16.1.9 Documentation of Statistical Methods

This section contains the following documents:

Statistical Analysis Plan, Version 4.0 – 04 July 2025

Note to File – 17 July 2025

Note to File – 04 September 2025

Note to File – 09 September 2025

Note to File – 02 October 2025

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STATISTICAL *ANALYSIS* PLAN

PROTOCOL: LDX0319

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

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STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

Document Information	
Protocol Number:	LDX0319
Internal Project Code:	SP245PJ020
Document Date:	04 July 2025
Document Version:	4.0
Prepared for:	Dompé farmaceutici s.p.a. [Dompé] Via Santa Lucia 6; 20122 Milan, Italy
Prepared by:	[redacted], Dompé [redacted]

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

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Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CONGA	Continuous Overall Net Glycemic Action
CRO	Contract Research Organization
CS	Clinically Significant
DB	Database
DMC	Data Monitoring Committee
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
MODD	Mean Of the Daily Differences

NCS	Not Clinically Significant
PK	Pharmacokinetics
PP	Per Protocol set
PPG	PostPrandial Glucose
PT	Preferred Term
QTcF	corrected QT interval by Fredericia
RND	Randomized set
RTF	Rich Text Format
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	28 October 2020
Final 2.0	Section 1 has been modified to add new protocol references. Section 4.8 has been added to better clarify the DMC activities. Sections 5.1, 6.1, 7.3, 8.2, 9.1 have been modified based on DMC requests. Sections 5.5, 5.9.2, 12.1 have been modified to add clarifications.	7 February 2023

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	Section 5.9.3 has been modified to request a listing instead of a summary table, given the heterogeneity of HLA DR-DQ haplotypes at baseline.	
	Although the current version of SAP (v2.0) was approved internally on 7 February 2023, the signature date was in December 2023 because the document had been put on hold due to internal discussions which did not result in any update. In the meanwhile, a change of team members occurred: - [redacted] Since not all signatories were onboard on this study on 07 February 2023, the document date has been updated from 07 February 2023 to 21 December 2023	22 December 2023
Draft 2.1	The following SAP sections have been updated based on Protocol v5.1: • Section 3: Study Design • Section 4: Statistical Analysis • Section 7: Evaluation of Efficacy Evaluation of Treatment Compliance and Exposure (Section 6) has been updated.	09 February2024

	Additional information regarding Reason for discontinuation summaries has been added in 5.1 section. Severe Hypoglycemia derivation has been updated in 9.1 section.	
Draft 2.2	The following SAP sections have been updated: • 4.4 and 7.1.2: Subgroup analysis, specification of possible convergence issues • 4.6: detail on handling missing start/end cycle date • 4.7 Changes in the planned analysis: miRNA signature at baseline - predictive analysis will be not covered in this SAP • 5.1 Subject enrolment and disposition: additional analyses on IMP/study discontinuation have been added • 5.9.3 HLA DR-DQ haplotypes: categories on HLA have been described • 6.1: Unscheduled visit summary included in the calculation of compliance • 6.1.2.2: algorithm updated in order to consider cycles with 0 caps taken • 7.1.3 sensitivity analysis: an additional sensitivity analysis has been described • 7.2.1: Secondary endpoints that include severe hypoglycemic events have been better described • 8.1: Events summaries for Adverse Events have been added • 7.3: Exploratory analysis added	2 July 2024
Final 3.0	List of changes: 3.2: detailed specification of baseline definition 3.5: overview of planned analysis adapted to the latest decisions	5 March 2025

	4.6: definition of retrieve dropouts added 4.7: interaction term removed from statistical model and CGM endpoints downgraded to exploratory 5.1: descriptive analysis added such as subjects screened and subjects randomized but not treated 5.9.1: detailed specification of fasting c-peptide value at baseline 6.1.1.1: inclusion of diary data in compliance special cases 7.1.3: sensitivity analysis added (removal of subjects took Biotin) 7.3: KM analysis added for primary endpoint	
Draft 3.1	The following changes have been done: 4.4: Threshold added for sub-group analysis 7.1.2, 7.1.3, 7.2.1: Details of MI approach added. Imputation of missing value at baseline has been added. 9.1: Derivation of subjects who don't require insulin therapy added 9.2: Specification of handling of duplicate diary data added 12.1: cleandata function updated based on CGM R package official code 7.2.1.9: daily insulin requirement MMRM analysis removed since it's already covered by the secondary endpoint (7.2.1.4 section). 7.1.3: sensitivity analysis regarding biotin removed. Only 1 subject took biotin, and it was taken after IMP end date.	21 March 2025
Draft 3.2	The following changes have been done:	9 April 2025

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	4.4, 7.1.2, 7.2.1, 7.2.1.9: Clarification on data scale to use for the analyses 4.6: [redacted] clarified 7.2: added strategy for primary analysis 7.3: Analysis on Il-6 and IL-8 clarified	
Final 4.0	The following changes have been made: • 3.1 Clarification regarding handling of Month 18 and Month 24 data from ongoing patients in the main statistical analysis • 3.5 Removal of 'Addendum' from final analysis description • 4.4: Clarification of subgroup categories inclusion. • 4.6: Clarify that retaken values can be used in primary endpoint derivation. • 5.5: Number of subjects ongoing at final analysis to be added to disposition table • 7.1.2: Added sex and age group into the baseline imputation MCMC models • 7.1.2: Specify that primary analysis will be tested for normality using Q-Q plots • 7.1.2: Specify that log transformations will be applied to the data (if necessary) before the MI process • 7.1.3: New sensitivity analysis excluding subjects taking PPIs has been added. Sensitivity analysis for wrong MMTT dose has been updated with PD Log details • 7.2.1.3: Specified weights for Fisher's exact test for presence of zero counts • 7.2.1.4: Table structure and output of average daily insulin requirement has been updated. MMRM code has been specified in an appendix. • 7.2.1.8: specification of tests to be used. • 7.2.1.9: added sensitivity analyses for severe hypoglycemic event and eGDR data issues. • 7.3: IL-6 and proinsulin/C-peptide ratio are now specified separately as categorical variables and summary tables and figures have been updated accordingly • 9.1: specification of order of derivations to be performed. Clarification that actual & earliest timepoint will be used. • 9.2: 2h-PPG value derivation changed	4 July 2025

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	• 10.2 Changed description to 'final analysis' instead of 'Addendum for Month 24' analysis. • Appendix III added.	

1. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of LDX0319 Clinical Trial. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol or Case Report Form (CRF) may necessitate updates to the Statistical Analysis Plan (SAP). In case of deviations from this updated SAP, explanations will be provided in the clinical study report.

Analysis of pharmacokinetic data is not covered by this document. A dedicated SAP will be created for this purpose. All other study data will be considered for the analyses regulated by this SAP.

The SAP v2.0 dated 7th February 2023 is based on study protocol Version No. 4 – 31 March 2022 [1] (based on revisions of protocol version No. 2 - Final, 7 Jul 2020 [2] and protocol version No. 3 - Final 30 Jul 2020 [3] according to Amendment No 2 - Final version 31 Mar 2022 [4]).

The present version of the SAP dated 4th July 2025 is based on Study Protocol Version No. 5.1 dated 12th October 2023 [9].

2. Study Objectives

The objective of this clinical trial is to assess whether ladarixin treatment has an effect in preserving β-cell function and delaying the progression of Type 1 Diabetes (T1D) in adolescent and adult patients. 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 approximately 130-140 randomized patients with recent onset T1D, to include up to an estimated 15-20% adolescents (14-17 years).
Patients will be randomly assigned (2:1) to receive either oral ladarixin treatment (400 mg b.i.d. for 13 cycles of 14 days on/14 days off - treatment group) or placebo (control group). Recruitment will be competitive among the study sites, until the planned number of patients is randomized.

Ladarixin and placebo will both be administered for 1 year. All patients will be followed-up for 24 months from the first administration of the Investigational Medicinal Product (IMP). The study database (DB) will be locked when the last patient randomized has completed month 12 visit (or being lost in follow-up).

At the time of the main statistical analysis (i.e. after all subjects have completed M12 Visit or withdrawn), all data of completed and discontinued patients will be locked, and all visits up to Month 12 for ongoing patients will be frozen. At that point, the DB will be unblinded : the primary endpoint and all secondary endpoints will be analyzed, and the follow-up will continue under open-label conditions up to month 24.

As data relating to Month 18 and Month 24 visits in ongoing patients is not frozen, it may be updated between the date of soft lock and hard lock for the main analysis. Such data will be included in the main analysis, but it is noted that it may not have been subject to the same cleaning and review process as the data up to Month 12.

The hard lock of the database - for the final analysis - will be done at month 24, including all data up to the Month 24 visit. All endpoints will be analyzed in the final analysis.

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;
- Month 24 = Week 104±2.

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

Fasting C-peptide at baseline derivation will follow the rule reported in section 5.9.1.

