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STATISTICAL ANALYSIS PLAN

PROTOCOL: LDX0419

A phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 400 mg twice a day oral ladarixin in patients with new-onset type 1 diabetes and preserved β-cell function at baseline.

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STATISTICAL ANALYSIS PLAN
APPROVAL PAGE

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Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CONGA	Continuous Overall Net Glycemic Action
CS	Clinically Significant
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGDR	estimated Glucose Disposal Rate
ENR	Enrolled set
FAS	Full Analysis set
HbA1C	Glycated hemoglobin
HLA	Human Leukocyte Antigen Complex
IC	Informed Consent
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRS	Interactive Response System
ITT	Intent to Treat
MAGE	Mean Amplitude Glycemic Excursions
MAR	Missing at Random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MI-RD	Multiple Imputation using retrieve dropouts
MMRM	Mixed Model for Repeated Measurements
MMTT	Mixed Meal Tolerance Test
MNAR	Missing Not At Random
MODD	Mean Of the Daily Differences
NCS	Not Clinically Significant
CCI	[redacted]
PP	Per Protocol set
PPG	PostPrandial Glucose

PT	Preferred Term
QTcF	corrected QT interval by Fredericia
RND	Randomized set
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SD	Standard Deviation
SE	Standard Error
SI	Standard International
SOC	System Organ Class
T1D	Type 1 Diabetes
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TIR	Time in range
TLF(s)	Tables, Listings and Figures
US	United States
WHO DD	World Health Organization Drug Dictionary

Revision History

Document Version	Changes Made	Document Date
Final 1.0	First release	CCI [redacted]
Final 2.0	Section 4.3: Definition of primary estimand; Section 4.7: Clarification on handling of missing data; Section 4.8: Description of the main change compared to the planned analysis in the protocol; Section 7.1.2: Inclusion of the MI-RD as method to handle missing data in the primary analysis.	CCI [redacted]
Final 3.0	The SAP has been revised considering the premature closure of the study. Efficacy analyses have been reduced in scope given the limited sample size of the study compared to the expected one.	7 May 2024

Document Version	Changes Made	Document Date
	The main sections impacted are: • Section Efficacy endpointsEfficacy endpoints: one single final analysis has been planned after DB lock; • Section 4.3: removal of the primary estimands; • Section 4.4 and 4.8: modified to reflect the reduction in the efficacy analyses; • Section 4.5 and 5.5: given the reduced sample size compared to the planned one, some analyses (subgroup analysis and Kaplan-Meier curve for the time-to-discontinuation analysis) have been removed from the statistical plan; • Section 7.1 and 7.2: given the reduced sample size compared to the planned one, some advanced analyses (logistic regression, multiple imputation approaches, sensitivity analysis) have been removed from the statistical plan; • Sections 12.1: clarifications. • Section 6 regarding Compliance has been updated • CGM parameters units have been added • Severe Hypoglicemia derivation has been updated in section 9.1 • Additional information regarding Reason for discontinuation summaries has been added in 5.1 section. • Additional details regarding stop enrollment and changes in planned analysis has been added • HLA DR-DQ haplotypes will be only listed • Section 7.2.1.6 updated • Details and correction of the Cox model • Derivation of severe hypoglicemia events has been added • Number of AEs added in AE summaries	

Document Version	Changes Made	Document Date
	• Section 6.1.2.2.: ON/OFF Compliance calculation in case of missing start/end cycle dates • Section 5.6: Difference between first IMP administration and first insulin administration will be calculated	

1. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of LDX0419 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 electronic Case Report Form (eCRF) 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.

The SAP V1.0 and V2.0 were based on study protocol Version No. 1 final – CCI [1] and Version No. 2 final – CCI [2] (for US only).
The present version of the SAP refers to the same versions of the study protocols and includes the updates to the analysis based on the company decision to prematurely stop the enrolment.
More details about this decision are described in the official document "Communication of enrolment interruption" dated 28 March 2022 [3] sent to the sites.

Please refer to section 4.8 for additional details on the changes of the originally planned analysis plan due to the premature closure of the study.

2. Study Objectives

The objective of this clinical trial is to assess whether ladarixin treatment is effective to improve glycemic control in newly diagnosed T1D adult patients with preserved β-cell function. The safety of ladarixin in the specific clinical setting will be also evaluated.

3. Study Design

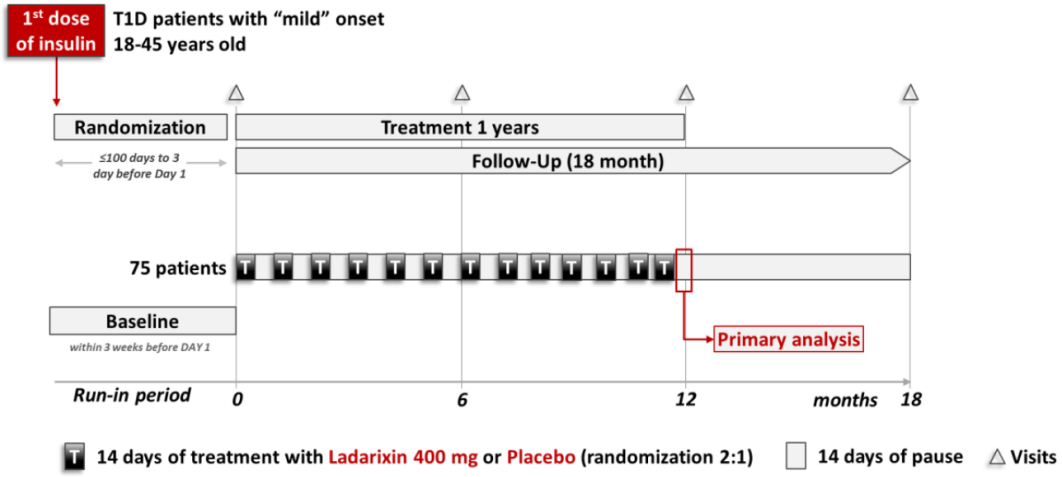
3.1 General design and plan

The study will be a phase 2, multicenter, double-blind, placebo-controlled study. It will involve 75 adults (18-45 years, inclusive) patients with new-onset T1D. Patients will be randomly (2:1) assigned to receive either ladarixin treatment or matched placebo (control group). The two groups will be balanced within centers.

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

Each patient will be involved in the study for a run-in period (Screening and Baseline assessments) followed by a randomization visit and a post-randomization period up to 18 months from the 1st IMP

dose. The study will proceed under double-blind condition up to the month 12 visit of the last patient randomized. Thereafter, the blind will be broken and remaining follow-up will proceed in an open fashion. This approach will allow to anticipate access to safety and efficacy data without significantly affecting data integrity.



3.2 Visit Schedule and Visit Windows

Assessments and study visits will be performed as listed in Table 1. Paragraph no. 7 "Study procedure and assessments" of Study Protocol contains additional details about scheduled visits and time windows.

For all measurements, the actual date and time of assessment, including date of sampling, will be recorded in the eCRF. Time frame for each assessment is reported in the following sections. Month/Week match is detailed below, together with acceptable windows:

- Month 6 = Week 26±2
- Month 12 = Week 52±2
- Month 18 = Week 78±2

Baseline is defined as the last visit prior to randomization. It is scheduled within 3 weeks to start of 1st treatment cycle. Unless otherwise specified, baseline values are defined as the measurements taken during this visit (unscheduled visits will not be considered for the definition of baseline value).

In case of multiple measurements during baseline visit, the last assessment will be considered as baseline evaluation.

Table 1: Study Flow Chart

100 days (run-in phase)

1st insulin **first IMP dose**

Procedures Tests to be performed at a centralized laboratory Test to be performed at the local laboratory	**Screening**	**Baseline (within 3 weeks to C1 start)**	**Randomization (within 3 days of C1**	**TREATMENT PERIOD (cycle = C) - 13 Cycles (C1 - C13)**									**FOLLOW-UP**
				C1 - C3	**Week11** (end of 3rd cycle)	**C4 - C6**	**Week 23** (end of 6th cycle)	**C7 – C9**	**Month 6** Week 26±2 **Visit while on C7**	**Week 35** (end of 9th cycle)	**C 10 - C13**	**Month 12** Week 52±2	**Month 18** Week 78 ±2
Informed Consent Form	X												
Eligibility criteria Randomization	X	X	X										
Auto-antibodies[1] & Fasting C-Peptide[2]	X												
Medical history	X												
BP/HR		X			X		X			X		X	X
weight, height, waist & waist/hip circumference		X							X			X	X
eGDR		X							X			X	X
Insulin requirement previous 3 days		X							X			X	X
Self Reported Severe Hypoglycemia		X							X			X	X
HLA DR-DQ haplotypes, Proinsulin,		X											
HbA1c, CCI		X							X			X	X
Safety Laboratory Test (hematology & biochemistry)[3]		X			X		X			X		X	X
MMTT [3]		X							X			X	X
Pregnancy Test		X			X		X			X			
12 lead ECG		X			X[5]		X[5]			X[5]			
CGM download[4]		X[4]							X[4]			X[4]	X[4]
IMP dispensation [5]			X		X		X			X			
Patient Diary delivery/check			X		X		X			X		X	X
Check discontinuation criteria [5]					X		X			X			
Patient Phone call [6]				X	X	X	X	X	X	X	X	X	X
AE/SAE recording	X----------X												
Prior and Concomitant Medication	X----------X												

[1] anti-GAD; IAA (if obtained within 10 days of the onset of insulin therapy); IA-2; ZnT8.

[2] fasting C-peptide must be ≥0.205 nmol/L on two occasions.

[3] tests performed at Baseline should be planned to ensure the samples are sent to the laboratory and results are be available in time for randomization.

