Statistical Analysis Plan

Dompé farmaceutici S.p.A.

Study Number: MEX0114

EudraCT Number: 2014-003968-20

Test Product: Ladarixin

A phase 2, multicentre, 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.

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Version Number and Date: Final Version 4.4, 17SEP2019

Statistical Analysis Plan Signature Page

Statistical Analysis Plan Final Version 4.4 (Dated 17SEP2019) for Protocol MEX0114.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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TFL Shells Signature Page

TFL Shells Final Version 4.4 (Dated 17SEP2019) for Protocol MEX0114.

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Upon review of this document, the undersigned approves this version of the Output Templates, authorizing that the content is acceptable for the reporting of this study.

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Modification History

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Version 1.0	18OCT2016	Claudio Iannacone	N/A – first version
Version 1.1	17JUL2017	Claudio Iannacone	Previous version not yet approved. No significant changes in the document. Minor changes to the body text.
Version 1.2	02AUG2017	Claudio Iannacone	Previous version not yet approved. No significant changes in the document. Minor changes to the body text.
Version 1.3	08SEP2017	Claudio Iannacone	Previous version not yet approved. No significant changes in the document. Minor changes to the body text.
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Version 2.0	06OCT2017	Claudio Iannacone	Version approved by Dompé farmaceutici on 09OCT2017.
Version 3.0	07JUN2019	Claudio Iannacone	Significant changes vs version 2.0: – Added two new efficacy endpoints (Proportion of patients maintaining a residual β-cell function) at weeks 13, 26, and 52 and C-peptide AUC above fasting value at weeks 13, 26, and 52); – Subgroups analyses on efficacy endpoints according to age class and fasting C-peptide on screening; – Added new major deviations criteria for exclusion from Per-protocol analysis set.
Version 4.0	26JUN2019	Claudio Iannacone	Version 3.0 not yet approved. Significant changes vs version 3.0: - C-peptide AUC above fasting value calculated also at Baseline;

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
			– BUN values will not be analyzed or listed in the statistical analysis.
Version 4.1	02JUL2019	Claudio Iannacone	Version 4.0 not yet approved. Used for revision and comments Significant changes vs version 4.0: - Added as secondary efficacy endpoints "Percent change from baseline of 2-hour AUC of C-peptide response to the MMTT" and "Proportion of patients with HbA1c < 7% and absence of episodes of severe hypoglycaemia from the previous visit"; - Cmax and Tmax of C-peptide analyzed over the study by means of a mixed linear model; - Descriptive analysis of demographics and other baseline characteristics performed on the ITT population;
Version 4.2	03SEP2019	Claudio Iannacone	Version 4.1 not yet approved. Used for revision and comments. Significant changes vs version 4.1: - Changed the approach used to address missing values in C-peptide values in MMTT; - Added an explorative analysis on AUC C-peptide stratified by the number of positivity in auto-antibodies at Screening visit; - Change the rule to define Prior and Concomitant Medications; - Classification of protocol deviations in minor and major categories removed;
Version 4.3	06SEP2019	Claudio Iannacone	Version 4.2 not yet approved. Used for revision and comments. No significant changes made vs version 4.2. Added in the document more details regarding the derivation and the statistical analysis of the variables.
Version 4.4	17SEP2019	Claudio Iannacone	Version 4.3 not yet approved. Used for revision and comments. No significant changes made vs version 4.3.

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
			- Added more details for the calculation of exposure to study medication - Added a summary table for the major protocol deviations - Added the analysis of the exploratory endpoint "Proportion of responders at week 52" (for definition see paragraph 16.3.1)