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Table 1: Study Flow Chart

100 days (run-in phase)

1st insulin

[redacted]

The subset of adolescents consented for the full **PK** analysis will perform additional blood samplings during the [redacted] treatment cycle, as per specific PK Flow Chart (protocol section 14.3.2)

Procedures Assay to be performed at a centralize laboratory Assay 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 PERIOD**	
				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	**Month 24** Week 104 ±2
Informed Consent Form	X													
Eligibility criteria Randomization	X	X	X											
Auto-antibodies	X													
Fasting C-Peptide [2]	X [2]	X[2]												
Medical history	X													
BP/HR		X			X		X			X		X		X
weight, height, waist & waist/hip circumference		X							X			X	X	X
eGDR		X							X			X	X	X
Insulin requirements previous 3 days		X							X			X	X	X
Self Reported Severe Hypoglycemia		X							X			X	X	X
HLA DR-DQ haplotypes, Proinsulin,		X												
HbA1c, microRNA 375, IL-8, IL-6, hs-CRP, NET, Proinsulin.		X							X			X	X	X
miRNA signature		X												
Safety Laboratory Test (hematology & biochemistry)[3]		X			X		X			X		X		X
MMTT [3]		X							X			X	X	X

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Pregnancy Test		X			X		X			X				
Sparse PK assessment [4]				X	X	X	X	X		X	X			
12 lead ECG		X			X[6]		X[6]			X[6]				
CGM download[5]		X[5]							X[5]			X[5]	X[5]	X[5]
[redacted][6]			X		X		X			X				
Patient Diary delivery/check			X		X		X			X		X	X	X
Check discontinuation criteria [6]					X		X			X				
Patient Phone call [7]				X	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 one re-assessment of fasting C-peptide allowed in case the value at first sampling is >0.205 nmol/L.

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 at least 2 assessments to be done within 96 hours after the last IMP dose in at least 2 treatment cycles.

5 **sensor to be positioned at least 10 days before the scheduled visits.**

6 [redacted] 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 [redacted] 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** [redacted] **as soon as possible during the visit**. If this expedite timing cannot be achieved, [redacted] might be [redacted] to patient named address by a selected courier (CRO to support shipment). As per treatment discontinuation criteria, no [redacted] will be [redacted] 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 m^2) 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.

7 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.

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3.3 Sample size justification

[redacted]

The aim of this prospective study is to provide further evidence of the beneficial effect of ladarixin on C-peptide preservation in the same setting. The study will be based on approximately 130-140 randomized patients, number defined on feasibility considerations. Hypothesis testing will be based on $AUC_{0\text{-}2h}$ C-peptide and will be performed with an exploratory purpose.

The null hypothesis is that there is no difference between placebo and ladarixin, and the rejection of the null hypothesis will support the postulated superiority of ladarixin over placebo. From a simulation based on the results provided in the [redacted], that showed a 15% difference in $\log(AUC_{0\text{-}2h}+1)$ C-peptide in favor of ladarixin vs. placebo, it is estimated that the sample size of 130-140 would provide >90% power to detect the same difference between treatment groups.

No interim analysis is planned.

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 and age group (Age 14-17 vs Age 18+) to ensure balanced assignment across treatment groups. The stratified permuted mixed 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, randomizing an excess of patients (a maximum of 33 for each site) to allow competitive recruitment within each center.

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 codes will be accessible to the independent statistician(s) who will produce the reports for the Data Monitoring Committee (DMC) evaluation. The treatment assignment information will be kept confidential and will not be disclosed to any other person than those ones involved in the DMC closed session.

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 and all clinical data have been cleaned and reconciled.

3.5 Overview of planned statistical analyses

The study plans for the following statistical analyses:

- Dry Run: A subset of analyses described in the present plan will be conducted prior DB Lock. The full list of outputs will be maintained in a separate document.
- Main statistical analysis: A subset of the analyses described in the present plan will be conducted when all enrolled subjects have completed the Month 12 (or lost in follow-up) visits, and the study database has been locked and unblinded after all data have been cleaned and reconciled. The full list of outputs will be maintained in a separate document.
- Final analysis: All the analyses described in the present plan will be conducted when all enrolled subjects have completed the open phase study post unblinding (up to 24 months) after all data have been cleaned and reconciled.
- Analyses for the DMC: these analyses will be produced periodically according to the DMC charter.
- PK analysis: this analysis is not covered in this SAP, and it will be conducted by the CRO appointed by Dompé when the collection of PK measurements on a selected subset of subjects is completed.

3.6 Efficacy endpoints

In the following sub-sections, a list of primary, secondary and exploratory endpoints are reported. Further details of the analyses are reported in section 7.

3.6.1 Primary endpoint

The primary efficacy endpoint is the following:

- Change from baseline in 2-hour AUC of C-peptide response to a Mixed Meal Tolerance Test (MMTT) at Month 6;

3.6.2 Secondary efficacy endpoints

The secondary efficacy endpoints are the following:

- Change from baseline in 2-hour AUC of C-peptide response to the MMTT at Month 12, 18 and 24;
- Change in HbA1c from baseline at Month 6, 12, 18 and 24;
- Proportion of patients with HbA1c of less than 7% who did not experience severe hypoglycemic events during treatment at Month 6, 12, 18, 24;
- Average (previous 3 days) daily insulin requirement (IU/kg/day) at Month 6, 12, 18 and 24;
- Proportion of patients with HbA1c <7% and daily insulin requirement <0.5 (IU/kg/day) at Month 6, 12, 18 and 24;
- Number of self-reported episodes of severe hypoglycemia at Month 6, 12, 18, 24;
- Percentage of patients not requiring insulin therapy at Month 6, 12, 18, 24;
- Estimated Glucose Disposal Rate (eGDR) at Month 6, 12, 18 and 24.

3.6.3 Exploratory efficacy endpoints

The exploratory efficacy endpoints are the following:

[redacted]

3.7 Safety endpoints

The safety endpoints are the following:

- Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs) throughout the study.
- Safety Laboratory Tests at Week 11, Week 23, Week 35, Month 12 and Month 24 (or withdrawal);
- Vital signs at Week 11, Week 23, Week 35, Month 12 and Month 24 (or withdrawal);

- eGDR and Body Mass Index (BMI) at Month 6, Month 12, Month 18 and Month 24;
- Electrocardiogram (ECG) at Week 11, Week 23, Week 35;
- Pregnancy at Week 11, Week 23, Week 35.

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 = 0.05 level (two-sided) when comparing treatments. For all inferential analyses, p-value will be rounded to three decimal places. Statistical significance will be declared if the p-value will be less than 0.05. For primary analysis only (section 7.1.2), p-values will be provided at 5th decimal place.

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 and undergoing study evaluations/procedures.

4.2.2 Randomized set

The Randomized 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 of the occurrence 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.

4.2.5 Per Protocol set

The Per Protocol set (PP) will consist of all patients from the FAS without any Major Protocol Deviations considered to impact the primary efficacy analysis. The PP set will be used for sensitivity analyses.

All the protocol deviations will be discussed case by case by the clinical team prior to or during the Blind Data Review Meeting (BDRM) and decisions on which deviations lead to exclusion from the PP analysis set will be made before the DB lock and described in the BDRM Report.

4.3 Usage of analysis sets

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

Table 2: Usage of analysis set

Analysis	ENR	RND	FAS	SAF	PP
Subject enrolment and disposition	X				
Protocol violations		X			
Study discontinuations		X			
Demographics and baseline characteristics			X		
Medical or surgical history and/or Concomitant Diseases			X		
Prior and concomitant medications			X		
Other baseline characteristics			X		
Compliance to IMP				X	
Exposure to IMP				X	
Analysis of primary efficacy endpoint			X		
Sensitivity analysis			X		X
Analysis of secondary efficacy endpoints			X		
MMTT over the study			X		
Analysis of exploratory efficacy endpoints			X		

Adverse events				X	
Clinical laboratory evaluation				X	
Vital signs, eGDR and BMI			X	X	
ECGs				X	
Pregnancy test over the study				X	
Permanent treatment discontinuation criteria				X	
Patient phone calls				X	

4.4 Sub-group analyses

Statistical tests for interaction (between subgroup and treatment arm) will be performed to decide about the need to further investigate subgroups of the trial population. The consistency of the treatment effect will be assessed using the same model as the one used for primary efficacy analysis including the subgroup variable (if not already present in the model) and the interaction factor between treatment and subgroup variable.

Every interaction test between treatment and each subgroup variable will be evaluated separately on the primary efficacy variable. Sub-group analysis of primary efficacy variable will be performed by considering the same scale of primary analysis (i.e. log-transformed scale or original scale).

The following subgroups will be defined based on demographic or baseline characteristics:

- age group (14-17 vs 18+);
- sex (Male, Female);
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander , Other);
- BMI (BMI≤25kg/m^2, 25kg/m^2<BMI≤30kg/m^2);
- Human Leukocyte Antigen Complex - HLA (Low Risk, Intermediate Risk, High Risk. Derivation in section 5.9.3);
- proinsulin/c- peptide ratio (<median vs ≥median, where the data used for the calculation will use the integer part of results as described in Section 7.3);
- site geographic region (Europe vs US vs Other)
- Autoantibodies (1, 2, >=3)

Each category of a subgroup variable (for instance subgroup variable=Sex with categories: Males and Females) should be represented by a sufficient number of patients (ideally at least 20% of the total number of patients.) For each category: need for a minimum of 75% of patients with observed (not missing) primary efficacy variable (Change from baseline in 2-hour AUC of C-peptide response to a Mixed Meal Tolerance Test (MMTT) at Month 6).

At the time of BDRM, categories of the subgroups above can be combined if the number of patients in each category is found to be too small.

If the aforementioned conditions are not fulfilled for a specific subgroup variable, this will be discussed at the BDRM. In cases of extremely low numbers in a category, the subgroup analysis may be removed (interaction test not performed), otherwise the interaction test between treatment and the subgroup variable will be performed and if convergence is met then the tests will be displayed .

Subgroup analysis will be performed if interaction tests are statistically significant at 15% nominal level.

