.3.6.1.1: Summary of Vital Signs and change from baseline	Safety Set	X	X
Table 14.3.6.1.2: Summary of Vital Signs and change from baseline	Full Analysis Set	X	X
Table 14.3.6.2.1: Summary of [redacted] BMI evaluations and change from baseline	Safety Set	X	X
Table 14.3.6.3: Summary of QTcF Interval (msec) and change from baseline	Safety Set	X	X
Table 14.3.6.4: 12-Lead Electrocardiogram: Shift from baseline to each post-baseline visit on Investigator's interpretation	Safety Set	X	X
Table 14.3.6.5: Pregnancy test over the study	Safety Set	X	X

** Corresponding listing will be provided (see next section)*

12.2.2 Listings

Title	Analysis Set	DMC	Final Analysis
Listing 16.1.7: Randomization schedule	Randomized Set		X
Listing 16.2.1.1: Disposition of subjects	Screened Set	X	X
Listing 16.2.1.2.1: Subjects enrolled but not randomized	Enrolled Set		X
Listing 16.2.1.2.2: Study discontinuation	Randomized Set	X	X
Listing 16.2.1.2.3: Permanent treatment discontinuation criteria	Randomized Set		X
Listing 16.2.1.2.4: Patients phone calls	Randomized Set		X
Listing 16.2.2.1: Inclusion criteria	Randomized Set	X	X
Listing 16.2.2.2: Exclusion criteria	Randomized Set	X	X
Listing 16.2.2.3.1: Major protocol deviations	Randomized Set	X	X
Listing 16.2.2.3.2: Minor protocol deviations	Randomized Set	X	X
Listing 16.2.3.1: Analysis sets	Enrolled Set		X
Listing 16.2.3.2: Subjects excluded from full analysis set	Enrolled Set	X	X
Listing 16.2.4.1: Demographic and baseline characteristics	Randomized Set	X	X
Listing 16.2.4.2: Medical or Surgical History	Randomized Set	X	X
Listing 16.2.4.3: Concomitant diseases	Randomized Set	X	X
Listing 16.2.4.4: Prior medications	Randomized Set	X	X
Listing 16.2.4.5: Concomitant medications	Randomized Set	X	X
Listing 16.2.4.6: Other baseline characteristics	Randomized Set	X	X
Listing 16.2.5.1: Compliance to study medication	Randomized Set	X	X
Listing 16.2.6.1.1: HbA1c results	Randomized Set		X
Listing 16.2.6.1.2: Daily insulin requirement (IU/Kg/day)	Randomized Set		X
Listing 16.2.6.1.3: Time in Range (TIR), Time above Range (TAR), Time below Range (TBR) by Continuous Glucose Monitoring (CGM)	Randomized Set		X
Listing 16.2.6.1.4: Additional glucose variability indices derived from CGM	Randomized Set		X
Listing 16.2.6.1.5: [redacted]	Randomized Set		X

Title	Analysis Set	DMC	Final Analysis
Listing 16.2.6.1.6: Exploratory efficacy endpoints	Randomized Set		X
Listing 16.2.6.1.7: Self-reported Hypoglycemia	Randomized Set	X	X
Listing 16.2.6.2: Exposure to study medication	Randomized Set	X	X
Listing 16.2.7.1: Pre-treatment adverse events	Randomized Set	X	X
Listing 16.2.7.2: Treatment emergent adverse events	Randomized Set	X	X
Listing 16.2.7.3: Serious treatment emergent adverse events	Randomized Set		X
Listing 16.2.7.4: Treatment emergent adverse drug reactions	Randomized Set		X
Listing 16.2.7.5: Serious treatment emergent adverse drug reactions	Randomized Set		X
Listing 16.2.7.6: Severe treatment emergent adverse events	Randomized Set		X
Listing 16.2.7.7: Treatment emergent adverse events leading to discontinuation	Randomized Set		X
Listing 16.2.7.8: Treatment emergent adverse events leading to death	Randomized Set		X
Listing 16.2.7.9: Hypoglycemic Episodes	Randomized Set	X	X
Listing 16.2.8.1: Laboratory parameters: Hematology	Randomized Set	X	X
Listing 16.2.8.2: Laboratory parameters: Biochemistry	Randomized Set	X	X
Listing 16.2.8.3: Patients with clinically significant laboratory values	Randomized Set	X	X
Listing 16.2.8.4: Pregnancy test results	Randomized Set	X	X
Listing 16.2.8.5: Vital signs	Randomized Set	X	X
Listing 16.2.8.6: [redacted] and BMI evaluation	Randomized Set	X	X
Listing 16.2.8.7: 12-lead electrocardiogram	Randomized Set	X	X

12.2.3 Figures

Title	Analysis Set	DMC	Final Analysis
Figure 14.2.2.2.4: Tipping point analysis	Full Analysis Set		X
Figure 14.2.3.1.3: Proportion of patients at each timepoint by treatment with HbA1c reduction from baseline of >=0.50% without episodes of severe hypoglycemia	Full Analysis Set	X	X
Figure 14.2.3.2.4: Boxplots at each timepoint by treatment of the HbA1c	Full Analysis Set	X	X
Figure 14.2.3.2.5: Boxplots for Change from baseline at each timepoint by treatment of the HbA1c	Full Analysis Set	X	X
Figure 14.2.3.2.6 Waterfall plot for Proportion of patients with HbA1c reduction from baseline of ≥ 0.50% (absolute difference) without episodes of severe hypoglycemia at week 27/28 - Logistic regression model considering complete cases only	Full Analysis Set		X
Figure 14.2.3.3.3: Boxplots at each timepoint by treatment of the daily insulin requirement (IU/kg/day)	Full Analysis Set	X	X
Figure 14.2.3.4.4: Boxplots at each timepoint by treatment of the Time in range (TIR) by CGM	Full Analysis Set	X	X
Figure 14.2.3.4.5: Boxplots for Change from baseline at each timepoint by treatment of the Time in range (TIR) by CGM	Full Analysis Set	X	X
Figure 14.2.3.4.8: Boxplots at each timepoint by treatment of the Time above range (TAR) by CGM	Full Analysis Set	X	X
Figure 14.2.3.4.9: Boxplots for Change from baseline at each timepoint by treatment of the Time above range (TAR) by CGM	Full Analysis Set	X	X
Figure 14.2.3.4.12: Boxplots at each timepoint by treatment of the Time below range (TBR) by CGM	Full Analysis Set	X	X
Figure 14.2.3.4.13: Boxplots for Change from baseline at each timepoint by treatment of the Time below range	Full Analysis Set	X	X
Figure 14.3.5.1.4: Hematology: Spaghetti Plot of observed data	Full Analysis Set	X	X
Figure 14.3.5.1.5: Hematology: Spaghetti Plot of change from baseline	Full Analysis Set	X	X
Figure 14.3.5.2.4: Biochemistry: Spaghetti Plot of observed data	Full Analysis Set	X	X
Figure 14.3.5.2.5: Biochemistry: Spaghetti Plot of change from baseline	Full Analysis Set	X	X
Figure 14.3.6.1.3: Vital signs: Spaghetti Plot of observed data	Full Analysis Set	X	X
Figure 14.3.6.1.4: Vital signs: Spaghetti Plot of change from baseline	Full Analysis Set	X	X
Figure 14.3.3.2: Time to onset of Hypoglycemic Episodes (Kaplan-Meier)	Full Analysis Set		X