[4] **sensor to be positioned at least 10 days before the scheduled visits**
(X) CGM sensor implantation can occur at Screening Visit and Week 23 Visit if the visit is scheduled 14-10 days before Baseline and before Week 26 respectively

[5] Dispensation of IMP (Patient Kits) must occur ONLY after check of inclusion/exclusion criteria (at the Randomization Visit) and of discontinuation criteria (at the Visits performed at the end of the 3rd, 6th, 9th treatment cycles). Results of ALT/AST, bilirubin, creatinine and albumin, ECG reading and pregnancy results **should be made available by the local laboratory in time to allow Patient Kits dispensation as soon as possible during the visit**. If this expedite timing cannot be achieved, Patient Kits might be delivered to patient named address by a selected courier (CRO to support shipment). As per treatment discontinuation criteria, no IMP will be dispensed in the case: QTcF is either > 500 msec or has increased by > 60 msec from baseline measurement on two consecutive ECG readings taken 1 hour apart; the patient develops any significant cardiovascular disease/abnormality, renal (eGFR <60mL/min/1.73 m2) or hepatic (increased ALT/AST > 3 x ULN and increased total bilirubin > 3mg/dL [>51.3 µmol/L]) dysfunction, hypoalbuminemia (serum albumin <3 g/dL), significant systemic infection that must be assessed on a case-by-case basis by the investigator regarding whether they are serious enough to warrant discontinuation, ketoacidosis or hypoglycemic coma; a female patient has become pregnant.

[6] Telephone calls will be scheduled on a regular basis to ensure optimization of metabolic control. It is expected that patients are contacted at least every 2 to 3 weeks during study participation. A telephone call will be anyway scheduled in the 2 weeks before a planned visit.

3.3 Sample size justification

Below, the calculation performed for the sample size at the time of the study planning.

The sample size of the study is calculated on the "proportion of patients with a HbA1c <7% and daily insulin requirement <0.50 IU/Kg/day", a post-hoc composite endpoint derived from data of the phase 2 trial (CCI), considering a larger effect size expected from the longer treatment length (one year versus 3 months).

Based on these assumptions, and considering a randomization ratio 2:1 (ladarixin:placebo) and a one-sided alpha of 0.05, seventy-five (75) patients randomized in the trial will allow to achieve a power of approximatively 80% to detect at least 35% of difference in terms of primary endpoint in favour of ladarixin vs placebo, assuming that the proportion of patients in the placebo group with a HbA1c <7% and daily insulin requirement <0.50 IU/Kg/day at 12 months will range between 45% and 55%.

Assuming that 10% of subjects will be not evaluable for primary analysis, a total of approximately 84 subjects is expected to be enrolled.

As reported in section 1, enrolment was prematurely stopped per company decision.

3.4 Randomization and blinding

Eligible Patient will be randomized in a 2:1 fashion to either ladarixin or placebo.

Randomization will be performed through IRS. Each Patient Kit number will be randomly associated with a treatment group. The randomization list will be provided to the facility responsible for IMP packaging/labelling for the purpose of IMP preparation. Each randomized patient will be allocated with randomization number according to the stratified randomization list. Dropouts after randomization will not be replaced.

Randomization will be stratified by site to ensure balanced assignment across treatment groups. The stratified permuted block randomization list will be generated with a computer procedure by an independent statistician not involved in the conduct of the study. A master randomization list will be generated, with patients balanced between sites in accordance to randomization ratio (2:1).

Access to individual patient treatment code will be allowed only in the event of a medical emergency where the knowledge of patient treatment is required to provide the patient with appropriate care. The investigator will be provided with a protected access to the randomization system to allow opening of the treatment allocation for a specific patient in case of a medical emergency.

Dompé Pharmacovigilance contact person will be provided also with envelopes of the randomization number code break (to reveal the planned treatment arm assigned at the Randomization Visit) in order to unblind a specific patient for safety reporting.
Unblinding events will be recorded and reported in the final study report.

The randomization code will be broken according to study procedures after the last enrolled patient has completed his/her follow-up visit at 12 months.

3.5 Overview of planned statistical analyses

The study was originally planned to perform the following statistical analyses:

- Final analysis: to be conducted when all enrolled subjects have completed the Month 12 follow-up visits, and the study database has been locked.
- Addendum at Final analysis: to be conducted when all enrolled subjects have completed the open phase study post unblinding up to Month 18.

Considering the premature closure of the study, a unique analysis will be performed when all enrolled subjects have completed all the follow-up visits and the study database has been locked.

3.6 Efficacy endpoints

3.6.1 Primary endpoint

The primary efficacy endpoint is the proportion of patients with HbA1c <7% and daily insulin requirement <0.50 IU/Kg/day at Month 12.

3.6.2 Secondary efficacy endpoints

The secondary efficacy endpoints are the following:

- Proportion of patients with HbA1c <7% and daily insulin requirement <0.50 IU/Kg/day at Month 6 and 18;
- Proportion of patients with a reduction in HbA1c > 0.5% from baseline and daily insulin requirement <0.50 IU/Kg/day at Month 6, 12, and 18;
- 2-hour Area Under the Curve (AUC) of C-peptide response to the Mixed Meal Tolerance Test (MMTT) at Month 6, 12, and 18;
- Time in range (TIR) by Continuous Glucose Monitoring (CGM) at Month 6, 12, and 18;
- HbA1c levels at Month 6, 12, and 18;
- Proportion of patients with HbA1c <7% who did not experience severe hypoglycaemic events during treatment at Month 6, 12, and 18;
- Additional Glucose Variability Indices derived from CGM at Month 6, 12, and 18;
- Number of self-reported episodes of severe hypoglycaemia at Month 6, 12, and 18;
- Average (previous 3 days) daily insulin requirements (IU/kg/day) at Month 6, 12, and 18;
- Estimated Glucose Disposal Rate (eGDR) at Month 6, 12, and 18;

CCI [redacted]

3.7 Safety endpoints

The safety endpoints are the following:

- Adverse Events (AEs) and Serious Adverse Events (SAEs) throughout the study.
- Safety Laboratory Tests at Week 11, Week 23, Week 35, Month 12 and Month 18 (or withdrawal);
- Vital signs at Week 11, Week 23, Week 35, Month 12 and Month 18;

4. Statistical Analysis

4.1 General

Appropriate descriptive statistics will be produced, according to the variable. For continuous data n, mean, standard deviation (SD), median and range (minimum and maximum) will be presented. For categorical data, frequency distributions and percentages will be presented.

Unless otherwise specified, hypothesis testing will be carried out at the alpha = 0.050 level (one-sided) when comparing treatments. For all inferential analyses, p-value will be rounded to three decimal places. Statistical significance will be declared if the rounded one-sided p-value will be less than or equal to 0.050.

Additional post-hoc analysis may be produced to further allow comparison between ladarixin and placebo, according to the results obtained. Any unplanned analyses as well as deviations from the original statistical plan will be clearly documented in the Clinical Study Report.

Derivation rules for efficacy and safety analyses are reported in Table 3 in section 9.

All the data collected and derived in the study will be presented in subject data listings.

4.2 Analysis sets

4.2.1 Enrolled set

The Enrolled set (ENR) will consist of all patients with signed written informed consent (IC) and undergoing to study evaluations/procedures.

4.2.2 Randomized set

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

4.2.3 Safety set

The Safety set (SAF) will consist of all randomized patients who receive at least one dose of the IMP. SAF population will be analyzed according to the actual treatment received and will be used to present results on safety data.

4.2.4 Full Analysis set

The Full Analysis Set (FAS) will consist of all randomized patients who receive at least one dose of the IMP (either ladarixin or placebo). FAS population will be analyzed according to ITT principle, i.e. by treatment allocation regardless happening of intercurrent events (treatment policy strategy). The FAS population will be used for the primary analyses of the study and to present results on efficacy data.

4.3 Primary estimand

Considering the premature closure of the study, the originally planned treatment policy strategy and estimand definition is not applicable. Summary analysis will be performed, descriptive in nature.

4.4 Usage of analysis sets

The usage of the analysis sets (see previous section) for the creation of tables and figures are illustrated in Table 2. 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 2).

Table 2: Usage of analysis set

Analysis	ENR	RND	FAS	SAF
Subject enrolment and disposition	X			
Protocol violations		X		
Study discontinuations		X		
Permanent treatment discontinuation criteria		X		

Patient phone calls		X		
Demographics and baseline characteristics			X	
Medical or surgical history and/or Concomitant Diseases			X	X
Prior and concomitant medications			X	X
Other baseline characteristics			X	
Compliance to IMP				X
Exposure to IMP				X
Analysis of primary efficacy endpoint			X	
Analysis of secondary efficacy endpoints			X	
MMTT over the study			X	
Analysis of CCI			X	
Adverse events				X
Clinical laboratory evaluation				X
Vital signs				X
ECGs				X
Pregnancy test over the study				X

4.5 Sub-group analyses

Considering the premature closure of the study and the limited sample size compared to the originally expected, the analysis of the primary endpoint in pre-defined subgroups (by age, sex, race, BMI, Human Leukocyte Antigen Complex – HLA, CCI , site geographic region) will not be performed.

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 be included in the denominator count when computing percentages. Instead, only the non-missing values will be evaluated for computing summary statistics for continuous endpoint. Any exception will be clarified as a note.