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ADA	American Diabetes Association
ADaM	Analysis Data Model
ADR	Adverse Drug Reaction
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CLcr	Calculated Creatinine Clearance (Cockcroft - Gault formula)
Cmax	Maximum Plasma Concentration
CRF	Case Report Form
CS	Clinically Significant
DBP	Diastolic Blood Pressure
dL	Deciliter
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ENR	Enrolled Analysis Set
g	Gram
HbA1c	Glycated Haemoglobin
HR	Heart Rate
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ITT	Intent to Treat Analysis Set
i.v.	Intravenous
IU	International Unit
kg	Kilogram
L	Litre
LLN	Lower Limit of Normal
MCR	Mediolanum Cardio Research
MedDRA	Medical dictionary for drug regulatory activities
mg	Milligram
miR-375	MicroRNA-375
mL	Millilitre
MMTT	Mixed Meal Tolerance Test

msec	Millisecond
NCS	Not Clinically Significant
ng	Nanogram
nmol	Nanomole
PT	Preferred Term
QTc	Corrected QT interval
QTcF	Fridericia's corrected QT interval
RND	Randomized Analysis Set
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAS	The Statistical Analysis System (software)
SBP	Systolic Blood Pressure
SDTM	Study Data Tabulation Model
SEM	Standard Error of the Mean
s.c.	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
Tmax	Time to reach Maximum Plasma Concentration
T1D	Type 1 Diabetes
ULN	Upper Limit of Normal
µg	Microgram
µmol	Micromole
WHO-DD	World Health Organization Drug Dictionary
WHO-DRL	World Health Organization Drug Reference List

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, exploratory and safety data for Protocol MEX0114. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on study protocol version 2, dated 27th August 2015. This SAP takes as well into account:

- Amendment No.1 version 1, dated 7th March 2016, applicable to the belgian investigational sites only
- Amendment No.2 version 1, dated 20th July 2016, applicable to the german investigational sites only

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. STUDY OBJECTIVES

The objective of this clinical trial is to investigate whether Ladarixin has sufficient activity (preservation of β-cell function and slowdown of the progression of type 1 diabetes) to warrant its further development. The safety of Ladarixin in the specific clinical setting will be also evaluated.

3.2. STUDY ENDPOINTS

3.2.1. EFFICACY ENDPOINTS

- 2-hour AUC of C-peptide response to the MMTT [**Primary endpoint**. Time point: week 13±1].
- 2-hour AUC of C-peptide response to the MMTT [Time points: baseline, weeks 26±2 and 52±2].
- Percent change from baseline of 2-hour AUC of C-peptide response to the MMTT [Time points: weeks 13±1, 26±2 and 52±2].
- Average (previous 3 days) insulin requirement (IU/kg/day) [Time points: baseline, weeks 13±1, 26±2 and 52+2]. For the patients reporting “off insulin” response in the CRF the daily insulin requirement value will be conventionally set to zero in the statistical analysis.
- HbA1c levels [Time points: baseline, weeks 13±1, 26±2 and 52±2].
- Basal (2 basal samples in the range between -20 to 0 min) to 180 min time course of C-peptide and glucose derived from the MMTT [Time points: baseline, weeks 13±1, 26±2 and 52±2].
- Cumulative severe hypoglycemic events occurring from randomization [Time points: weeks 13±1, 26±2 and 52±2].
- Proportion of patients maintaining a residual β-cell function [Time points: baseline, weeks 13±1, 26±2 and 52±2].
- Proportion of patients with HbA1c < 7% and absence of episodes of severe hypoglycemia from the previous visit [Time points: weeks 13±1, 26±2 and 52+2].
- C-peptide AUC (15-120 min) above fasting value [Time points: baseline, weeks 13±1, 26±2 and 52±2].

3.2.2. EXPLORATORY ENDPOINTS

- Basal (2 basal samples in the range between -20 to 0 min) to 180 min time course of glucagon derived from the MMTT [Time points: baseline, weeks 13±1, 26±2 and 52±2].
- Auto-antibodies (GAD, IA-2, IAA, ZnT8), [Time points: baseline, weeks 13±1, 26±2 and 52±2].
- MicroRNA-375 (miR-375) [Time points: baseline, weeks 13±1, 26±2 and 52±2].
- T-cell response ex vivo to major β-cell antigens (pro-insulin, GAD65) - selected sites only [Time points: baseline, weeks 13±1, 26±2 and 52±2].
- 2-hour AUC of C-peptide response to the MMTT stratified by the number of positivity in auto-antibodies (1, 2, 3, and 4) at Screening visit.