The primary endpoint will be analyzed by means of the same Analysis of Covariance (ANCOVA) model as described in section 7.1.2. Because age, sex, and BMI are both ANCOVA covariates and subgroup variables, when testing interaction between treatment and these subgroups variables, only the interaction term will be added in the model.

4.5 Interim analyses

No interim analyses will be performed.

4.6 Handling of missing and incomplete data

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

Missing values of the 2-hour AUC C-peptide will be imputed with [redacted] of the non-missing values that precede and follow the missing one(s). The [redacted] will be applied in case of one or two consecutive missing values.

No [redacted] will be applied if more than 2 consecutive missing values. If three consecutive missing values, no AUCs will not be calculated.

Missing data at 120 minutes (final) will be replaced by the last non-missing value.

If a subject is missing the post-MMT C-peptide value, but has retaken the test on the same date and time then the retaken value will be used to calculate the AUC.

Since patients who discontinue the treatment with the IMP will not be withdrawn from the study but will be asked to complete safety and efficacy assessments as per the protocol, for the primary analysis missing data will be addressed by modeling patients with missing data using retrieved dropouts (i.e.

subjects that discontinued the treatment but have the Month 6 measurement, see SAP section 7.1.2). This approach is based on the assumption that the missing data, if it had been assessed, would have been similar to the observed data in retrieved dropouts. If there are not enough retrieved dropouts, a "Jump-to-Reference" analysis instead of retrieved drop-out analysis will be performed: the missing C-peptide data at month 6 will be imputed by using placebo group data; this approach does not assume benefits for ladarixin in case of discontinuation and limits a post-discontinuation clinical effect to that of placebo.

These analyses will also be applied to HbA1c.

In case of missing intermediate start/end cycle dates (e.g., start/end cycle 5 missing, but end cycle 4 and start 6 available), the expected date for the missing intermediate cycles will be derived through the following algorithm:

- the number of days between the last available date before the missing intermediate visit and the first available date after the missing intermediate visit will be divided by the number of missing inter-visit periods, where Inter-visit period is the time between the end of a cycle and the start of the next cycle, or the time between start and end of a given cycle
- The date for the missing intermediate visit will be imputed as follows: date of the visit before the missing intermediate visit + the integer part of the result derived at the previous bullet point. Below an example:
  - End cycle 3 date = 20sep2022
  - Start/End date missing for C4, C5, C6
  - Start cycle 7 date = 17feb2023
  - (Start Date C7-Start DateC3)/7 = 21.4 = 21 days
  - Start C4 (imputed) = End date C3+21 days = 11oct2022
  - End C4 (imputed) = Start C4+21 days = 01nov2022
  - And so on.

Other critical missing data, if any, will be discussed prior to treatment unblinding. Decisions will be taken during the BDRM and will be fully documented in the BDRM Report.

4.7 Changes in the planned analysis

A tipping-point sensitivity analysis will be performed for further exploring the potential impact of violations in assumptions about the missing data on the primary efficacy endpoint (section 7.1.2).

The following analysis reported in Protocol v5.1 section 9.6.7 will not be performed: "miRNA signature at baseline will be performed to identify patients responding to ladarixin treatment (predictive analytics)".

[redacted], not specified in the protocol, has been added in the SAP as exploratory analysis.

Since the actual sample size is approximately 40% of the originally planned size and there are significant imbalances within levels of some covariates, interactions with the treatment have been removed from the model for the primary endpoint (and for secondary endpoints that use the same model; for details, see Section 7.2.1 of the SAP) to ensure greater robustness of the model and better interpretability of the results. Analysis of interaction with treatment has been covered in SAP section 4.4 Sub-group analysis.

The following secondary endpoints have been downgraded (as per non-conformity document # [redacted]) without a Protocol Amendment, and the analyses of the following secondary endpoints will be considered as exploratory endpoints:

- [redacted]
- [redacted]

The analyses of secondary endpoints that included CGM data have been downgraded due to several limitations regarding data integrity stemming from the management of data downloads from the device. Specifically, given the nature of the data, the integrity was considered compromised due to the potential for undetected data manipulations, as well as the absence or inadequacy of source documentation at the site. Taking these considerations into account, and also acknowledging that this condition did not compromise patient safety, rights and wellbeing, it was deemed appropriate to retain the data and analyze it as an exploratory analysis.

4.8 Data Monitoring Committee

DMC meetings will be performed during the trial to monitor the safety of the patients and to protect study subjects from undue harm. Further details will be provided in the DMC Charter, where all roles and responsibilities will be defined.

Access to unblinded information on the efficacy analyses is allowed on DMC request to balance patient safety risk against a possible gain in efficacy.

The DMC will consider the appropriateness of trial continuation if there is emerging evidence that Ladarixin is harmful. Since the DMC does not monitor the primary endpoint for early efficacy termination, no Type I error adjustment is necessary.

For the DMC review, the analyses will be provided separately for adolescents (age 14-17) and adults (age 18+).

Only for the DMC purpose, the following graphs will be provided:

- a Spaghetti plot of individuals' observed data for all laboratory parameters over time without treatment arm distinction.
- a Spaghetti plot of individuals' observed data for all vital signs values over time without treatment arm distinction.
- a Spaghetti plot of individuals' observed data for QTcF Interval over time without treatment arm distinction.

These specific DMC requests are not included in the final analysis. Other DMC requests may be included in the SAP, specifying if they are requested for DMC meeting only or both for DMC and final analysis.

4.9 Blind data review meeting

A BDRM will be held before the DB lock and the unblinding of the data. Any other details will be provided in the BDRM Report.

4.10 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.4) on a Windows 10 operating system.

CGM data at patient level will be processed using *cgmanalysis* package [6] 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:

a. Subjects enrolled (N);
b. Subjects enrolled but not randomized and reasons for non-allocation (N, %);
c. Subjects randomized (N, %);
d. Subjects randomized but not treated (N, %);
e. Subject randomized by country and site (N, %);
f. Subjects in each analysis set (FAS, SAF, PP) and reasons for exclusion (N, %);

For bullet points b and c the percentage denominator will be the number of ENR subjects (for point c, percentages will only be shown for the overall column and not by treatment group) , for the bullet points d, e, f the percentage denominator will be the number of randomized subjects within each treatment group and overall.

For the second bullet point, the following information will be reported in the corresponding listing 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)
  - Result of corresponding parameter

Listings will be provided based on ENR set.

The following output will be produced as summary statistics in order to have a detail on IMP/study discontinuation:

- proportion of subjects who discontinued the IMP and who discontinued the study (categories: <6 months vs 6-12 months vs >12 months);

5.2 Protocol violations

All the protocol deviations will be discussed case by case before unblinding of the treatment code with the clinical team prior to or during the BDRM and described in the BDRM Report.

Number of occurrences and of subjects with at least one major deviation, at least one minor protocol deviation, and at least one major deviation leading to exclusion from the PP analysis set will be summarised for each treatment.

5.3 Permanent treatment discontinuation criteria

A summary table showing at each available timepoint the number and percentages of subjects meeting at least one discontinuation criteria will be produced by treatment group. Percentages will be calculated on the number of subjects who have reached the specific visit

In addition, reason for discontinuation, will be produced by treatment group, by considering the number of subjects who discontinued the study treatment at the specific visit as denominator for percentages.

5.4 Patient phone calls

A summary table showing at each available timepoint 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;
- Number of subjects who are still ongoing in the study and yet to complete each of Month 18 and Month 24 visit (applicable at the time of the primary analysis, i.e. after all subjects have completed M12 Visit or withdrawn). 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).

If more than 30% of randomized subjects discontinue the study prematurely, the distribution of the time from randomization to discontinuation will be summarized using time-to-event method (Kaplan-Meier estimates and plots will be provided with 95% confidence interval bounds calculated per Greenwood [7] method, the respective number of patients at risk, and the log-rank test p-value). Subjects who have not prematurely discontinued the trial will be censored at study termination.

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 (Europe, US, Other). This will be derived in the following way:
  - Europe: Italy, Germany, Belgium, Slovenia, France, Spain, Serbia, Georgia
  - Other: Israel
  - US: USA
- Demography
  - Age (years)
  - Age group (14-17, 18+)
  - 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 informed consent (days)
- BMI (BMI≤25kg/m^2, 25kg/m^2<BMI≤30kg/m^2)

5.7 Medical and surgical history

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), sorted in decreasing order of total frequency. Subjects experiencing more than one past/concomitant disease event will be counted only once within each SOC and PT.

Medical history and concomitant diseases will be analyzed separately.

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 7). 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, sorted in decreasing order of total frequency

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.

The following situations can occur:

Screening assessment	Baseline assessment	Analysis
Fasting C-peptide < 0.205	Not collected [1]	Value collected at screening assessment

Fasting C-peptide < 0.205	Fasting C-peptide < 0.205 [2]	Value collected at screening assessment
Fasting C-peptide < 0.205	Fasting C-peptide >= 0.205 [2]	Value collected at screening assessment
Fasting C-peptide >= 0.205	Fasting C-peptide >= 0.205	Screening failure
Fasting C-peptide >= 0.205	Not collected	Screening failure
Fasting C-peptide >= 0.205	Fasting C-peptide < 0.205	Value collected at baseline assessment

Note 1: According to protocol, baseline assessment has been done only if fasting C-pep at screening assessment is above 0.205.
Note 2: In cases where the Baseline assessment is (incorrectly) repeated at baseline, the screening assessment will be used in the analysis.
Note 3: Fasting C-peptide values for subjects who were transitioned from [redacted] to LDX0319 study are considered as screening values (reference: [redacted]).