4.8 Changes in the planned analysis

Due to the company decision to stop the enrolment, fewer patients compared to the originally planned will be available for the analysis. Thus, he following changes were implemented:

- one single final analysis is planned after DB lock;

- no formal hypothesis testing will be performed;
- all analyses will be descriptive in nature;
- no advanced analytical methods will be applied, specifically;
  - Primary endpoint no more analyzed by means of logistic regression model: comparison between treatment arms performed by means of a Chi-square test at each time point.
  - No multiple imputation approaches to manage potential missing data;
- no sensitivity analyses will be performed;
- no sub-group analyses will be performed;

4.9 Blind Data Review Meeting

A Blind Data Review Meeting (BDRM) will be held before the database lock and 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 [4] 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.

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

- Subjects enrolled (overall);
- Subjects enrolled but not randomized and reasons for non-allocation (overall);
- Subjects randomized;
- Subjects in each analysis set (FAS, SAF) and reasons for exclusion;

For the overall report, the percentage denominator will be the number of ENR subjects. For the “by treatment group” calculations, the percentage denominator will be the number of randomized subjects within each arm.

For the second bullet point, the following information will be listed as well:

- Reason for discontinuation. If reason for discontinuation = “Inclusion Criteria not met / Exclusion Criteria met” the following information will be listed:

- Specification about Inclusion/Exclusion criteria not met/met
- Corresponding Parameters, whether a threshold level of a laboratory/ECG parameter is expected to meet the criterion (Inclusion criteria #3 and #5, Exclusion criteria #2, #3, #4, #5)
- Results of corresponding parameter (for example, both C-peptide values)

Listings will be provided based on ENR set.

5.2 Protocol violations

All the protocol violations 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.

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

5.3 Permanent treatment discontinuation criteria

A summary table showing at each available time point 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 time point 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;
- Number of subjects who completed each planned visit.
- Subjects who discontinued the IMP and reasons (taken from EOT form)
  - Subjects who discontinued the IMP but complete the study
  - Subjects who discontinued the IMP and discontinued the trial prematurely
- Subjects who discontinued the trial prematurely (and reason);

- Broken randomization code (and reason).

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:

- Geographic region of the site (EU, US, Other)
- Demography
    - Age (years)
    - Sex (Male, Female)
    - If female, potential childbearing (Yes, No)
    - Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other)
    - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Pregnancy test result (Positive or Negative), if appropriate
- T1D diagnosis
    - Diagnosis of T1D confirmed (Yes, No)
    - Time from T1D diagnosis to inform consent (days)
    - Time from first insulin administration to first IMP administration (days). The following formula will be used: date of first IMP administration – date of first insulin administration.
- BMI (BMI≤25kg/m2 vs 25kg/m2<BMI≤30kg/m2 vs BMI>30kg/m2)

5.7 Medical or Surgical History and/or Concomitant Diseases

A disease is considered as medical/surgical history if it is ended before screening visit.

A disease is considered as 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).

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, and
- end on or after the date of informed consent or are ongoing at the study completion or discontinuation.

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 (see Table 6). 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 Fasting C-Peptide

Summary statistics by treatment of fasting C-Peptide (nmol/L) at baseline will be provided. In case of repetition of fasting C-Peptide evaluation (according to protocol), the repeated assessment will be considered as the only evaluation.

5.9.2 Auto-Antibodies

Auto-antibodies (anti-GAD; IAA, if obtained within 10 days of the onset of insulin therapy; IA-2 antibody; ZnT8) results to confirm T1D diagnosis and of fasting C-peptide will be descriptively summarized. In case of repetition of evaluation (according to protocol), the repeated value will be considered as the only evaluation value.

5.9.3 HLA DR-DQ haplotypes

HLA DR-DQ haplotypes at baseline will be listed only.

6. Evaluation of Treatment Compliance and Exposure

6.1 Compliance to study treatment regimen

Descriptive analyses 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;
- from IMP accountability form
    - number of returned blisters;
    - number of capsules taken;
    - number of returned unused capsules;
    - IMP intake compliance, ON -treatment period compliance (only by cycle);

Patients are instructed to receive study treatment (either ladarixin or placebo) as follows:
- 400 mg b.i.d (2 capsules at each administration, twice per day);
- for 13 cycles, each lasting 28 days;
- each cycle is composed by 14 consecutive days on-treatment and 14 consecutive days off-treatment.

Calculation of compliance to treatment regimen must consider not only the amount of treatment intake, but also the correct alternation between period “ON” and period “OFF” and their duration. To assess the overall compliance to treatment regimen, the following 3 criteria will be taken into account:
- Compliance to IMP intake;
- Compliance to duration of period “ON” (period of the cycle when the patient is ON treatment);
- Compliance to duration of period “OFF” (period of the cycle when the patient is OFF treatment).

6.1.1 IMP intake compliance

6.1.1.1 Over the entire treatment period

IMP intake compliance over the entire treatment period will be calculated as follow:

$$IMP\ intake\ compliance\ (\%) = \frac{total\ n.of\ capsules\ taken\ during\ the\ treatment\ period}{total\ n.of\ capsules\ dispensed\ during\ the\ treatment\ period} \times 100$$

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 a complete treatment period over 13 cycles the dispensed number of capsules and the number of capsules the patient is expected to take is the same and is equal to 728.
For a cycle that is interrupted due to treatment discontinuation the expected #capsules may differ from the # dispensed as follows:

- If interrupted before the expected last intake, the expected # capsules will be derived as:

$$Expected\ \#\ capsules\ = 56 * \#\ completed\ k\ cycles\ (k = 1 \ldots\ i-1) + 4 * (\ Date\ treatment\ discont\ in\ Cycle\ (i) -\ Data\ start\ Cycle\ (i)\ + 1)$$

In the expected #capsules calculation, it is assumed that the discontinuation occurs after last daily intake.

- If interrupted after the expected last intake, the expected number of capsules will be:

$$Expected\ \#\ capsules = 56 * \#\ completed\ k\ cycles\ (k = 1 \ldots\ i-1)\ +\ 56$$

IMP intake compliance over the entire treatment period will be summarized by treatment by means of summary statistics.

In addition, compliance to IMP over the entire treatment period will also be presented for the following categories: <80%, 80%-100% (excluded), 100%, >100%.

6.1.1.2 By cycle

Compliance by cycle with respect to IMP intake will be assessed following the formula below:

$$IMP\ intake\ compliance\ at\ cycle\ (i)\ (\%) = \frac{total\ number\ of\ capsules\ taken\ during\ the\ cycle}{total\ number\ of\ capsules\ dispensed\ during\ the\ cycle} \times\ 100$$

If cycle (i) is completed, the dispensed number of capsules and the number of capsules the patient is expected to take is the same and is equal to 56.
If cycle (i) is interrupted due to treatment discontinuation:

- If interrupted before the expected last intake, the expected number of capsules will be derived as:

$$Expected\ \#\ of\ capsules = 4 * (\ Date\ treatment\ discont\ in\ Cycle\ (i) -\ Data\ start\ Cycle\ (i)\ + 1)$$

- If interrupted after the expected last intake, the expected number of capsules will be 56

6.1.1.3 Global criteria for IMP intake compliance

A subject will be classified as "Globally Compliant to IMP intake" (="Y") if:

a) IMP intake compliance over the entire treatment period in the range 80% - 100% (80 and 100 included)
AND
b) no more than 2 consecutive cycles with IMP intake compliance <80% or >120%
AND
c) no more than 4 cycles with IMP intake compliance <80% or >120%,

otherwise he will be classified as Non-Compliant ("N").
Note: conditions (b) and (c) to be checked only for patients who completed the entire treatment period.

The following variables will also be derived:
- #cycles with IMP intake compliance <80% or >120%, (only for patients who completed the entire treatment period).
- 3 or more consecutive cycles with IMP intake compliance <80% or >120% [Y/N], (only for patients who completed the entire treatment period).

6.1.2 Compliance to duration of period "ON-treatment"

By study protocol for each cycle each patient is supposed to take IMP for 14 days; compliance to duration of "ON-treatment" period is evaluated as the comparison between the expected duration (14 days) and the actual (observed) duration.

6.1.2.1 Over the entire treatment period

Compliance to ON-Treatment period will be calculated as follow:

$$Period\ ON\ compliance\ (\%) = \frac{Total\ observed\ duration\ of\ period\ ON}{Total\ expected\ duration\ of\ period\ ON} \times 100$$

The total expected duration of period ON for a subject who complete regularly the study is 182 days (14 days * 13 cycles).

The actual (observed) duration of k-th period ON (k=1… 13) from each cycle is defined as:

$$k-th\ cycle\ duration\ ON\ = \ Date\ last\ intake\ in\ Cycle\ (k) - Data\ start\ Cycle\ (k)\ + 1$$

The observed Total Duration period ON over the entire treatment period is given by the sum of the k periods ON from each cycle.

In case of treatment discontinuation, the last cycle can be affected. Considering the first k completed cycles (k=1…. I-1):
- Expected total duration of period ON = 14*k [1]
- Actual (observed) Total Duration ON is given by the sum of the k observed periods ON [2].

The last i-th cycle, interrupted due to treatment discontinuation is included as follows:

- If interrupted before the expected last intake, the duration of the period ON to be added to [1] and [2] is derived as:

i-th Cycle Duration ON = Date treatment discontinuation – Data start Cycle (i) +1

With this formula we are assuming that the IMP is taken on the day of discontinuation.

- If the trial will be discontinued after the expected last intake, the expected duration of the i-th period ON is 14 days.