3.2.3. SAFETY ENDPOINTS

Vital signs (blood pressure and heart rate) [time points: Screening, end of 1st treatment cycle (i.e. pre-dose visit, 2nd cycle), week 13+1].

Routine laboratory tests (hematology, clinical chemistry) [time points: Screening, end of 1st treatment cycle (i.e. pre-dose visit, 2nd cycle), weeks 13±1 (or withdrawal)].

Incidence of Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs) [time frame: throughout the study].

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

4.1.1. DESCRIPTION OF THE STUDY

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled study carried out in patients with new-onset type 1 diabetes (T1D) to investigate whether Ladarixin has sufficient activity (preservation of β-cell function and slow-down of the progression of T1D) to warrant its further development.

4.1.2. SAMPLE SIZE

Seventy-two (72) patients with new-onset T1D will be randomized, after consenting in written for the study and after having undergone clinical investigations for compliance with the selection criteria and approval by the Investigator.

According to the log(x+1) transformed data [initially selected by TrialNet as the appropriate transformation for MMTT C-peptide AUC] and the sample size calculated on the data stratified by an adult population (> 18 years), 72 patients will provide 85% power to detect a 50% between-group difference in the 2-hour MMTT C-peptide AUC (2:1) at 0.05 significance level (one-sided test), assuming a 24% drop-out rate.

4.1.3. DESCRIPTION OF TREATMENTS

Patients will be randomized with a 2:1 ratio to either Ladarixin or placebo. The Investigational Medicinal Product

(IMP) will be provided as hard gelatin capsules for oral administration. Ladarixin will be administered orally at the dose of 400 mg twice a day for 3 cycles of 14 days on / 14 days off. Placebo will be administered with the same treatment schedule.

The two daily doses will be administered at about 12 hours' interval (morning and evening; ideally between 8.30/9.30 and 20.30/21.30). At each administration, 2 capsules will be swallowed with a glass of water, at least 2 hours apart from breakfast or dinner.

4.1.4. DESCRIPTION OF THE STUDY FLOW

Each patient will be involved in the study for a screening period up to 100 days followed by a post-randomization period up to 52±2 weeks.

The study consists of the following periods:

1) **Screening period**, including 2 or more visits during a period up to 100 days; this includes the time required to confirm the diagnosis.

Potential study patients with a recent clinical diagnosis of T1D will be identified from those referring to the site for diagnosis confirmation (auto-antibody testing) and/or disease management.

Enrolment is defined as signature of the Informed Consent Form (ICF) for study participation. From enrolment, patients will be admitted to an intensive diabetes management, according to current ADA recommendation. Patients will self-monitor glucose levels at least 4 times a day and will take insulin as prescribed by the Investigator throughout the study participation. To ensure standardized glycemic control in the treatment groups, the Investigator will provide guidance for insulin regimen adjustment.

Compliance with inclusion/exclusion criteria will be finally verified vs demographic, laboratory test results and clinical information (baseline assessments to be completed within 3 weeks before randomization).

2) **Randomization:** Patients fulfilling **all** the inclusion criteria and **none** of the exclusion criteria will be randomized, randomization to occur within 100 days from the 1st insulin administration. Randomization is defined as **Study Day 0** with reference to day when IMP administration is started, which is defined as **Study Day 1**.
3) **Treatment period**, including 3 treatment cycles of 2 weeks each with 2 weeks' interval between cycles and 2 corresponding pre-dose assessment visits.

Assessments to be done before the 1st dose in the 1st treatment cycle are part of the screening evaluation. Thereafter, patients will refer to the site within 1 week ("pre-dose visits") before the expected date when the 2nd or 3rd treatment cycle is due to start to confirm no condition that prevents their continuing participation into the study has arisen. The amount of IMP for each treatment cycle will be dispensed only after compliance with criteria for drug administration has been confirmed.

4) **Follow-up period**: 3 follow-up visits scheduled at weeks 13±1 (month 3), 26±2 (month 6) and 52±2 (month 12).