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 will be descriptively summarized.

To determine positivity/negativity for anti-GAD, IAA, IA-2, ZnT8 the following thresholds were used: anti-GAD: negative if <5 IU/mL and positive if >=5 IU/mL; IAA: negative if <0.4 U/mL and positive if >=0.4 U/mL; IA-2: negative if <5.4 U/mL and positive if >=5.4 U/mL; ZnT8: negative if <15 U/mL and positive if >=15 U/mL.

In addition, a summary of the frequency distribution of positive antibodies will be displayed (0, 1, 2, 3, 4, Missing), calculated as sum of positive results within anti-GAD, IAA, IA-2 and ZnT8.

5.9.3 HLA DR-DQ haplotypes

A summary of HLA DR-DQ haplotypes at baseline will be provided by means of frequency distributions.

The following categories will be derived:

Category 1	**Category 2**	**Derivation**
DRB1*03/DRB1*03	Intermediate Risk	If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres = “DR17” and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres = “DR17”.

DRB1*03/DRB1*04	High Risk	If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres = “DR4” and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres = “DR17” (or viceversa)
DRB1*03/DRB1*X	Intermediate Risk	If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres in ("DR1" "DR5" "DR7" "DR8" "DR10" "DR11" “DR12” "DR13" "DR15" "DR16") and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres = “DR17” (or viceversa)
DRB1*04/DRB1*04	Intermediate Risk	If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres = “DR4” and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres = “DR4”
DRB1*04/DRB1*X	Intermediate Risk	If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres in ("DR1" "DR4") and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres (“DR1” "DR7" "DR8" "DR11" "DR12" "DR3" "DR16" "DR13" “DR15”) (or viceversa)
Non DR3/Non DR4	Low Risk”	If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres in ("DR1" "DR7" "DR8" "DR9" "DR13") and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres in ("DR1" "DR7" "DR8" "DR9" "DR10" "DR11" "DR13" "DR15" "DR16") (or viceversa)

Listing of HLA DR-DQ haplotypes at baseline will be provided as well.

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;

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.

Thus, calculation of compliance to treatment regimen considers the amount of capsules intake, 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).

If a patient didn't perform Visit X and IMP accountability information are collected as unscheduled visit, those information will be considered as well in the compliance calculation.

In case of missing start/end cycle days, please refer to SAP section 4.6.

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:

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

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%.

If the Kit was not returned (therefore the accountability cannot be performed) and the number of capsules taken is missing in CRF, the information from diary (paper and electronic) will be considered. In particular, the number of capsules taken at Cycle X (i.e. Cycle with the kit not returned and number of caps taken missing) will be calculated as sum of number of capsules with diary dates between Cycle X start date and Cycle X end date.

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:

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

- If treatment discontinuation is 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 the subject 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 treatment 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

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

- 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 +28 days
- End Cycle X date will be equal to start cycle X date
- "On period" duration 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 the subject 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 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 the subject 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 (Date 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 study drug

The extent of exposure to IMP in weeks will be summarized overall with descriptive statistics by treatment group. The extent of exposure (weeks) will be calculated using the formula reported in Table 3.

7. Evaluation of Efficacy

7.1 Analysis of primary endpoint

7.1.1 Testing strategy

The following null hypothesis is defined:

H_0: the change from baseline in the 2-hour C-peptide AUC post MMTT at Month 6 in ladarixin ($\mu_{LADARIXIN}$) is equal the placebo one ($\mu_{PLACEBO}$):

$$H_0: \mu_{LADARIXIN} = \mu_{PLACEBO}$$

$$H_1: \mu_{LADARIXIN} \neq \mu_{PLACEBO}$$

The null hypothesis will be rejected if p-value (coming from the adjusted ANCOVA model on C-peptide AUC; section 7.1.2) will be lower than 0.05 (two-sided test). The rejection of the null hypothesis H_0 will support the postulated explorative suggestion of superiority of ladarixin over placebo.

7.1.2 Analysis details

The primary endpoint at Month 6 will be analyzed by means of Multiple Imputation using retrieve dropouts (MI-RD). Specifically, to handle missing data at Month 6, MI will be performed based on the subjects' allocated treatment arm and baseline value as covariates in a regression model using data from subjects that discontinued the treatment but have the Month 6 measurement (i.e. retrieve dropouts).

If there are not enough retrieved dropouts for convergence of the MI regression model, MI will be performed by the Jump-to-Reference (J2R) approach using data from subjects in the placebo arm with assessment at Month 6. The final decision will be taken at the time of the analysis and reported in the CSR. Specifically, measurements for patients on the placebo arm without observed Month 6 data will be imputed using a monotone regression model based on 6-month observed data of placebo patients, with baseline, sex and age group as covariates. For patients on the ladarixin arm who had missing Month 6 data, the same imputation model based on the 6-month observed data of placebo patients will be implemented. One thousand datasets will be generated for the primary endpoint. The random seed number will be 200582. No rounding or range restriction will be applied to imputed continuous values.

Imputation of missing value at baseline: In case of missing baseline data, the imputation process will start by a partial imputation to impute the baseline missing data. The model will be based on a multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation models will include the treatment, sex, age group, baseline value, and observed values of the endpoint at 6-month. 1000 imputation will be performed with seed number 40482.

Each of the 1000 imputed datasets will be analyzed using ANCOVA models adjusting for:

- The respective baseline values

- Centre (as random effect),
- Baseline characteristics:
  - age group (age 14-17, Age 18+),
  - sex (Female,Male), and
  - BMI (BMI≤25kg/m^2, 25kg/m^2<BMI≤30kg/m^2)

In case G-Matrix for the estimation of the variance of the random effect component is not positive definite in at least one imputation model, the random effect will be removed from the model above, which will provide only fixed-effect estimations.
In addition, in case of strong unbalance in a specific baseline characteristic variable in terms of number of patients between groups, the variable will be removed from the model. This will be discussed at the time of the DRM.

Rubin's rule will be used for combining results to draw inference.

The adjusted estimated treatment differences between ladarixin and placebo at Month 6 will be displayed together with the corresponding 95% confidence intervals and p-values. The tests (p-value) of the fixed effects (baseline, treatment, age group, sex and BMI group) will be presented; the estimated least squares means of the two treatment groups with the corresponding 95% confidence interval will also be presented.

Assumption of normal distribution will be assessed by means of a visual review of the Normal Q-Q plot.

If the assumption of normality is not met, Log transformation of 2-hour AUC C-peptide will be applied to meet normality assumption.For consistency with the [redacted] the log (AUC 0-2h +1) C-peptide transformation will be used for the hypothesis testing. Log-transformation will be performed before MI process.

A similar methodology will be applied to the analysis of HbA1c, as reported in section 7.2.1.

7.1.3 Sensitivity analysis

The following sensitivity analyses are defined to assess robustness of results on primary endpoint versus adherence to protocol and presence of missing data:

1. The analysis of the primary endpoint will be repeated on the PP set instead of FAS using the same methodology described in section 7.1.2; this analysis will assess the robustness of results to protocol deviations.

2. The analysis of the primary endpoint will be repeated in the FAS population considering complete cases only (i.e. without considering patients with missing primary endpoint at Month 6 instead of MI-RD). This analysis will assess the robustness of results to the method of handling missing data. Comparison between treatments will be performed according to ANCOVA modeling detailed in section 7.1.2.

3. A second assessment of robustness of primary results versus method of handling missing data will be performed in the FAS population using MI under missing at random (MAR) assumption instead of MI-RD. Only baseline and 6-month data will be used for the MAR imputation (i.e. data at subsequent timepoints will not be considered).

   MI will be implemented as follows:

   - A separate imputation model will be used for each treatment arm. The imputation models will include the baseline value, age group, sex , BMI category, and observed values of the endpoint at 6-month.

   No range restriction will be applied to imputed continuous values.

   Imputed data will consist of 1000 imputed datasets. The random seed number for the imputation model will be 1804 and 2508 for Ladarixin and Placebo respectively.

   Each of the 1000 imputed datasets will be analyzed using observed and imputed data using ANCOVA models as described in section 7.1.2. Rubin's rule will be used for combining results to draw inference. The adjusted estimated treatment differences between ladarixin and placebo at Month 6 will be displayed together with the corresponding 95% confidence intervals and p-values.

4. A tipping point analysis will be used as a sensitivity analysis for missing data for assessment of superiority (if shown) of ladarixin in terms of the primary endpoint at the final analysis. The tipping point analysis will assess how severe departures from MI-RD assumptions must be**,** in order to overturn conclusions from the primary superiority analysis. The tipping point analysis will be based on iterative application of MI. In the first iteration, MI-RD method is assumed as described in section 7.1.2. In successive iterations, the imputed values for the ladarixin arm are shifted at a constant to represent a worse effect in each iteration. This can be achieved by using the N completed datasets obtained under MI-RD and shift the imputed values. The tipping point is the shift at which the p-value becomes non-significant. Outline of tipping point:

   - Use MI-RD to impute missing values;
   - Assuming that the tipping point is between –5 and 0, the following actions will be performed for Δ = 0, -0.1, -0.2, …, -1.0, …, -2.0, …, -5.0:
     - Add Δ to the imputed values at the Ladarixin arm;

- Analyze the completed data sets using the same method outlined in in section 7.1.2;

- the plot of all p-values for Δ between –5 and 0 will be created;
- based on the plot, the approximate value of the tipping point $Tp_{46pprox.}$ is identified considering a threshold for the p-values of 0.05;
- after identification of $Tp_{46pprox.}$, a finer research of the tipping point will be performed in the range $Tp_{46pprox.}$. ± 1 by incrementing Δ of 0.01 and following the usual steps:
  - Add Δ to the imputed values at the Ladarixin arm;
  - Analyze the completed data sets using the same method outlined in in section 7.1.2;
- The tipping point is the smallest Δ at which p-value ≥ 0.05.