6.1.2.2 By Cycle

Period ON compliance at cycle (i) will be calculated as follow:

$$Period\ ON\ compliance\ at\ cycle\ (i)(\%) = \frac{observed\ duration\ of\ period\ ON\ at\ cycle\ i}{expected\ duration\ of\ period\ ON\ at\ cycle\ i} \times 100$$

The observed duration of period ON for each cycle is defined as:

$$Duration\ period\ ON, cycle\ (i) = Date\ last\ intake\ in\ cycle\ (i) - Data\ start\ cycle\ (i) + 1$$

The expected duration of period ON is 14 days.
For a cycle that is interrupted due to treatment discontinuation the rule to be applied is the same as the one reported above in section 6.1.2.1:

- If interrupted before the expected last intake, the duration of the period ON is derived as:
  - i-th Cycle Duration ON = Date treatment discontinuation – Data start Cycle (i) +1 (if the day of discontinuation the IMP was taken)
  - i-th Cycle Duration ON = Date treatment discontinuation – Data start Cycle (i) (if the day of discontinuation the IMP was not taken)
  - expected duration will be = observed duration
- If interrupted after the expected last intake, the expected duration of period ON is 14 days

Note:
Date start cycle and date last intake in the cycle are considered as they are, regardless of whether the intake of the 1st day occurred only in the evening and the intake of the last day occurred only in

the morning. This may happen, but conventionally days and not day periods (morning / evening) will be considered. For these cases is possible that intake may last 15 days instead of 14.

In case the kit was dispensed, it was returned, and the number of capsules taken is 0 (therefore we cannot define the start cycle date and end cycle date), we will follow the following convention:

- Start Cycle x date will be as scheduled date: start cycle x-1 date (previous cycle) +28 days
- End Cycle x date will be equal to start cycle x date
- On period will be set to 0 days

6.1.2.3 Global criteria for duration of ON-Treatment period

A subject will be classified as "Globally Compliant to ON-treatment period" (="Y") if:

a) Compliance to Period "ON" duration over the entire treatment period in the range 80% - 120% (80 and 120 included)
AND
b) no more than 2 consecutive cycles with compliance to "Period ON" duration <80% or >120%
AND
c) no more than 4 cycles with compliance to "Period ON" duration <80% or >120%,

otherwise he will be classified as Non-Compliant (="N").
Note: conditions (b) and (c) to be checked only for patients who completed the entire treatment period.

The following variables will also be derived:

- #cycles with compliance to "Period ON" length <80% or >120%, (only for patients who completed the entire treatment period).
- 3 or more consecutive cycles with "Period ON" length compliance <80% or >120% [Y/N], (only for patients who completed the entire treatment period).

6.1.3 Compliance to duration of period "OFF"

By study protocol for each cycle each patient is supposed to have a 14-days period OFF treatment after the 14-days ON-treatment period. Compliance to duration of period "OFF" is the comparison between the expected duration (14 days) and the actual (observed) duration.

6.1.3.1 Over the entire treatment period

Period OFF compliance will be calculated as follow:

$$Period\ OFF\ compliance\ (\%) = \frac{Total\ observed\ duration\ of\ period\ OFF}{Total\ expected\ duration\ of\ period\ OFF} \times 100$$

The total expected duration of period OFF for a subject who complete regularly the study is 168 days (14 days * 12 cycles).
The duration of k-th period OFF (k=1,…,12) from each cycle is defined as:

$$k-th\ Cycle\ Duration\ OFF = Date\ start\ Cycle\ (k+1) - Date\ last\ intake\ in\ Cycle\ (k) - 1$$

The total observed duration OFF is given by the sum of the k periods OFF.
In case of treatment discontinuation during cycle (i):

- If discontinued before last intake of the period ON:
  - Expected Total period OFF=14*(i-1)
  - Observed Total period OFF=sum from k=1 to i-1 of the i-1 period OFF

- If discontinued after last intake of the period ON:
  - Expected Total period OFF=14*(i-1) + period OFF for i-th cycle (see [*])
  - Observed Total period OFF=sum from k=1 to i-1 of the i-1 period OFF + period OFF for i-th cycle (see [*])

[*] In case i-th cycle is interrupted due to treatment discontinuation after the expected last intake, the expected and observed duration of period OFF for i-th cycle is derived as:

$$i-th\ Cycle\ Duration\ OFF = Date\ trial\ discontinuation - Date\ last\ intake\ in\ Cycle\ (i)$$

6.1.3.2 By Cycle

No compliance by cycle defined for the “OFF-Treatment”.

6.1.3.3 6.1.3.3 Global criteria for duration of OFF-Treatment period

A subject will be classified as “Globally Compliant to OFF-treatment period” (=”Y”) if:

a) Compliance to “OFF-Treatment” duration over the entire treatment period is <150%

otherwise he will be classified as Non-Compliant (=”N”).

6.1.4 Compliance to Treatment regimen

Subject will be considered compliant to study treatment regimen if conditions defined in section 6.1.1.3, 6.1.2.3 and 6.1.3.3 are met (i.e. subject compliant to global criteria regarding IMP intake, ON-treatment period, OFF-treatment period).

Overall compliance to treatment regimen will be presented (Y/N) by treatment and overall.

6.1.5 Started Cycles

Per each subject the number of cycles started during the entire treatment period will be counted. The i-th cycle is defined as started if at least 1 IMP intake is reported in the cycle (Data start Cycle (i) is not missing).

The number of started cycles over the entire treatment period will be summarized by treatment and overall by means of summary statistics.

A listing of information about IMP ACCOUNTABILITY and IMP DISPENSATION will be provided by cycle and overall.
A listing will also be produced by reporting all detail regarding compliance criteria described above by cycles and overall.

6.2 Exposure to IMP

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 reported in Table 3.

7. Evaluation of Efficacy

All analyses will be considered descriptive in nature. No multiplicity correction of type I error is required.

7.1 Analysis of primary endpoint

Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients with HbA1c < 7% and daily insulin requirement <0.5 (IU/kg/day) will be calculated at Month 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.

7.2 Analysis of secondary efficacy endpoints

All secondary endpoints will be analysed at each available time point by means of descriptive statistics as detailed in sections 7.2.1.1-7.2.1.10.
The following results will be displayed graphically:

- The proportion at each time point by treatment of patients with HbA1c <7% and daily insulin requirement <0.5 (IU/kg/day);
- The means (±SEs) at each time point by treatment of the HbA1c and its change from baseline;
- The proportion at each time point by treatment of patients with HbA1c of less than 7% who did not experience severe hypoglycemic events during treatment;
- The means (±SEs) at each time point by treatment of the daily insulin requirement (IU/kg/day);
- The means (±SEs) at each time point by treatment of the 2-hour AUC of C-peptide post MMTT and its change from baseline;
- The means (±SEs) at each time point by treatment of the TIR by CGM and its change from baseline.

In each graph, where possible, significant p-values from the below analyses will be reported in the plot area, in correspondence of the associated time point.

7.2.1.1 Proportion of patients with HbA1c <7% and daily insulin requirement <0.5 (IU/kg/day)

Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients with HbA1c < 7% and daily insulin requirement <0.5 (IU/kg/day) will be calculated for each time point. 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.

7.2.1.2 Proportion of patients with a reduction in HbA1c >0.5% from baseline and daily insulin requirement <0.50 IU/Kg/day

Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients with a reduction in HbA1c > 0.5% from baseline and daily insulin requirement <0.5 (IU/kg/day) will be calculated for each time point. 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.

7.2.1.3 2-hour AUC of C-peptide response to the MMTT

2-hour AUC of C-peptide post MMTT and its change from baseline will be summarized at each available timepoint and comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality are not confirmed (by Kolmogorov-Smirnov test), two-sample Mann–Whitney U test.

7.2.1.4 Time in range (TIR) by CGM

TIR by CGM and its change from baseline will be summarized at each available timepoint and comparison between treatments will be performed by means of two-sample t-test or, if

assumptions of normality are not confirmed (by Kolmogorov-Smirnov test), two-sample Mann–Whitney U test.

7.2.1.5 HbA1c levels

HbA1c and its change from baseline will be summarized at each available timepoint and comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality are not confirmed (by Kolmogorov-Smirnov test), two-sample Mann–Whitney U test.

7.2.1.6 Proportion of patients with HbA1c <7% who did not experience severe hypoglycemic events during treatment

Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients with HbA1c < 7% and absence of episodes of severe hypoglycemia during treatment will be calculated for each time point. 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.
The proportion of patients with HbA1c <7% is calculated at timepoint level: number of events occurring at a specific timepoint.
Severe hypoglycemic events are considered cumulatively and only event up to month 12 will be considered (condition will be evaluated by considering treatment period only).
In particular:

- if a subject experienced the event at a specific timepoint, it will be considered as a subject with the event for all subsequent timepoints.

7.2.1.7 Events happened between month 12 and month 18 will not be considered in this endpoint, since they are out of treatment period. Therefore, condition of event/not event at month 12 will be the same as month 18.*Additional Glucose Variability Indices derived from CGM*

Glucose AUC outside the target range of 70 – 180 mg/dL, 2-hour postprandial glucose (PPG), Mean Amplitude Glycemic Excursions (MAGE) considering 1 SD as threshold, continuous overall net glycemic action (CONGA)-n (1, 2 and 4 hours), Mean Of the Daily Differences (MODD), mean daily blood glucose, and SD will be compared between treatments by means of two-sample t-test or, if assumptions of normality is not confirmed (by Kolmogorov-Smirnov test), two-sample Mann–Whitney U test.

7.2.1.8 Number of self-reported episodes of severe hypoglycemia

The effect of treatment on the cumulative number of severe hypoglycemic events will be evaluated by means of a Cox proportional hazards model. The Andersen-Gill intensity model with model-based variance will be utilized. The corresponding SAS code is provided in Appendix 12.2.

Summary statistics of blood glucose level (mg/dL) will be provided by treatment arm at each time point for patients reporting severe hypoglycemia. Derivation of patients reporting severe hypoglicemia will be the same as the one described in 7.2.1.6 section, except that in this case events happened between month 12 and month 18 will be considered as well.