4.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 14.3 of the study protocol; additional events for the Belgian and German investigational sites can be found in Section 14.3 of Amendment No.1 (for Belgian investigational sites) and of Amendment No.2 (for German investigational sites).

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

1) Primary analysis of primary efficacy variable has been modified in order to be consistent with the definition of the primary endpoint.

In the study protocol the following analysis was proposed:

"The 2-hour C-peptide AUC after the MMTT at week 13±1 will be analyzed with Student t-test for unpaired data using PROC TTEST within SAS®, including terms for treatment and Centre. The estimated treatment difference between Ladarixin and placebo will be also presented together with the corresponding 95% confidence interval."

In the present SAP the primary analysis has been modified as follows:

"The 2-hour C-peptide AUC after the MMTT (log(x+1) transformed data) at week 13±1 will be analyzed with Student t-test for unpaired data using PROC TTEST within SAS®, including terms for treatment. The estimated treatment difference between Ladarixin and placebo will be also presented together with the corresponding 95% confidence interval.".

2) The analysis corresponding to the 2-hour AUC C-peptide (log(x+1) transformed data) secondary efficacy endpoint has been reformulated as "The comparisons between groups on 2-hour AUC of C-peptide efficacy endpoint will be carried-out using a mixed linear model with 2-hour AUC of C-peptide as dependent variable, treatment group, visit, treatment by visit interaction 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 study protocol the following was stated: "Analysis of the 2-hour AUC of C-peptide at the 3 time points (baseline, weeks 26±2 and 52±2) will be performed through a single repeated measurements model using PROC MIXED within SAS®. The adjusted least square means will be estimated for each combination of time point and treatment. The treatment effect within each time point will be compared using a two-sided test at 0.05 level. The tests of the fixed effects will be presented, together with the estimated least squares means and summary statistics of the AUC for each of the two treatments at each time point. The estimated treatment difference between Ladarixin and placebo at each time point will be presented together with the corresponding 95% confidence interval. The confidence interval will be generated at a statistical level of 0.05".

3) The analysis corresponding to the average insulin requirement secondary efficacy endpoint has been reformulated as "The comparisons between groups on insulin requirement secondary efficacy endpoints will be carried-out using a mixed linear model with average daily insulin requirement as dependent variable, treatment group, visit, treatment by visit interaction 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 study protocol, the following was stated: "The mean in average daily insulin requirement at the 4 time points (baseline, weeks 13±1, 26±2 and 52±2) will be analysed using a repeated measurements model using PROC MIXED within SAS®."

4) The analysis corresponding to the HbA1c secondary efficacy endpoint has been reformulated as "The comparisons between groups on HbA1c secondary efficacy endpoint will be carried-out using a mixed linear model with HbA1c value as dependent variable, while treatment group, visit, treatment by visit interaction 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 study protocol, the following was stated: "The mean in HbA1c value at the 4 time points (baseline, weeks 13±1, 26±2 and 52±2) will be analysed using a repeated measurements model using PROC MIXED within SAS®."

5) In the study protocol, the default summary statistics for quantitative variables were the number of observations (n), mean, standard deviation (SD), standard error of the mean, median, minimum (min) and maximum (max), lower and upper 95% confidence limits for those patients with data.

This was modified as follows:

"The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) for those patients with data. For quantitative efficacy

variables, standard error of the mean and lower and upper 95% confidence limits (CI) will be also presented."