5. The analysis of the primary endpoint will be repeated by considering as missing values the baseline results for subjects with wrong MMTT dose. These events are reported in PD Log as major PD (Description: Study Procedures-Other and Issue: MMTT assessment was not performed per protocol) and they will be flagged in SAS datasets. The same MI approach applied for imputing baseline (seed number 40482) and for primary endpoint (seed number 200582) will be performed for this sensitivity analysis.
6. The analysis of the primary endpoint will be repeated without subjects who have reported taking Proton Pump Inhibitors (PPIs). These records are reported in the CRF with ATC4 filed = "PROTON PUMP INHIBITORS". The same MI approach applied for imputing baseline and primary endpoint will be performed for this sensitivity analysis.

Sensitivity analyses will be performed by considering the same scale of primary analysis (i.e. original scale or log-transformed scale). If the log-transformed scale is to be applied then any imputation will be performed after the transformation.

7.2 Analysis of secondary efficacy endpoints

7.2.1 Analysis details

The following secondary endpoints #1 and #2 will be analyzed using the MI-RD (or J2R) model for imputing the missing data as described for primary endpoint (Section7.1.2):

1. Change from baseline in 2-hour AUC of C-peptide response to a MMTT [Time frame: Month 12, 18 and 24]
2. Change in HbA1c from baseline [Time frame: Month 6, 12, 18 and 24]

No normality check will be performed for the above mentioned secondary endpoints. The secondary endpoint #1 will follow the same scale of primary analysis (i.e. original scale or log-transformed scale), while the secondary endpoint #2 will be analyzed in original scale only.

At the time of primary analysis, for Month 18 and Month 24 timepoints, missing endpoint data will not be imputed for patients that are ongoing in the study and they have not yet reached the Month 18/Month 24 visit respectively. Subjects who don't have yet reached Month X will be defined in the following way:

- Month 18: if the expected Month 18 visit (i.e. randomization date+80 weeks) is greater than the cut-off date (DB Soft-lock date+15 calendar days)
- Month 24: if the expected Month 24 visit (i.e. randomization date+106 weeks) is greater than the cut-off date (DB Soft-lock date+15 calendar days)

Otherwise, if the subject is ongoing and the expected Month X visit is lower (or equal) to the cut-off date, meaning that the subject should have reached Month X visit (considering the visit window), the missing timepoint will be imputed.

For analysis at timepoints 12M, 18M and 24M, intermittent missing data, not present for the primary analysis, will be managed as follows:

Step 1: Imputation of intermittent (non-monotone) missing: regardless of the method for the MI (MI-RD or J2R), the MI requires a preliminary imputation of the intermittent (non-monotone) missing data based on a multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation model will include the treatment, baseline value, age group, sex and observed values of the endpoint at each post-baseline timepoint. The MCMC method will be used with single chains and 200 burn-in iterations. The random seed number will be 240115

Step 2a: For timepoints evaluated with the MI-RD:

Retrieve dropouts are defined as subjects who discontinued the IMP prior or on Month X (Month 6, Month 12, Month 18, Month 24), but have the parameter (C-peptide or HbA1c) not-missing at analysis timepoint.

After management of the intermittent missing, each regression model for the multiple imputation at the time frame Month 12, 18 and 24, in addition to what is included in the MI-RD model of the primary endpoint (treatment arm and baseline), will include the intermediate assessments i.e: for endpoint at month 12 the imputation model will use baseline and Month 6 value as covariates). A separate model for each time frame (12M, 18M, 24M), informed by the corresponding set of retrieved dropouts, will be implemented.

The regression model for the multiple imputation at the time frame Month 6 for "Change in HbA1c from baseline", will use the same model of the primary endpoint (no intermediate assessments and no imputation of intermediate missingness).

In case of convergence issues in the imputation model using retrieve dropouts for a visit, the multiple imputation will be performed by the Jump-to-Reference approach. Thereafter, all following visits will also be imputed by the Jump-to-Reference approach.

Step 2b: For timepoints evaluated with the Jump-to-Reference (J2R):

For patients on the placebo arm with measurements missing at Month 12, the value will be imputed using the monotone regression model based on 12-month observed data of placebo patients, with baseline, intermediate measurements and age group and sex as covariates. For patients on the ladarixin arm who had missing Month 12 data, the imputation model with only subject's baseline value and age group and sex as covariates based on the 12-month observed data of placebo patients will be implemented. The same approach for Month 18 and Month 24.

Step 3: An ANCOVA model for each timepoint will be performed without considering intermediate data. Therefore, the analyses will be performed by means of ANCOVA models adjusting for:

- The respective baseline values
- Centre (as random effect)
- Baseline characteristics:
  - age group (<18, >=18),
  - sex (Female,Male), and
  - BMI (BMI≤25kg/m^2, 25kg/m^2<BMI≤30kg/m^2)

The same assumption regarding G matrix will be applied for endpoints #1 and #2 as well.

Descriptive analyses will be performed on all secondary endpoints (section 3.6.2) at each available timepoints by means of descriptive statistics (section 4.1). Descriptive analysis on Log (AUC+1) C-Peptide will be provided as well.

In case of continuous measures, analyses will be provided for:

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

In case of categorical variables, shift tables showing difference as to the respective classifications at baseline will be provided.

In addition to the above summary statistics, comparisons between treatments will be performed as detailed in sections 7.2.1.1-7.2.1.9.

The following results will be displayed graphically:

- The means (±SEs) at each timepoint by treatment of the 2-hour AUC of C-peptide post MMTT and its change from baseline;
- The means (±SEs) at each timepoint by treatment of HbA1c and its change from baseline;
- The proportion at each timepoint by treatment of patients with HbA1c of less than 7% who did not experience severe hypoglycemic events during treatment;
- The means (±SEs) at each timepoint by treatment of the Average (previous 3 days) daily insulin requirement (IU/kg/day);
- The proportion at each timepoint by treatment of patients with HbA1c <7% and daily insulin requirement <0.5 (IU/kg/day).

In each graph, where possible, significant p-values from the below analyses (sections 7.2.1.1-7.2.1.9) will be reported in the plot area, corresponding to the associated timepoint.

7.2.1.1 Change from baseline in 2-hour AUC of C-peptide response to the MMTT [Time frame: Month 12, 18 and 24]

Change from baseline in 2-hour AUC of C-peptide post MMTT will be analyzed using the approach described in section 7.1.2, 7.2.1. Imputation will follow the steps s described in 7.2.1) This analysis will be performed by considering the same scale of primary analysis (i.e. original scale or log-transformed scale). If the log-transformed scale is to be applied then any imputation will be performed after the transformation. The adjusted estimated treatment differences between ladarixin and placebo at each timepoint will be estimated, using the same ANCOVA model presented in the section 7.1.2, and displayed together with the corresponding 95% confidence intervals and p-values. The tests (p-value) of the fixed effects (baseline, treatment, age group, sex and BMI group) will be presented; the estimated least squares means of the two treatment groups with the corresponding 95% confidence interval will also be presented.

7.2.1.2 Change from baseline in HbA1c [Time frame: Month 6, 12, 18 and 24]

Change in HbA1c from baseline will be analyzed using the approach described in section 7.1.2, 7.2.1. Imputation will follow the steps as described in 7.2.1). The adjusted estimated treatment differences between ladarixin and placebo at each timepoint will be estimated, using the same ANCOVA model presented in section 7.1.2, and displayed together with the corresponding 95% confidence intervals and p-values. The tests (p-value) of the fixed effects (baseline, treatment, age group, sex and BMI group) will be presented; the estimated least squares means of the two treatment groups with the corresponding 95% confidence interval will also be presented.

7.2.1.3 Proportion of patients with HbA1c <7% who did not experience severe hypoglycemic events during treatment [Time frame: Month 6, 12, 18 and 24]

Number and proportion along with the 95% confidence interval (Clopper-Pearson's formula) of patients with HbA1c < 7% at Month X and absence of episodes of severe hypoglycemia during treatment (up to and including minimum(Month X, Month 12) 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 where, if necessary (to avoid issues or errors due to zero counts), weighted frequencies will be used for the test and confidence intervals.

The proportion of patients with HbA1c <7% is calculated by timepoint: the numerator is the number of patient with events occurring at a specific timepoint (Month x visit), without cumulating patients with events up to that timepoint.
Patients with severe hypoglycemic events are considered cumulatively and only events up to month 12 will be considered (condition will be evaluated by considering treatment period only).
In particular:

- if a subject experienced the severe hypoglycemic event at a specific timepoint, it will be counted as a subject with the event for all subsequent timepoints.
- Events that happen between month 12 and month 24 will not be included 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 24.

If HbA1c ≥ 7% or the subject has experienced a severe hypoglycemic event, then endpoint = "No" even in case of one missing component. If either the HbA1c or severe hypoglycemic event data is missing, but the other satisfies the criteria for the endpoint, then the response to the endpoint will be missing.