7.2.1.9 Average (previous 3 days) daily insulin requirement (IU/kg/day)

Average daily insulin requirement (CRF - INSULIN REQUIREMENT form) and its change from baseline will be summarized at each available timepoint and comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality are not confirmed (by Kolmogorov-Smirnov test), two-sample Mann–Whitney U test.

7.2.1.10 Estimated Glucose Disposal Rate

eGDR comparison between treatments will be performed by means of two-sample t-test or, if assumptions of normality are not confirmed (by Kolmogorov-Smirnov test), two-sample Mann–Whitney U test.
Summary statistics by treatment will be provided along with summary of the change from baseline at each time point for the eGDR-related parameters:

- Weight (Kg) and Height (cm),
- BMI (Kg/m2) – derived from CRF,
- Waist circumference (cm) and Waist-to-Hip Ratio,
- Hypertension status (Yes, No).

7.3 MMTT over the study

Summary statistics of C-peptide (nmol/L) during MMTT will be provided by treatment at each visit and time-interval (Basal1, Basal2, Average Basal, @15min, @30min, @60min, @90min, and @120min after the meal). In addition, for each visit, the following parameters will be summarized:

- C-peptide 0-120 min AUC (nmol/L)
- C-peptide 15-120 min AUC (nmol/L)
- C-peptide Cmax (nmol/L)
- C-peptide Tmax (min)

Individual plots of the Cmax and Tmax means (±SEs) will be presented. Based on the observed trends, additional ad-hoc analyses might be performed.

Derivation rules are reported in Table 3.

7.4 Analysis of CCI [redacted]

CCI [redacted] will be analyzed at each available time points by means of descriptive statistics. Specifically, analyses will be provided for CCI [redacted]. Comparison between treatments

will be performed by means of CCI [redacted] or, if assumptions of normality is not confirmed CCI [redacted]

Where applicable the investigator's interpretation (Normal, Abnormal NCS, Abnormal NC, No Result) will be summarized and compared by means of a CCI [redacted] or, if more appropriate, a CCI [redacted] at each time point CCI [redacted] will not be considered for the comparison).

The following results will be displayed graphically:

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

8. Evaluation of Safety

8.1 Adverse events

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 (see Table 5). The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE;
- Pre-treatment AE.

In case of TEAE, the event can be classified as:

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

according to the available parts of the onset and the end dates (see Table 5).

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 summaries will be presented, displaying frequencies and percentages of patients reporting AEs. In the summaries, primary SOC will be presented alphabetically and the PT will be sorted within SOC in descending overall frequencies .
Along with AEs, number of events will be reported. On each of these summaries, patients will be counted only once per SOC and, within each SOC, patients will be counted only once per PT.

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 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 serious TEAE, at least one non-serious TEAE, at least one ADR, at least one serious ADR, 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;
- 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);
- 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 severe hypoglycemic events 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;
- 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 who have discontinued/completed the study without an event will be censored at the date of discontinuation/completion. In case of patients still ongoing and free from event at the time of DB lock, they will be censored at the DB lock date.

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 and at subsequent visits.
- 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.

8.3 Vital signs

Summary statistics by treatment will be provided along with summary of the change from baseline at each time point for the following vital signs:

- Systolic Blood Pressure (mmHg),
- Diastolic Blood Pressure (mmHg), and
- Heart Rate (bpm);

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 time point.

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 3: Variable derivation rules

Parameter	Calculation
HbA1c <7% and daily insulin requirement <0.50 IU/Kg/day at Time point T_x	at Time point T_x: • if HbA1c ≥7% OR daily insulin requirement ≥0.50 IU/Kg/day, then endpoint = 'No' (even in case of one missing component) • if HbA1c <7% AND daily insulin requirement <0.50 IU/Kg/day, then endpoint = 'Yes' (both component should be non-missing)
AUC	All AUC calculations (0-120min and 15-120min) will be based on actual rather than scheduled timings and will be calculated using the trapezoidal rule. In case of partial information collected during an assessment: • if actual time is not recorded, the scheduled time will be used instead; • missing values will be imputed via linear interpolation; • when C-peptide values are below the limit of detection, the limit value (0.2 ng/mL, any exception will be clarified) will be assumed in the calculation of AUC. Basal value to be used in the AUC calculation is the Average Basal C-peptide (next section). The last non-missing time of Basal #1 and Basal #2 values will be used to calculate the time differences in the AUC. C-peptide 0-120 min AUC (nmol/L) values will be calculated based on all Basal-120min C-peptide values. C-peptide 15-120 min AUC above fasting (nmol/L) will be calculated based on the changes from Basal in 15-120min C-peptide values. Unscheduled assessments will be excluded from the analysis.
C-peptide parameters	Average Basal C-peptide (nmol/L) = Mean (Basal #1 C-peptide; Basal #2 C-peptide); C-peptide Cmax (nmol/L) = Maximum C-peptide value between post basal values; C-peptide Tmax (min) = Time at which the C-peptide Cmax is reached In case both Basal #1 and Basal #2 C-peptide are missing, the Average Basal C-peptide will be set as missing.
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.

Parameter	Calculation
Time from first insulin administration to inform consent	Time from first insulin admin. to IC (days) = Date of IC signature - Date of first insulin admin +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.
Date of first/last IMP intake	The date of first IMP intake will be taken from the Diary form (Treatment Cycle No.1, Day 1). In case of missing value, the date of dispensation of 1st kit will be used instead (CRF - IMP DISPENSATION). In case of treatment discontinuation, the date of last IMP intake will be taken from the last available Diary form, otherwise the CRF date of visit reporting a Criteria for discontinuation of the IMP will be used.
Extent of exposure	Extent of exposure (days) = Date of last IMP intake - Date of first IMP intake +1. The rule for conversion from days to weeks is specified at the end of this table.
CGM parameters	See section **Errore. L'origine riferimento non è stata trovata.**
Identification of severe hypoglycemic event	At Baseline: CRF - SELF REPORTED SEVERE HYPOGLYCEMIA form: Did the patient experience any severe hypoglycemic episodes? At the following timepoint: A subject experiences a severe hypoglycemic event if there is at least one event in SEVHYPOD form (e-diary) or SEVHYPODP form (paper diary). The following rule will be applied in order to link the severe hypoglycemic event to the corresponding timepoint: -If the date of severe hypoglycemic episodes is not missing, the event will be considered in the subsequent closes timepoint by considering the study visit and the date of severe hypoglycemic episodes -If the date of severe hypoglycemic episodes is missing, it will be derived from diary data information
Time to severe hypoglycemic event from first dose of treatment	Time to severe hypoglycemic event = Date of onset of severe hypoglycemic episode - Date of first IMP intake +1. Date of onset of severe hypoglycemic episode will be derived according to the rule reported above.
Time from randomization to study discontinuation	Time from randomization to study discontinuation (days) = Date of study discontinuation - Date of randomization +1.
reduction in HbA1c from baseline at Time point T_X	at Time point T_x: HbA1c reduction = HbA1c at T_X - HbA1c at baseline

Parameter	Calculation
reduction in HbA1c > 0.5% from baseline and daily insulin requirement <0.50 IU/Kg/day at Time point T_x	at Time point T_x: • if HbA1c reduction ≤ 0.5% OR daily insulin requirement ≥ 0.50 IU/Kg/day, then endpoint = 'No' (even in case of one missing component) • if HbA1c reduction > 0.5% AND daily insulin requirement <0.50 IU/Kg/day, then endpoint = 'Yes' (both component should be non-missing)
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 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days

9.2 CGM value derivation

The Dexcom G6 Continuous Glucose Monitoring System (Dexcom G6 System) will be used to perform CGM during the study. Dexcom G6 System 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 written entirely in the statistical programming language R (R Foundation for Statistical Computing, Vienna, Austria) will be used given its compatibility with raw data structure coming from Dexcom G6 System.

Gaps in glucose data shorter or equal than 30 minutes will be imputed using linear interpolation. The *cgmanalysis* package 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 (by study protocol, at least 10 days before each scheduled visit the CGM sensor should be positioned):
  - *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 cgmvariables function will be used for the CGM parameters (sections 7.2.1.4 and 7.2.1.7). The package has been modified in order to perform additional simultaneous analyses (see Appendix 12.1 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 4: Variable in cgmanalysis

Endpoint	**Variable in *cgmanalysis***	**Unit**
TIR	percent_time_70_180	%
Glucose AUC outside the target range of 70/180 mg/dL	average_auc_70 + average_auc_180	mg/dL/min
MAGE (1 SD)	r_mage	mg/dL
CONGA-1, CONGA-2 and CONGA-4	conga_1, conga_2, conga_4	mg/dL
MODD	modd	mg/dL
Mean daily blood glucose	average_sensor	mg/dL
SD	standard_deviation	mg/dL
2h-PPG	average_auc_per_day*	mg/dL

**raw data must be filtered with observations ≤ 120 minutes from meals (eDiary)*

9.3 Partial date conventions

Table 5: 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	*In case of Treatment Discontinuation:* If start date > Date of last IMP intake, then Follow-up study period for TEAE occurrence. Otherwise, Treatment study period for TEAE occurrence. *In case of NO Treatment Discontinuation:* If start date ≥ Date of "Month 12 visit", then Follow-up study period for TEAE occurrence. Otherwise, Treatment study period for TEAE occurrence.
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.