6) The analyses of new efficacy endpoints have been planned:
   - Proportion of patients maintaining a residual β-cell function [Time points: weeks 13±1, 26±2 and 52±2].
   - C-peptide AUC (15-120 min) above fasting value [Time points: baseline, weeks 13±1, 26±2 and 52±2].
   - Percent change from baseline of 2-hour AUC of C-peptide response to the MMTT [Time points: weeks 13±1, 26±2 and 52±2].
   - Proportion of patients with HbA1c < 7% and absence of episodes of severe hypoglycemia from the previous visit [Time points: weeks 13±1, 26±2 and 52+2].
   - Proportion of responders at week 52, defined as patients with percent decrease from baseline in 2-hour AUC of C-peptide above the median percent decrease from baseline to Week 52.
7) Planned subgroups descriptive analyses on the efficacy endpoints according to age class at Screening (≤ 25 and > 25 years) and to fasting C-peptide (Pre-MMTT) (≤ median value and > median value) at Screening visit.
8) A subgroup analysis on 2-hour AUC of C-peptide response to the MMTT stratified by the number of positivity in auto-antibodies (1, 2, 3, and 4) at Screening visit has been planned.
9) The approach to deal missing C-peptide values has been changed: the sentence "missing C-peptide values will be imputed via linear interpolation" of the study protocol has been changed in "Missing C-peptide values will be imputed with the average of the C-peptide value that precedes and follows the missing value. Missing data in C-peptide at 180 minutes (final) will be replaced by the last non-missing value.".
10) In the study protocol was stated "When C-peptide values are below the limit of detection (0.2 ng/mL), a value of 0.2 ng/mL will be assumed in the calculation of area under the curve." This rule to address the C-peptide values below 0.2 ng/mL will not be applied. C-peptide values will analysed as reported in the CRF.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

1. No analyses for Data Monitoring Committee (DMC) meeting or Interim Data Analysis are scheduled;
2. Interim transfer of clinical data listings: four interim transfers are expected during the study, upon request of the Sponsor;
3. Only the Final Analysis will be performed for this study.

Statistical analysis will be performed by SPARC Consulting, Milan, Italy on behalf of IQVIA RDS Italy, Milan, Italy on study data provided by Mediolanum Cardio Research (MCR), Milan, Italy.

SAS source (raw) data will be transferred as SAS datasets, together with laboratory reference range, and any support datasets. Transfer will occur via secured (encrypted, password-protected e-mail).

The statistical analysis will be based on analysis datasets according to the CDISC format.

Production SAS programmers will create SDTM datasets from the Source (Raw) datasets as per the mapping instructions given in the SDTM mapping specifications. Simultaneously, the Validation (QC) SAS programmer will create the same SDTM datasets independently and will do a comparison with production datasets to validate them. Similarly, ADaM datasets will be created from SDTM datasets as per ADaM specifications using double programming approach for production and QC.

Validated draft SDTM and ADaM datasets will be sent to the Study Lead Biostatistician for review and approval.

When the final source data transfer is made available (after database lock), the production and validation programs will be re-run to create the final SDTM and ADaM datasets deliverable to be used for the final statistical analysis.

The statistical SAS output generated after running SAS programs will be copied in a Word file and paginated as specified in the Paragraph 18 of this document.

Tables, Listings and Figures will be presented according to TFL Shells Version 4.4 (Dated 17SEP2019).

5.1. DATA MONITORING COMMITTEE (DMC)

There will be no statistical analyses for DMC for this study.

5.2. INTERIM ANALYSIS

There will be no Interim Analysis for this study.

5.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by SPARC Consulting, Milan, Italy on behalf of IQVIA RDS Italy, Milan, Italy following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Study Treatment.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) for those patients with data. For quantitative efficacy variables, standard error of the mean (SEM) and lower and upper 95% confidence limits (CI) for mean will be also presented.

For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. If appropriate, 95% confidence intervals around the proportions will be presented using the Clopper-Pearson's formula.

6. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be performed on a case-by-case basis before the database lock. A blind data review meeting will be held before database lock and before opening randomization codes, in order to assign the patients to each of the analysis sets according to the specified definitions. Patient's exclusion from each of the analysis sets will be documented and justified in a Blind Data Review Report.

6.1. ALL SUBJECTS ENROLLED SET [ENR]

The enrolled (ENR) set will contain all patients who provided informed consent for this study.

6.2. RANDOMIZED ANALYSIS SET [RND]

The Randomized Analysis (RND) set will contain all patients in the ENR set who were randomized to the study, regardless of whether they received study medication or not.

6.3. SAFETY ANALYSIS SET [SAF]

The Safety Analysis (SAF) set will contain all patients in the RND set who received any study medication and will be based on the treatment actually received.