7.2.1.4 Average (previous 3 days) daily insulin requirement (IU/kg/day) [Time frame: Month 6, 12, 18 and 24].

Average daily insulin requirement (CRF - INSULIN REQUIREMENT form) analysis will be carried-out using a mixed model for repeated measurements (MMRM) with treatment group, visit, treatment by visit interaction, age group, sex and BMI group as fixed factors of the model and patient as random effect. An unstructured covariance matrix for each patient is considered and the Kenward-Roger adjustment is used for the degrees of freedom. In the case where the model does not converge, different covariance structures will be used, following the below order:

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

The corresponding SAS code will be found in Appendix III. The adjusted estimated treatment differences between ladarixin and placebo at each timepoint and overall will be displayed together

with the corresponding 95% confidence intervals and p-values. The tests of the fixed effects (treatment, age, sex and BMI) p-values will be presented, together with the estimated least squares means for treatment, with the corresponding 95% confidence interval and p-value.

Assumption of normal distribution of average daily insulin requirement will be assessed by means of Kolmogorov-Smirnov test. If required, the data transformation (log-transformation) will be applied and specified in the notes.

7.2.1.5 Proportion of patients with HbA1c <7% and daily insulin requirement <0.5 (IU/kg/day) [Time frame: Month 6, 12, 18 and 24]

Number and proportion along with 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 where, if necessary (to avoid issues or errors due to zero counts), weighted frequencies will be used for the test and confidence intervals.

7.2.1.6 Number of self-reported episodes of severe hypoglycemia [Time frame: Month 6, 12, 18 and 24]

The effect of treatment on the cumulative number of severe hypoglycemic events will be evaluated by means of the Andersen-Gill intensity model with model-based variance (generalized Cox proportional hazards model to allow for analysis of recurrent data) The corresponding SAS code is provided in Appendix II section 12.3.

Summary statistics of blood glucose level (mg/dL) will be provided by treatment arm at each timepoint for patients reporting severe hypoglycemia. Derivation of patients reporting severe hypoglycemia will be the same as the one described in 7.2.1.3 section, except that in this case events occurring between month 12 and month 24 will be considered as well.

7.2.1.7 Percentage of patients not requiring insulin therapy [Time frame: Month 6, 12, 18 and 24]

Percentage of patients not requiring insulin therapy will be summarized descriptively and comparison between treatments will be performed by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point where, if necessary (to avoid issues or errors due to zero counts), weighted frequencies will be used for the test and confidence intervals.

7.2.1.8 Estimated Glucose Disposal Rate (eGDR) [Time frame: Month 6, 12, 18 and 24]

eGDR (post-baseline value and change from baseline) 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. If a treatment group has a sample size at a certain visit of less than 20 subjects then the exact test will be used.

7.2.1.9 Additional secondary analyses

Additional secondary analyses will include the analysis of the 2-hour AUC C-peptide and HbA1c values by mixed model for repeated measurements (MMRM) with AUCs C-peptide, and HbA1c values as dependent variable and treatment group, visit, treatment by visit interaction, age, sex and BMI as fixed factors of the model and patient as random effect. The same strategy for covariance matrix and for the degrees of freedom previosly reported in paragraph 7.2.1.4 will be adopted.

The following results will be displayed:

- The adjusted LS means will be estimated for each combination of time point and treatment and it will be displayed together with the corresponding 95%CIs
- P-values for fixed effects will be presented
- The estimated treatment difference between ladarixin and placebo at each time point will be presented together with the corresponding 95%CIs.

The additional secondary analysis on 2-hour C-peptide will be performed by considering the same scale of primary analysis (i.e. original scale or log-transformed scale).

Sensitivity analyses on secondary endpoints will be performed to assess the robustness of the self-reported severe hypoglycemia. Specifically, tables concerning self-reported severe hypoglycemic events and blood glucose levels will be repeated removing subjects that have been identified by medical monitors as having implausible results.

Sensitivity analysis will also be performed for the secondary endpoint of estimated glucose disposal rate (eGDR). Site 055 performed hip circumference measurements incorrectly, however the entered data could not be corrected. The hip circumference values for site 054 are of a similar range (much lower than values for other sites) however due to circumstances it cannot be confirmed prior to database lock that the measurements were also done incorrectly at site 054. Tables analyzing and summarizing eGDR will be repeated excluding patients from site 054 and 055.

7.3 Analysis of exploratory efficacy endpoints

Explorative endpoints (section 3.6.3) will be analyzed at each available timepoints by means of descriptive statistics (section 4.1). Specifically, analyses will be provided for baseline visit, each post-baseline visit, and the change from baseline measurements to each visit. Comparison between treatments will be performed 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.

Where applicable, the investigator's interpretation (Normal, Abnormal NCS, Abnormal NC, No Result), the proinsulin/c-peptide ratio and the IL-6 results will be summarized and compared by means of a Chi-square test or, if more appropriate, a Fisher's Exact test at each time point where, if necessary (to avoid issues or errors due to zero counts), weighted frequencies will be used for the test and confidence intervals.

For IL-8 analysis, only the integer results will be considered for analysis purposes (i.e. records with symbols ">" or "<" will be removed).

For IL-6 analysis, the following categories will be created:

- <2.06
- 2.06 <= IL-6 <=4.78
- 4.78 < IL-6 < 6
- >=6

The integer part of the results will be considered for assigning categories (i.e. symbols ">" or "<" will be removed).

A similar approach will be used for proinsulin/c-peptide ratios considering the integer part of the results for assigning the following categories:

- <0.018
- >=0.018

The analysis of change from baseline in Log (2-hour AUC_{mean}+1) of C-peptide response to the MMTT [timeframe: Month 6, 12, 18 and 24] will be performed following the same approach of the secondary efficacy endpoint described in section 7.2.1.1 (MI approach).
The 2-hour AUC_{mean} of C-Peptide, used as starting variable for Log transformation, is calculated in the following way:

$$AUC_{mean} = AUC\ (0\text{-}2h) / actual\ time$$

In which the actual time is calculated as difference between max actual time and basal time, for each subject.

In addition, the following results will be displayed graphically:

- Boxplot at each timepoint by treatment of IL-8 ;
- Bar plot at each timepoint by treatment of IL-6;
- Boxplot at each timepoint by treatment of High-Sensitive C-Reactive Protein (hs-CRP);
- Boxplot at each timepoint by treatment of Neutrophil Extracellular Traps (NET);
- Barplot at each timepoint by treatment of Proinsulin/ C-peptide ratio.

A graphical representation of missing data on primary endpoint will be displayed. Specifically, a KM plot will be constructed by considering as Event the missingness of primary endpoint, and subjects with non-missing primary endpoint will be censored.

Status	Outcome	Date
Subjects reach Visit M6 but primary endpoint missing	Event	Visit M6 date
Subjects discontinued the study prior M6	Event	Date of discontinuation
Subjects with primary endpoint result	Censored	Date of primary endpoint assessment

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 6). 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 following study period definitions and the available parts of the onset and the end dates (see Table 6):

'On treatment' period is defined as time from first dose of IMP up to Month 12 Visit (excluded) or, in case of treatment discontinuation/completion, up to date of last IMP intake.

'Follow-up' period is defined as time from Month 12 Visit up to end of study or, in case of treatment discontinuation/completion, from the day after last IMP intake up to end of study.

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 serious TEAEs, 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[7];

- the respective number of patients at risk and Kaplan-Meier estimates at different time points;
- the median and its 95% confidence interval;
- the log-rank test p-value.

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

8.2 Clinical laboratory evaluation

Analysis of clinical laboratories data will be performed by treatment for Hematology and Biochemistry tests. In case of different units of measure considered for the same laboratory parameter, all values will be converted into Standard International (SI) units (if applicable) or to the same unit.

The following summaries will be provided:

- A summary table showing for all laboratory tests the values and changes from baseline to each subsequent visit;
- A summary table showing for all laboratory tests the frequency of patients reporting an abnormal (clinically or not clinically significant) laboratory value at baseline 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.

Proportion of patients reporting an abnormal laboratory value will be provided by visit. CS abnormal values at any visit will be reported as well.

8.3 Vital signs

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

- Vital signs:
  - Systolic Blood Pressure (mmHg),
  - Diastolic Blood Pressure (mmHg), and
  - Heart Rate (bpm);
- eGDR and BMI evaluations:
  - Weight (Kg) and Height (cm),

- BMI (Kg/m^2) – derived from CRF,
- Waist circumference (cm) and Waist-to-Hip Ratio,
- Hypertension status (Yes, No).

8.4 ECGs

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

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

8.5 Pregnancy test over the study

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

9. Derivations and date convention

9.1 Variable derivation

[redacted]	Standard/Forms/Template			
	Title	Statistical Analysis Plan Template		
	Code	Version	Effective Date	Page
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Table 3: Variable derivation rules

Parameter	Calculation
AUC	All AUC calculations (0-120min and 15-120min for C-peptide) will be based on actual rather than scheduled timings and will be calculated using the [redacted]. 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 [redacted]; • 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. [redacted] will be performed after calculation of average basal values. 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); In case both Basal #1 and Basal #2 C-peptide are missing, the Average Basal C-peptide will be set as missing. C-peptide Cmax (nmol/L) = Maximum C-peptide value between post basal values; C-peptide Tmax (min) = Earliest time at which the C-peptide Cmax is reached Always use actual timepoint, unless time is missing then use scheduled timepoint.