AE START DATE	AE STOP DATE	RULE for TEAE definition	RULE for "Treatment"/"Follow-up" study period definition for TEAE summaries
	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.*

Table 6: 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 (TFL) should be numbered, if applicable, following the ICH E3 guideline.
- All tables/figures/listings will be presented in landscape format.
- The standard font size is 9 points “Courier New” for all tables. Listings will be presented with an 8 or 7 points Arial.
- Titles will be center-aligned; footnotes will be left-aligned.
- Each table/figure/listing will have 2 titles:
  - The 1st title will be the table/figure/listing number with the description of the table/figure/listing;
  - The 2nd title will be a description of the study set presented in the table/figure/listing.
- Some tables will have a third title (before 2nd title) with a description of the statistical method used in those tables.
- Any footnote added to explain the table/listing/figure contents will be presented in the following format:
  - Note 1: …
  - Note 2: …
  - Note 3: …
- In the tables, listing and figures the treatment under comparison will be labelled as “Ladarixin” and “Placebo”
- Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.
- The last two footnotes of each table/figure will be footers indicating:
  - the reference listing of the data;
  - the program name, the date and time of generation and the SAS® version used.
- Unless otherwise stated, listings will be presented by randomised treatment, and sorted by the treatment group, patient number, and visit.
- In all the listings on safety variables, a column with a flag (§) for treatment misallocation will identify the treatment misallocations.
- The derived variables will be identified in the listings with a flag (*).
- In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes.
- Numeric variables will be listed generally with the same number of decimal places as in the actual data; units will be presented enclosed in square brackets ([ ])., when appropriate.

11. Reference

1. Study protocol, A phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 400 mg twice a day oral ladarixin in patients with new-onset type 1 diabetes and preserved β-cell function at baseline, Protocol Version - Date: Version No. 1 final – CCI .
2. Study protocol, A phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 400 mg twice a day oral ladarixin in patients with new-onset type 1 diabetes and preserved β-cell function at baseline, Protocol Version - Date: Version No. 2 final – CCI .
3. Communication of enrolment interruption dated 28 March 2022.
4. (Vigers T, Chan CL, Snell-Bergeon J, Bjornstad P, Zeitler PS, Forlenza G, et al., 2019)(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
5. Kalbfleisch, J. D., and Prentice, R. L. (1980). The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons.

(Kalbfleisch, J. D. and Prentice, R.L., 1980)

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", congan = 1, 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 designed 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 	
	Minor manipulation of the imported files may be done by data management and programming in order to make the files readable by the algorithm.

R code	Notes

if(printname == T) {
print(basename(files[f]))
}
# Column names to lower case 	
colnames(table) = tolower(colnames(table))
cgmupload["subject_id",f] <- table$subjectid[1]
# Format columns. 	
table$timestamp <-
base::as.POSIXct(lubridate::parse_date_time(table$timestamp,
dateparseorder,tz = "UTC"))
table$sensorglucose <- suppressWarnings(base::as.numeric(table$sensorglucose))
interval <- pracma::Mode(base::diff(base::as.numeric(table$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] <-
 	
base::floor(((base::length(which(!is.na(table$sensorglucose)))/(totaltime/interval))*100))
cgmupload["num_days_good_data",f] <-
base::round(base::length(which(!is.na(table$sensorglucose)))/(86400/interval))
 	
table <- table[!is.na(table$timestamp) & !is.na(table$sensorglucose),]
 	
cgmupload["total_sensor_readings",f] <-
base::as.numeric(base::length(base::which(!is.na(table$sensorglucose))))
cgmupload["average_sensor",f] <-
base::mean(table$sensorglucose[base::which(!is.na(table$sensorglucose))],na.rm =
T)
cgmupload["estimated_a1c",f] <-
base::round((46.7 + (base::mean(table$sensorglucose[
base::which(!is.na(table$sensorglucose))]))) / 28.7,digits = 1)
cgmupload["gmi",f] <- base::round(3.31 + (0.02392 *
base::mean(table$sensorglucose[
base::which(!is.na(table$sensorglucose))])), digits = 1)
cgmupload["q1_sensor",f] <-
base::as.numeric(base::summary(table$sensorglucose[
base::which(!is.na(table$sensorglucose))])[2])
cgmupload["median_sensor",f] <-
base::as.numeric(base::summary(table$sensorglucose[
base::which(!is.na(table$sensorglucose))])[3])
cgmupload["q3_sensor",f] <-
base::as.numeric(base::summary(table$sensorglucose[
base::which(!is.na(table$sensorglucose))])[5])	

R code	Notes

```
  cgmupload["standard_deviation",f] <-
    stats::sd(table$sensorglucose[base::which(!is.na(table$sensorglucose))])
  cgmupload["cv",f] <-
    (stats::sd(table$sensorglucose[base::which(!is.na(table$sensorglucose))]))/
    base::mean(table$sensorglucose[base::which(!is.na(table$sensorglucose))])
  cgmupload["min_sensor",f] <-
    base::min(table$sensorglucose[base::which(!is.na(table$sensorglucose))])
  cgmupload["max_sensor",f] <-
    base::max(table$sensorglucose[base::which(!is.na(table$sensorglucose))])

  # Excursions over 120 calculations.
  BGover120 <-
    base::as.numeric(table$sensorglucose[base::which(!is.na(
      table$sensorglucose))],length = 1)
  BGover120[BGover120 < 120] <- 0
  BGover120[BGover120 >= 120] <- 1
  BG120.rle <- base::rle(BGover120)
  excursions120 <-
    base::as.numeric(BG120.rle$lengths[base::which(BG120.rle$values == 1)])

  cgmupload["excursions_over_120",f] <-
    base::length(base::which(excursions120 >
                       ((aboveexcursionlength * 60)/interval)))
  cgmupload["min_spent_over_120",f] <- base::sum(BGover120) * (interval/60)
  cgmupload["percent_time_over_120",f] <-
    ((base::sum(BGover120) * (interval/60))/
       (base::length(table$sensorglucose) * (interval/60))) * 100

  # Over 140.
  BGover140 <-
    base::as.numeric(table$sensorglucose[base::which(!is.na(
      table$sensorglucose))],length = 1)
  BGover140[BGover140 < 140] <- 0
  BGover140[BGover140 >= 140] <- 1
  BG140.rle <- base::rle(BGover140)
  excursions140 <-
    base::as.numeric(BG140.rle$lengths[base::which(BG140.rle$values == 1)])

  cgmupload["excursions_over_140",f] <-
    base::length(base::which(excursions140 >
                       ((aboveexcursionlength * 60)/interval)))
  cgmupload["min_spent_over_140",f] <- base::sum(BGover140) * (interval/60)
  cgmupload["percent_time_over_140",f] <-
    ((base::sum(BGover140) * (interval/60))/
       (base::length(table$sensorglucose) * (interval/60))) * 100

  # Over 180.
  BGover180 <-
```

R code	Notes
base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],length = 1) BGover180[BGover180 < 180] <- 0 BGover180[BGover180 >= 180] <- 1 BG180.rle <- base::rle(BGover180) excursions180 <- base::as.numeric(BG180.rle$lengths[base::which(BG180.rle$values == 1)]) cgmupload["excursions_over_180",f] <- base::length(base::which(excursions180 > ((aboveexcursionlength * 60)/interval))) cgmupload["min_spent_over_180",f] <- base::sum(BGover180) * (interval/60) cgmupload["percent_time_over_180",f] <- ((base::sum(BGover180) * (interval/60))/ (base::length(table$sensorglucose) * (interval/60))) * 100 # Over 200. BGover200 <- base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],length = 1) BGover200[BGover200 < 200] <- 0 BGover200[BGover200 >= 200] <- 1 BG200.rle <- base::rle(BGover200) excursions200 <- base::as.numeric(BG200.rle$lengths[base::which(BG200.rle$values == 1)]) cgmupload["excursions_over_200",f] <- base::length(base::which(excursions200 > ((aboveexcursionlength * 60)/interval))) cgmupload["min_spent_over_200",f] <- base::sum(BGover200) * (interval/60) cgmupload["percent_time_over_200",f] <- ((base::sum(BGover200) * (interval/60))/ (base::length(table$sensorglucose) * (interval/60))) * 100 cgmupload["avg_excur_over_140_per_day",f] <- as.numeric(cgmupload["excursions_over_140",f])/ as.numeric(cgmupload["num_days_good_data",f]) cgmupload["avg_excur_over_200_per_day",f] <- as.numeric(cgmupload["excursions_over_200",f])/ as.numeric(cgmupload["num_days_good_data",f]) # Over 250. BGover250 <- base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],length = 1) BGover250[BGover250 < 250] <- 0 BGover250[BGover250 >= 250] <- 1 BG250.rle <- base::rle(BGover250)	

R code	Notes
excursions250 <- base::as.numeric(BG250.rle$lengths[base::which(BG250.rle$values == 1)]) cgmupload["excursions_over_250",f] <- base::length(base::which(excursions250 > ((aboveexcursionlength * 60)/interval))) cgmupload["min_spent_over_250",f] <- base::sum(BGover250) * (interval/60) cgmupload["percent_time_over_250",f] <- ((base::sum(BGover250) * (interval/60))/ (base::length(table$sensorglucose) * (interval/60))) * 100 # Under 54. BGunder54 <- base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],length = 1) BGunder54[BGunder54 <= 54] <- 1 BGunder54[BGunder54 > 54] <- 0 BG54.rle <- base::rle(BGunder54) excursions54 <- base::as.numeric(BG54.rle$lengths[base::which(BG54.rle$values == 1)]) cgmupload["excursions_under_54",f] <- base::length(base::which(excursions54 > ((belowexcursionlength * 60)/interval))) cgmupload["min_spent_under_54",f] <- base::sum(BGunder54) * (interval/60) cgmupload["percent_time_under_54",f] <- ((base::sum(BGunder54) * (interval/60))/ (base::length(table$sensorglucose) * (interval/60))) * 100 # Under 60. BGunder60 <- base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],length = 1) BGunder60[BGunder60 <= 60] <- 1 BGunder60[BGunder60 > 60] <- 0 BG60.rle <- base::rle(BGunder60) excursions60 <- base::as.numeric(BG60.rle$lengths[base::which(BG60.rle$values == 1)]) cgmupload["excursions_under_60",f] <- base::length(base::which(excursions60 > ((belowexcursionlength * 60)/interval))) cgmupload["min_spent_under_60",f] <- base::sum(BGunder60) * (interval/60) cgmupload["percent_time_under_60",f] <- ((base::sum(BGunder60) * (interval/60))/ (base::length(table$sensorglucose) * (interval/60))) * 100 # Under 70.	