6.4. INTENT TO TREAT SET [ITT]

The Intent to Treat (ITT) set will contain all patients who were randomized and received at least one dose of study medication (either Ladarixin or placebo). It will be based on the treatment randomized, regardless of the treatment actually received. The ITT set will be used to present efficacy data.

6.5. PROTOCOL DEVIATIONS

All the protocol deviations will be discussed case by case by the clinical team during the review of the data before the lock of the study database and described in the Blind Data Review Report.
However, the following protocol deviations are anticipated to be considered as major:

- Inclusion and exclusion criteria not respected;
- Received treatment other than they were randomized to;
- Missing information on IMP administration that does not allow calculation of IMP exposure/compliance;
- Overall study treatment compliance < 80%;
- Incorrect Boost dose at one or more MMTT visits;
- Missing data for the primary endpoint (AUC C-peptide from MMTT at week 13);
- Primary endpoint (AUC C-peptide from MMTT) at week 13 assessed out-of-window visit (± 1 week);
- Use of prohibited concomitant medications prior to enrolment and up to the end of the study participation (Concomitant treatment with phenytoin, warfarin, sulphanylurea hypoglycemics (e.g. tolbutamide, glipizide, glibenclamide/glyburide, glimepiride, nateglinide) and high dose of amitriptyline (> 50 mg/day), concomitant treatment with metformin, sulfonylureas, glinides, thiazolidinediones, exenatide, liraglutide, DPP-IV inhibitors or amylin, or any medications known to influence glucose tolerance (e.g. β-blockers, angiotensin-converting enzyme inhibitors, interferons, quinidine antimalarial drugs, lithium, niacin, etc.), current administration of any immunosuppressive medications (including oral, inhaled or systemically injected steroids) and use of any investigational agents, including any agents that impact the immune response or the cytokine system);
- Concurrent illnesses/TEAEs that may impact the glycemic control or trial read-out, to be defined case by case.

7. GENERAL CONSIDERATIONS

7.1. REFERENCE START DATE AND STUDY DAY

Randomization is defined as Study Day 0 with reference to day when IMP administration is started, which is defined as Study Day 1.

In general, reference start date is defined as the day of the first dose of study medication (Study Day 1: first day in

Week 1), and will appear in every listing where an assessment date or event date appears. However, different reference start date could be used in the statistical analysis according to the objective of the analysis. In such case, notes defining the reference start date will be added in the statistical tables and line listings.

Study Day will be calculated from the reference start date, and will be used to show start / stop day of assessments and events.

- If the date of the event is on or after the reference start date then:

Study Day = (date of event – reference start date) + 1

- If the date of the event is prior to the reference start date then:

Study Day = (date of event – reference start date)

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day and any corresponding duration will be presented based on the imputations specified in Appendix 2 (Partial Date Conventions).

7.2. STUDY BASELINE

Unless otherwise specified, study baseline is defined as the last non-missing measurement taken prior to IMP administration (including unscheduled assessments). In the analysis of MMTT variables (Glucose, C-peptide and Glucagon) (reported and calculated parameters) the Basal of those variables is defined as the average of the two basal values (Basal #1 and Basal #2 (pre-meal values)). If one of the two basal values is missing the non-missing basal value will be considered as Basal in the analysis of MMTT variables.

7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

No unscheduled visits have been foreseen in the study.

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.

Listings will include scheduled, unscheduled and early discontinuation data.

7.4. WINDOWING CONVENTIONS

Actual dates of visits will be used for calculations of time intervals. No visit windowing will be performed for this study. Out-of-window visits will not be reallocated to the nearest timepoint.

7.5. STATISTICAL TESTS

All statistical tests will be performed one sided with α=0.05 and 95% confidence intervals will be employed, unless otherwise specified in the description of the analyses.

7.6. COMMON CALCULATIONS

For some quantitative measurements, change from baseline will be calculated as:

- Absolute: Value at Visit X – Baseline Value

- Relative: ((Value at Visit X – Baseline Value)/Baseline Value) *100

7.7. SOFTWARE VERSION

All statistical analyses will be conducted using The SAS System version 9.4 under Windows 10 PRO operating system.