Parameter	Calculation
Time from T1D diagnosis to informed consent	Time from T1D diagnosis to IC (days) = Date of IC signature - Date of T1D diagnosis +1. Missing/partial dates will not be imputed. Since these dates are crucial for enrolment, their complete presence in the final database is expected.
Time from first insulin administration to informed 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. Since these dates are crucial for enrolment, their complete presence in the final database is expected.
Date of first/last IMP intake	Date of first IMP is the date of first IMP administration at C1 (from CRF IMP dispensation form, random visit) . Date of last IMP is the date collected in CRF under End of Treatment form. If the subject discontinued the IMP and the date in EOT form is missing, the latest date between last cycle X date and last date reported in the diary 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.
Subjects who don't require insulin therapy	At timepoint X, a subject doesn't require insulin therapy if "Average Insulin Requirement" in "Daily Insulin Requirement Evaluation" form is equal to 0.
CGM parameters	See section 9.2

Parameter	Calculation
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 closest 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.
Conversion of Time Intervals	If a time interval was calculated in minutes, hours or days and needs to be converted into months or years the following conversion factors will be used: • 1 month = 30.4375 days • 1 year = 365.25 days
Cycle X	For Visit X: Cycles are assigned based on the variable name as from the CRF design (IMP and IMPACC forms). The number contained in the variable names goes from 1 to 13 and corresponds to the cycle number. For Unscheduled visits: Kit number is used to link the corresponding cycle to compliance information.

9.2 CGM value derivation

The [redacted] Continuous Glucose Monitoring System [redacted] will be used to perform CGM during the study. [redacted] 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 [redacted].

Gaps in glucose data shorter or equal than 30 minutes will be imputed using [redacted]. 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 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 7.2.2.3 and 7.2.2.7). The package has been modified in order to perform additional simultaneous analyses (see Appendix 12.1 for the entire R code). Table 6 reports the correspondence between required endpoint and cgmvariables outcomes.

For the calculation of 2h PPG, the raw data from [redacted] have to be filtered in order to keep only observations at approximately 120 minutes from meals (observations at 120 ± 5 minutes from a meal), where the exact time of meals (breakfast, lunch and dinner) are taken from eDiary/paper Diary. The filter on CGM data will be done in CSV files, prior importing them in R to calculate CGM parameters. If time of meal is missing, the adjacent CGM observations will not be considered. In case of duplication of results (i.e. both paper Diary and eDiary have been compiled), the record with date/time not missing will be used. If still duplicated, the type of diary assigned at randomization will be used.

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_sensor*	mg/dL

**raw data must be filtered with observations 120 ± 5 minutes from meals (eDiary)*

9.3 Seed numbers to be used for MI strategies

Table 5: Seed numbers

Analysis	Seed number
All analyses – baseline value imputation	40482
Primary analysis (MI-RD)	200582
Primary analysis (J2R)	200582
Sensitivity analysis (PP)	200582
Sensitivity analysis (Tipping point)	200582
Imputation intermittent missingness	240115
Sensitivity analysis (MAR –monotone missing data)– active treatment	1804
Sensitivity analysis (MAR –monotone missing data) – Placebo	2508

Analysis	**Seed number**
Exploratory efficacy analysis [(2-hour AUC_{mean}+1]	200582

9.4 Partial date convention

Table 6: Algorithm for Treatment Emergence of Adverse Events

AE START DATE	AE STOP DATE	RULE for TEAE definition	RULE for "Treatment"/"Follow-up" study period definition for TEAE summaries
Known	Known, Partial or Missing	If AE start date < IMP start date, then not TEAE If AE start date >= IMP start date, then TEAE	*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.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st	

[redacted]	Standard/Forms/Template			
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AE START DATE	AE STOP DATE	RULE for TEAE definition	RULE for "Treatment"/"Follow-up" study period definition for TEAE summaries
		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.*

NOTE: For the calculation of AE rates in the follow-up period, only patients remaining after treatment discontinuation/completion OR who have reached Month 12 visit will be considered in the denominator.

Table 7: Algorithm for Prior/Concomitant medications

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

10. Tables, Figures and Listings

10.1 Output convention:

- 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 randomized treatment, and sorted by the patient number, treatment group and visit.
- In all the listings on safety variables, treatment misallocation will be identified based on the randomized/actual treatment column..
- 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.
- The last footnote of each listing will be a footer indicating the program name, the date and time of generation and the SAS® version used.

10.2 List of TLFs and specifications

- The full list of TLFs for DMC, main statistical analysis and final analysis, will be provided in a separate document (Appendix I, Section 12.2). SAS code for main efficacy analysis will be provided in a separate document

11. Literature

1. Study protocol, A phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 400 mg twice a day oral ladarixin in patients with recent onset type 1 diabetes and a low residual β-cell function at baseline, Protocol Version - Date: Version No. 4 final – 31 March 2022.
2. Study protocol, A phase 3, 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 a low residual β-cell function at baseline, Protocol Version - Date: Version No. 2 final – 7 July 2020.
3. Study protocol, A phase 3, 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 a low residual β-cell function at baseline, Protocol Version - Date: Version No. 3 final – 30 July 2020.
4. Study Amendment No 2 - Final version 31 Mar 2022.
5. Lachin JM et al., Sample size requirements for studies of treatment effects on beta-cell function in newly diagnosed type 1 diabetes. PLoS ONE 2011; 6:e26471.
6. Vigers T, Chan CL, Snell-Bergeon J, Bjornstad P, Zeitler PS, Forlenza G, et al. (2019) Cgmanalysis: An R package for descriptive analysis of continuous glucose monitor data. PLoS ONE 14 (10): e0216851. https://doi.org/10.1371/journal.pone.0216851
7. Kalbfleisch, J. D., and Prentice, R. L. (1980). The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons.
8. Study protocol, A phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the effect and safety of 400 mg twice a day oral ladarixin in patients with recent onset type 1 diabetes and a low residual β-cell function at baseline, Protocol Version - Date: Version No. 5.1– 12 October 2023.
9. Piemonti L, Keymeulen B, Gillard P, et al. Ladarixin, an inhibitor of the interleukin-8 receptors CXCR1 and CXCR2, in new-onset type 1 diabetes: A multicentre, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2022 Sep;24(9):1840-1849. doi: 10.1111/dom.14770.

12. Appendices

12.1 R code for CGM

R code	Notes
[redacted]	

[redacted]	Standard/Forms/Template			
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R code	Notes
[redacted]	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
[redacted]	

[redacted]	Standard/Forms/Template			
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R code	Notes
[redacted]	

[redacted]	Standard/Forms/Template			
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R code	Notes
[redacted]	

R code	Notes
[redacted]	

[redacted]	Standard/Forms/Template			
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R code	Notes
[redacted]	

R code	Notes
[redacted]	

[redacted]	Standard/Forms/Template			
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R code	Notes
[redacted]	

R code	Notes
[redacted]	

[redacted]	Standard/Forms/Template			
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R code	Notes
[redacted]	

[redacted]	Standard/Forms/Template			
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R code	Notes
[redacted]	

R code	Notes
[redacted]	[redacted]

R code	Notes
[redacted]	

[redacted]	Standard/Forms/Template			
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R code	Notes
[redacted]	[redacted]

R code	Notes
[redacted]	

R code	Notes
[redacted]	[redacted]

R code	Notes
[redacted]	[redacted]

12.2 Appendix I

Tables, Figures and Listings shells will be included in a separate document.
The selected list of outputs for the specific analyses, e.g. DMC and final analysis are provided in the document '[redacted].

12.3 Appendix II

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

where TRT01PN = 1 = Ladarixin and 2 = Placebo.

12.4 Appendix III

```
proc mixed data=input_dataset;
  class siteid usubjid trt01pn avisitn agegr1n sexn bmigrn;
  model aval2 = trt01pn trt01pn*avisitn avisitn agegr1n sexn bmigrn / ddfm=kr solution;
  repeated avisitn / subject=usubjid type=TYPE r;
  random siteid / subject=usubjid;
```

lsmeans trt01pn trt01pn*avisitn / pdiff cl; run;

Where TYPE= ”toeph", "toep" or "cs" depending on covariance structure used according to section 7.2.1.4.

docusign

Certificate Of Completion

Envelope Id: [redacted]
Status: Completed
Subject: Complete with Docusign: LDX0319_SAP_v4.0_2025-07-04.docx
Source Envelope:
Document Pages: 86
Signatures: 4
Envelope Originator:
Certificate Pages: 6
Initials: 0
[redacted]
AutoNav: Enabled
[redacted]
EnvelopeId Stamping: Disabled
IP Address: [redacted]
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking

Status: Original
7/4/2025 5:32:50 AM
Holder: [redacted]
[redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 7/4/2025 5:44:21 AM Viewed: 7/4/2025 5:45:01 AM Signed: 7/4/2025 5:45:42 AM
Electronic Record and Signature Disclosure: Not Offered via Docusign		
[redacted] Security Level: Email, Account Authentication (Required)	Signed by: [redacted] Signer Name [redacted] Signing Reason: I approve this document Signing Time: 04-Jul-2025 | 11:49:30 CEST [redacted] Signature Adoption: Drawn on Device Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 7/4/2025 5:44:22 AM Viewed: 7/4/2025 5:46:41 AM Signed: 7/4/2025 5:50:34 AM
Electronic Record and Signature Disclosure: Accepted: 7/4/2025 5:46:41 AM ID: [redacted]		

Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 7/4/2025 5:44:22 AM Viewed: 7/7/2025 6:59:23 AM Signed: 7/7/2025 7:00:40 AM
Electronic Record and Signature Disclosure: Accepted: 3/15/2023 6:53:34 AM ID: [redacted]		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 04-Jul-2025 | 13:20:36 CEST [redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 7/4/2025 5:44:23 AM Viewed: 7/4/2025 7:20:32 AM Signed: 7/4/2025 7:21:00 AM
Electronic Record and Signature Disclosure: Accepted: 7/4/2025 7:20:32 AM ID: [redacted]		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	7/4/2025 5:44:23 AM
Certified Delivered	Security Checked	7/4/2025 7:20:32 AM
Signing Complete	Security Checked	7/4/2025 7:21:00 AM
Completed	Security Checked	7/7/2025 7:00:40 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 12/13/2021 12:58:48 PM
Parties agreed to: [redacted]

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You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: [redacted]

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To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at [redacted] and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

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To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to [redacted] and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

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To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to [redacted] and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

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To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

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- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify [redacted] - Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by [redacted] - Part 11 during the course of your relationship with [redacted] - Part 11.