R code	Notes

```
  BGunder70 <-
    base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],
                     length = 1)
  BGunder70[BGunder70 <= 70] <- 1
  BGunder70[BGunder70 > 70] <- 0
  BG70.rle <- base::rle(BGunder70)
  excursions70 <-
    base::as.numeric(BG70.rle$lengths[base::which(BG70.rle$values == 1)])

  cgmupload["excursions_under_70",f] <-
    base::length(base::which(excursions70 >
                               ((belowexcursionlength * 60)/interval)))
  cgmupload["min_spent_under_70",f] <- base::sum(BGunder70) * (interval/60)
  cgmupload["percent_time_under_70",f] <-
    ((base::sum(BGunder70) * (interval/60))/
       (base::length(table$sensorglucose) * (interval/60))) * 100

  # Time in range.
  BGinrange <-
    base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],
                     length = 1)
  BGinrange <- ifelse(BGinrange %in% 70:180, 1,0)
  cgmupload["min_spent_70_180",f] <- base::sum(BGinrange) * (interval/60)
  cgmupload["percent_time_70_180",f] <-
    ((base::sum(BGinrange) * (interval/60))/
       (base::length(table$sensorglucose) * (interval/60))) * 100

  # Custom intervals
  if(!is.null(customintervals[[1]])) {
    lows <- unlist(lapply(customintervals, '[[', 1))
    highs <- unlist(lapply(customintervals, '[[', 2))
    for (r in 1:length(customintervals)) {
      # Range
      BGinrange <-
base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],
                               length = 1)
      BGinrange <- ifelse(BGinrange %in% lows[r]:highs[r], 1,0)
      minname <- paste0("min_spent_",lows[r],"_",highs[r])
      cgmupload[minname,f] <- base::sum(BGinrange) * (interval/60)
      percname <- paste0("percent_time_",lows[r],"_",highs[r])
      cgmupload[percname,f] <-
        ((base::sum(BGinrange) * (interval/60))/
           (base::length(table$sensorglucose) * (interval/60))) * 100
      # Below
      BGunder <-
        base::as.numeric(table$sensorglucose[base::which(!is.na(table$sensorglucose))],
                         length = 1)
      BGunder[BGunder <= lows[r]] <- 1
```

R code	Notes

BGunder[BGunder > lows[r]] <- 0
BGunder.rle <- base::rle(BGunder)
excursionsunder <-
base::as.numeric(BGunder.rle$lengths[base::which(BGunder.rle$values == 1)])
 	
cgmupload[paste0("excursions_under_",lows[r]),f] <-
base::length(base::which(excursionsunder >
((belowexcursionlength * 60)/interval)))
cgmupload[paste0("min_spent_under_",lows[r]),f] <- base::sum(BGunder) * (interval/60)
cgmupload[paste0("percent_time_under_",lows[r]),f] <-
((base::sum(BGunder) * (interval/60))/
(base::length(table$sensorglucose) * (interval/60))) * 100
# Above 	
BGover <-
base::as.numeric(table$sensorglucose[base::which(!is.na(
table$sensorglucose))],length = 1)
BGover[BGover < highs[r]] <- 0
BGover[BGover >= highs[r]] <- 1
BGover.rle <- base::rle(BGover)
excursionsover <-
base::as.numeric(BGover.rle$lengths[base::which(BGover.rle$values == 1)])
 	
cgmupload[paste0("excursions_over_",highs[r]),f] <-
base::length(base::which(excursionsover >
((aboveexcursionlength * 60)/interval)))
cgmupload[paste0("min_spent_over_",highs[r]),f] <- base::sum(BGover) * (interval/60)
cgmupload[paste0("percent_time_over_",highs[r]),f] <-
((base::sum(BGover) * (interval/60))/
(base::length(table$sensorglucose) * (interval/60))) * 100
}
}
# Find daytime AUC. 	
if ("wake" %in% colnames(table)) {
daytime_indexes <-
base::which(table$wake == 1)
} else {
daytime_indexes <-
base::which(base::as.numeric(base::format(table$timestamp,"%H")) %in%
daystart:dayend)
}
daytime_sensor <- table$sensorglucose[daytime_indexes]
xaxis <-
base::seq(from = 0, length.out = base::length(daytime_sensor),by =
(interval / 60))
 	
# Remove NAs if they are present. 		

R code	Notes

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(daytime_sensor %in% 70:180, 1,0)
cgmupload["min_spent_70_180_day",f] <- base::sum(BGinrange,na.rm = T) * (interval/60)
cgmupload["percent_time_70_180_day",f] <-
(base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(daytime_sensor) * (interval/60)) * 100
 	
BGinrange <- ifelse(daytime_sensor < 54, 1,0)
cgmupload["min_spent_under_54_day",f] <- base::sum(BGinrange,na.rm = T) * (interval/60)
cgmupload["percent_time_under_54_day",f] <-
(base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(daytime_sensor) * (interval/60)) * 100
 	
BGinrange <- ifelse(daytime_sensor < 60, 1,0)
cgmupload["min_spent_under_60_day",f] <- base::sum(BGinrange,na.rm = T) * (interval/60)
cgmupload["percent_time_under_60_day",f] <-
(base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(daytime_sensor) * (interval/60)) * 100
 	
BGinrange <- ifelse(daytime_sensor < 70, 1,0)
cgmupload["min_spent_under_70_day",f] <- base::sum(BGinrange,na.rm = T) * (interval/60)
cgmupload["percent_time_under_70_day",f] <-
(base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(daytime_sensor) * (interval/60)) * 100
 	
BGinrange <- ifelse(daytime_sensor > 180, 1,0)
cgmupload["min_spent_over_180_day",f] <- base::sum(BGinrange,na.rm = T) * (interval/60)
cgmupload["percent_time_over_180_day",f] <-
(base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(daytime_sensor) * (interval/60)) * 100
 	
BGinrange <- ifelse(daytime_sensor > 200, 1,0)
cgmupload["min_spent_over_200_day",f] <- base::sum(BGinrange,na.rm = T) * (interval/60)
cgmupload["percent_time_over_200_day",f] <-
(base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(daytime_sensor) * (interval/60)) * 100	

R code	Notes

BGinrange <- ifelse(daytime_sensor > 250, 1,0)
cgmupload["min_spent_over_250_day",f] <- base::sum(BGinrange,na.rm = T) * (interval/60)
cgmupload["percent_time_over_250_day",f] <- (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(daytime_sensor) * (interval/60)) * 100
 	
# Other daytime sensor glucose variables. 	
cgmupload["daytime_avg_sensor_glucose",f] <- base::mean(stats::na.omit(daytime_sensor))
cgmupload["daytime_min_sensor_glucose",f] <- base::min(daytime_sensor)
cgmupload["daytime_max_sensor_glucose",f] <- base::max(daytime_sensor)
cgmupload["daytime_sd",f] <- stats::sd(daytime_sensor)
 	
# 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 / 60))
 	
# 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(nighttime_sensor %in% 70:180, 1,0)
cgmupload["min_spent_70_180_night",f] <- base::sum(BGinrange,na.rm = T) * (interval/60)
cgmupload["percent_time_70_180_night",f] <- (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(nighttime_sensor) * (interval/60)) * 100	

R code	Notes
BGinrange <- ifelse(nighttime_sensor < 54, 1,0) cgmupload["min_spent_under_54_night",f] <- base::sum(BGinrange,na.rm = T) * (interval/60) cgmupload["percent_time_under_54_night",f] <- (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(nighttime_sensor) * (interval/60)) * 100 BGinrange <- ifelse(nighttime_sensor < 60, 1,0) cgmupload["min_spent_under_60_night",f] <- base::sum(BGinrange,na.rm = T) * (interval/60) cgmupload["percent_time_under_60_night",f] <- (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(nighttime_sensor) * (interval/60)) * 100 BGinrange <- ifelse(nighttime_sensor < 70, 1,0) cgmupload["min_spent_under_70_night",f] <- base::sum(BGinrange,na.rm = T) * (interval/60) cgmupload["percent_time_under_70_night",f] <- (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(nighttime_sensor) * (interval/60)) * 100 BGinrange <- ifelse(nighttime_sensor > 180, 1,0) cgmupload["min_spent_over_180_night",f] <- base::sum(BGinrange,na.rm = T) * (interval/60) cgmupload["percent_time_over_180_night",f] <- (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(nighttime_sensor) * (interval/60)) * 100 BGinrange <- ifelse(nighttime_sensor > 200, 1,0) cgmupload["min_spent_over_200_night",f] <- base::sum(BGinrange,na.rm = T) * (interval/60) cgmupload["percent_time_over_200_night",f] <- (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(nighttime_sensor) * (interval/60)) * 100 BGinrange <- ifelse(nighttime_sensor > 250, 1,0) cgmupload["min_spent_over_250_night",f] <- base::sum(BGinrange,na.rm = T) * (interval/60) cgmupload["percent_time_over_250_night",f] <- (base::sum(BGinrange,na.rm = T) * (interval/60))/(base::length(nighttime_sensor) * (interval/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)	

R code	Notes

}
 	
# Total AUC. 	
sensorBG <- base::as.numeric(table$sensorglucose,length = 1)
xaxis <-
base::seq(from = 0, length.out = base::length(sensorBG),by =
(interval / 60))
 	
# 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])
 	
# AUC over 180. 	
sensorover180 <- table$sensorglucose
sensorover180 <- sensorover180[sensorover180 >= 180]
sensorover180 <- sensorover180[!is.na(sensorover180)]
xaxis <-
base::seq(from = 0, length.out = base::length(sensorover180),by =
(interval / 60))
 	
# Calculate cumulative AUC, and subtract recatangle where length = 180 & 	
# width = minutes. 	
if (base::length(sensorover180) > 1) {
aucs <- pracma::cumtrapz(xaxis,sensorover180)
aucs <-
(aucs[base::length(sensorover180)]) - (xaxis[base::length(xaxis)] * 180)
cgmupload["auc_over_180",f] <- aucs
} else {
cgmupload["auc_over_180",f] <- 0
}
cgmupload["average_auc_180",f] <-
base::as.numeric(cgmupload["auc_over_180",f]) /
base::as.numeric(cgmupload["num_days_good_data",f])	

# AUC lower 70. 	
sensorlower70 <- table$sensorglucose
sensorlower70 <- sensorlower70[sensorlower70 < 70]
sensorlower70 <- sensorlower70[!is.na(sensorlower70)]
xaxis <-
base::seq(from = 0, length.out = base::length(sensorlower70),by =
(interval / 60))
	This section has been modified in order to calculate the AUC between 70 (upper limit) and the glucose curve (lower limit).

R code	Notes

# Calculate cumulative AUC, and subtract recatangle where length = 70 & 	
# width = minutes. 	
if (base::length(sensorlower70) > 1) {
  aucs <- pracma::cumtrapz(xaxis,sensorlower70)
  aucs <-
  -(aucs[base::length(sensorlower70)]) + (xaxis[base::length(xaxis)] * 70)
 	
  cgmupload["auc_lower_70",f] <- aucs
} else {
  cgmupload["auc_lower_70",f] <- 0
}
cgmupload["average_auc_70",f] <-
  base::as.numeric(cgmupload["auc_lower_70",f]) /
  base::as.numeric(cgmupload["num_days_good_data",f])
 	
cgmupload["interval (sec)",f] <- interval	

# Calculate MAGE. 	
# Smooth data using an exponentially weighted moving average, calculate SD of 	
# unsmoothed data. 	
table$smoothed <-
  base::as.numeric(zoo::rollapply(zoo::zoo(table$sensorglucose), 9,
  function(x) c(1,2,4,8,16,8,4,2,1) %*%
  (x / 46),fill = NA))
table$smoothed[1:4] <- base::mean(stats::na.omit(table$sensorglucose[1:4]))
table$smoothed[(base::length(table$smoothed)-3):
  base::length(table$smoothed)] <-
  base::mean(table$sensorglucose[(base::length(table$sensorglucose)-3):
  base::length(table$sensorglucose)])
 	
sd <- stats::sd(table$sensorglucose)
# Identify turning points, peaks, and nadirs. 	
tpoints <- pastecs::turnpoints(table$smoothed)
peaks <- base::which(tpoints[["peaks"]] == TRUE)
pits <- base::which(tpoints[["pits"]] == TRUE)
# Calculate the difference between each nadir and its following peak. If the 	
# data starts on a peak, remove it. Otherwise remove the final pit to create an 	
# even number of pits and peaks. 	
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]	

R code	Notes

# Calculate the average of the differences greater than the entire dataset 	
# SD, 2SD, etc. 	
if (magedef == "1sd") {
cgmupload["r_mage",f] <-
base::mean(stats::na.omit(differences[base::which(differences > sd)]))
} else if (magedef == "1.5sd") {
cgmupload["r_mage",f] <-
base::mean(stats::na.omit(differences[base::which(differences >
(sd * 1.5))]))
} else if (magedef == "2sd") {
cgmupload["r_mage",f] <-
base::mean(stats::na.omit(differences[base::which(differences >
(sd * 2))]))
} else {
cgmupload["r_mage",f] <-
base::mean(stats::na.omit(differences[base::which(differences >
magedef)]))
}
 	
#J-index
cgmupload["j_index",f] <-
0.001 * (base::mean(table$sensorglucose, na.rm = T) +
stats::sd(table$sensorglucose, na.rm = T))^2	

# CONGA # n <- (congan * 3600) # conga.times <- table$timestamp + n # conga.times <- conga.times[!is.na(conga.times)] # conga.times <- conga.times[base::order(conga.times)] # conga.times <- conga.times[base::which(conga.times %in% table$timestamp)] # begin.times <- conga.times - n # suppressWarnings(congas <- table$sensorglucose[base::which(table$timestamp %in% conga.times)] - # table$sensorglucose[base::which(table$timestamp %in% begin.times)]) # cgmupload[base::paste0("conga_",congan),f] <- stats::sd(congas,na.rm = T) congan=1 n <- (congan * 3600) conga.times <- table$timestamp + n conga.times <- conga.times[!is.na(conga.times)] conga.times <- conga.times[base::order(conga.times)] conga.times <- conga.times[base::which(conga.times %in% table$timestamp)] begin.times <- conga.times - n suppressWarnings(congas <- table$sensorglucose[base::which(table$timestamp %in% conga.times)] - table$sensorglucose[base::which(table$timestamp %in% begin.times)]) cgmupload[base::paste0("conga_",congan),f] <- stats::sd(congas,na.rm = T)	This section has been modified in order to calculate the CONGA at 1h, 2h and 4h simultaneously.

R code	Notes
congan=2 n <- (congan * 3600) conga.times <- table$timestamp + n conga.times <- conga.times[!is.na(conga.times)] conga.times <- conga.times[base::order(conga.times)] conga.times <- conga.times[base::which(conga.times %in% table$timestamp)] begin.times <- conga.times - n suppressWarnings(congas <- table$sensorglucose[base::which(table$timestamp %in% conga.times)] - table$sensorglucose[base::which(table$timestamp %in% begin.times)]) cgmupload[base::paste0("conga_",congan),f] <- stats::sd(congas,na.rm = T) congan=4 n <- (congan * 3600) conga.times <- table$timestamp + n conga.times <- conga.times[!is.na(conga.times)] conga.times <- conga.times[base::order(conga.times)] conga.times <- conga.times[base::which(conga.times %in% table$timestamp)] begin.times <- conga.times - n suppressWarnings(congas <- table$sensorglucose[base::which(table$timestamp %in% conga.times)] - table$sensorglucose[base::which(table$timestamp %in% begin.times)]) cgmupload[base::paste0("conga_",congan),f] <- stats::sd(congas,na.rm = T)	

# MODD. 	
table$time <- lubridate::round_date(table$timestamp,"5 minutes")
table$time <- base::strftime(table$time, format = "%H:%M",tz = "UTC")
moddtable <-
base::data.frame(base::matrix(ncol = 2,nrow =
base::length(unique(table$time))))
base::colnames(moddtable) <- c("time","mean_differences")
moddtable$time <- base::unique(table$time)
# For each time, calculate differences (absolute values) and average them. 	
for (r in 1:nrow(moddtable)) {
moddtable$mean_differences[r] <-
base::mean(base::abs(base::diff(table$sensorglucose[
base::which(table$time == moddtable$time[r])])))
}
# Average the averages. 	
cgmupload["modd",f] <-
base::mean(stats::na.omit(moddtable$mean_differences))
 	
# LBGI and HBGI (based on dc1386 appendix) 	
a <- 1.084
b <- 5.381
y <- 1.509
table$gluctransform <- y * ((base::log(table$sensorglucose)^a)-b)
table$rBG <- 10 * (table$gluctransform^2)	

R code	Notes

rl <- table$rBG[base::which(table$gluctransform < 0)]
rh <- table$rBG[base::which(table$gluctransform > 0)]
cgmupload["lbgi",f] <- base::mean(stats::na.omit(rl))
cgmupload["hbgi",f] <- base::mean(stats::na.omit(rh))
}
 	
# 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(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(250,400)), aboveexcursionlength = 35, belowexcursionlength = 10, magedef = "1sd", congan = 1, daystart = 0, dayend = 24, id_filename = F, format = "rows", printname = F)	Cleandata will fill in gaps shorter than 30 minutes but will not remove the 24-hour chunks containing larger gaps. Parameters customintervals, aboveexcursionlength, belowexcursionlength, congan, daystart, dayend will not be used.

12.2 SAS code for Andersen-Gill intensity model

The following SAS code will be used to implement Andersen-Gill intensity model:

```
title 'Intensity Model';
proc phreg data=dataset covm ;
        class trt01pn (ref="2");
        model (Tstart, Tstop) * status (0) = trt01pn;
        hazardratio trt01pn;
run;
```

- The *covm* option specifies that the model-based covariance matrix will be used
- In *Ref* option the Placebo group should be specified
- a *TStart* variable to represent the (k – 1) recurrence time or the value 0 if k = 1
- a *TStop* variable to represent the kth recurrence time or the follow-up time if k = K + 1
- a *Status* variable indicating whether the TStop time is a recurrence time or a censored time; for example, Status=1 for a recurrence time and Status=0 for censored time

12.3 List of Tables, Listings and Figures

Mock shells and index for tables, listings and figures are reported provided in the file “LDX0419 Mock shells - Version 3.0_2024-05-07.docx” attached to this document.