Dompé

Note to File

Study #: LDX0319

Protocol Title: A phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the effect and safety of 400 mg twice a day oral ladarixin in patients with recent onset type 1 diabetes and a low residual β-cell function at baseline.

Date: 17 July 2025

Authored by: [redacted], Biostatistician, [redacted] Dompé

Issue: During the preparation of the key first results of the final analysis, a typo was identified in SAP version 4.0 (section 9.1) concerning the limit of detection of C-peptide values and the assumed limit value used in the calculation of the primary endpoint. The SAP quotes the limit of detection to be 0.2 ng/mL, but ACM laboratories have confirmed that the limit of detection is 0.05 ng/mL.

The following rules will be followed for limit values:

- If the C-peptide value is recorded as "<0.02" with units of nmol/L then 0.02 nmol/L is to be used in the calculation of AUC.
- If the C-peptide value is recorded as "<x.xx" with units of ng/mL or Ug/L, then then values disregarding the "<" will be converted to nmol/L and used in the calculation of AUC.
- For C-peptide values without the "<", the recorded value in the raw data is used and converted to nmol/L if necessary.

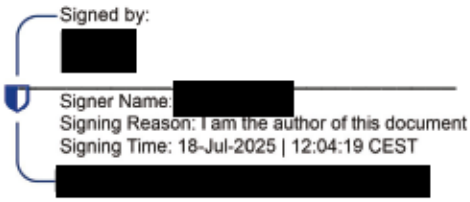
When converting values to preferred units of nmol/L, 4 decimal points will be used to record the converted value in the SDTM.

Date and Signature:

Job Title, Company: Biostatistician, [redacted] Dompé

Name: [redacted]

Signature and date



Dompé

Job Title, Company: [redacted], Dompé

Name: [redacted]

Signature and date

Signed by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 18-Jul-2025 | 17:21:33 CEST
[redacted]

Job Title, Company: Clinical Operations [redacted], Dompé

Name: [redacted]

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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 18-Jul-2025 | 11:19:13 CEST
[redacted]

Job Title, Company: [redacted] Biostatistician, [redacted]

Name: [redacted]

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Signer Name: [redacted]
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Certificate Of Completion

Envelope Id: [redacted]
Status: Completed
Subject: Complete with Docusign: LDX0319_NTF_SAP_2025-07-17.docx
Source Envelope:
Document Pages: 2
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[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 7/18/2025 5:13:56 AM Viewed: 7/18/2025 11:21:19 AM Signed: 7/18/2025 11:21:47 AM
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[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 7/18/2025 5:13:56 AM Viewed: 7/18/2025 5:14:39 AM Signed: 7/18/2025 5:15:11 AM
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Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 18-Jul-2025 | 12:04:19 CEST [redacted] Signature Adoption: Uploaded Signature Image Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I am the author of this document	Sent: 7/18/2025 5:13:57 AM Viewed: 7/18/2025 6:04:13 AM Signed: 7/18/2025 6:04:50 AM
Electronic Record and Signature Disclosure: Accepted: 7/18/2025 6:04:13 AM ID: [redacted]		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 18-Jul-2025 | 11:19:13 CEST [redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 7/18/2025 5:13:57 AM Viewed: 7/18/2025 5:19:07 AM Signed: 7/18/2025 5:19:39 AM
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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	7/18/2025 5:13:57 AM
Certified Delivered	Security Checked	7/18/2025 5:19:07 AM
Signing Complete	Security Checked	7/18/2025 5:19:39 AM
Completed	Security Checked	7/18/2025 11:21:47 AM

Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

Electronic Record and Signature Disclosure created on: 12/13/2021 12:58:48 PM
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Note to File

Study #: LDX0319

Protocol Title: A phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the effect and safety of 400 mg twice a day oral ladarixin in patients with recent onset type 1 diabetes and a low residual β-cell function at baseline.

Date: 4 September 2025

Authored by: [redacted] Biostatistician, [redacted] Dompé

Issue:

During the first review of the final analysis outputs and listings several issues were identified that required clarification.

Since the unlocking and relocking of the database in August 2025 was performed and hip measurement data was corrected for site 55, the sensitivity analysis outlined in section 7.2.1.8 will now only exclude data from site 054.

The categorization of the IL-6 values in section 7.3 will be updated to present the categories as follows:

- <=2.06
- 2.06 < IL-6 <=4.78
- 4.78 < IL-6

All imputations of data at the limit of detection will be unchanged.

Finally, for derivation of HLA DR-DQ haplotypes the following changes will be made to avoid overlapping categories:

- For DRB1*03/DRB1*X: “If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres not in ("DR4", "DR17", " ") and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres = “DR17” (or viceversa)”
- For DRB1*04/DRB1*x: “If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres = "DR4" and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres not in (“DR4”, "DR17", " ") (or viceversa)”
- For Non DR3/Non DR4: “If lab_acm.lbtestcd = “HD1S1” and lab_acm.lborres not in ("DR4", "DR17", " ") and lab_acm.lbtestcd =“HD1S2” and lab_acm.lborres not in ("DR4", "DR17", " ") (or viceversa)” .

Date and Signature:

Job Title, Company: Biostatistician, [redacted] Dompé

Name: [redacted] on behalf of [redacted]

Signature and date

_____

Job Title, Company: [redacted], Dompé

Name: [redacted]

Signature and date

_____

Job Title, Company: Clinical Operations [redacted], Dompé

Name: [redacted]

Signature and date

_____

Dompé

Job Title, Company: [redacted] Biostatistician, [redacted]

Name: [redacted] on behalf of [redacted]

Signature and date

_____

Dompé

Note to File

Study #: LDX0319

Protocol Title: A phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the effect and safety of 400 mg twice a day oral ladarixin in patients with recent onset type 1 diabetes and a low residual β-cell function at baseline.

Date: 9 September 2025

Authored by: [redacted], Biostatistician, [redacted] Dompé

Issue: During the first review of the final analysis outputs, it was noted that the analysis of severe hypoglycemia (Tables 14.2.4.5.1 and 14.2.4.5.2) required clarification. There were a number of subjects that had instances of more than 1 severe hypoglycemia event occurring within a day, and only the first event of each day was being included in the statistical model. This situation had not been covered in the SAP.

For the final outputs, the model will be updated to take account of multiple events within a day. Multiple events occurring within a day will be counted as distinct if they occur more than 120 minutes apart. If events occur <=120 minutes apart on the same day, only the first of those events will be considered in the analysis and will serve as the reference start point for the 120-minute period surrounding that event.

All severe hypoglycemia events will be presented in Listing 16.2.6.1.4 with events not considered in the analysis highlighted.

Date and Signature:

Job Title, Company: Biostatistician, [redacted] Dompé

Name: [redacted]

Signature and date

_____

Job Title, Company: [redacted], Dompé

Name: [redacted]

Signature and date

_____

Job Title, Company: Clinical Operations [redacted], Dompé

Name: [redacted]

Signature and date

_____

Dompé

Job Title, Company: [redacted] Biostatistician, [redacted]

Name: [redacted] on behalf of [redacted]

Signature and date

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Dompé

Note to File

Study #: LDX0319

Protocol Title: A phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the effect and safety of 400 mg twice a day oral ladarixin in patients with recent onset type 1 diabetes and a low residual β-cell function at baseline.

Date: 2 October 2025

Authored by: [redacted], Biostatistician, [redacted] Dompé

Issue: Upon reviewing the second draft of the main statistical analysis, it was noticed that in table 14.2.5.7.1, the p-value presented in the outputs for the comparison between treatments assumes unequal variances. It was subsequently clarified that the following procedure was applied to all t-tests to assess the equality of variances:

An initial test for equality of variances was conducted using the Folded-F test at a significance level of α=0.05. If the resulting p-value (ProbF) was less than 0.05, unequal variances were assumed, and the Welch/Satterthwaite p-value was reported. If the p-value was greater than or equal to 0.05, or if the result was missing, equal variances were assumed, and the pooled t-test p-value was used.

The choice of p-value will be clarified in a footnote.

Date and Signature:

Job Title, Company: Biostatistician, [redacted] Dompé

Name: [redacted] on behalf of [redacted]

Signature and date

Signed by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 08-Oct-2025 | 17:17:02 CEST
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Job Title, Company: [redacted], Dompé

Name: [redacted]

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Name: [redacted]

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Job Title, Company: [redacted] Biostatistician, [redacted]

Name: [redacted] on behalf of [redacted]

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