8. STATISTICAL CONSIDERATIONS

8.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

In the analysis of secondary efficacy variables 2-hour AUC of C-peptide response to the MMTT, average (previous 3 days) insulin requirement (IU/kg/day), HbA1c levels, and C-peptide AUC (15-120) above fasting value the following fixed factors will be considered in the mixed linear model:

- Treatment group
- Visit
- Treatment by visit interaction

In the analysis of percent change from baseline in 2-hour AUC of C-peptide response to the MMTT the baseline value of 2-hour AUC of C-peptide will be considered as a covariate of the mixed linear model. Moreover, treatment group, visit and the treatment by visit interaction will be the fixed effects of the mixed linear model.

In the analysis of actual values of the efficacy endpoints C-peptide, Glucose and Glucagon over the study the following fixed factors will be considered in the mixed linear model:

- Treatment group
- Visit
- Time
- Treatment by visit interaction
- Treatment by time interaction
- Treatment by visit and by time interaction

In the analysis of 2-hour AUC C-peptide according to the number of positivity in auto-antibodies counted at Screening visit the following fixed factors will be considered in the mixed linear model:

- Treatment group
- Visit
- Treatment by visit interaction
- Number of positivity
- Treatment by number of positivity interaction

8.2. MULTICENTRE STUDIES

This study will be conducted by multiple investigators at multiple centers. Site-related differences will not be evaluated and presented in the statistical output as the study does not foresee a randomization stratified by Centre.

8.3. MISSING DATA

If the actual time for Mixed Meal Tolerance Test is not recorded, the scheduled time will be used.

Missing C-peptide values will be imputed with the average of the C-peptide value that precedes and follows the missing value. Missing data in C-peptide at 180 minutes (final) will be replaced by the last non-missing value.

The last available basal sample time will be used as the first sample time in the computation of the AUC, and the average of the basal sample values (Basal #1 and Basal #2) will be used as the first sample value in the computation of the AUC.

Other missing data will not be replaced.

The number of patients with missing data will be presented under the *"unknown"* category. Missing values will be included in the denominator count when computing percentages.

When continuous data will be summarized, only the non-missing values will be evaluated for computing summary statistics.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No alpha adjustment for multiple comparisons will be introduced, because only the comparison between Ladarixin and placebo group on the primary efficacy endpoint will be considered as confirmatory.

8.5. ACTIVE-CONTROL STUDIES INTENDED TO SHOW NON-INFERIORITY OR EQUIVALENCE

Not applicable for this study.

8.6. EXAMINATION OF SUBGROUPS

Subgroup descriptive analyses will be performed on the efficacy endpoints (listed in paragraph 3.2.1) according to age class at Screening (≤ 25 and > 25 years). to fasting C-peptide (Pre-MMTT) (≤ median value and > median value) at Screening visit and to number (1 to 4) of positive auto-Ab at Screening/diagnosis . Statistical comparisons between the two treatment groups will be performed only if the number of patients (n) of the two treatment groups is quite balanced within each stratum and with n ≥ 10 per treatment group in each stratum. Such statistical comparisons will be performed using non-parametric statistical tests.

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations shell for this study and therefore the format and content of the summary tables, figures and listings to be provided.

The reference analysis set of each table and line listing is reported in the corresponding table and line listing.

10. DISPOSITION, WITHDRAWALS AND PROTOCOL DEVIATIONS

The number of patients enrolled, a summary of analysis populations, a summary of reasons for exclusion from analysis populations, a summary of reasons for premature withdrawal of patients from the study, and an individual data listing of the patients who prematurely interrupted the treatment/study will be presented.

Furthermore, a summary and an individual data listing of protocol deviations and major protocol deviations will be produced.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Summary demographic data and other baseline characteristics will be tabulated for the ITT population.

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:

- Demographic variables:
  - Age (years)
  - Gender (Male, Female)
  - Race (White/Caucasian, Asian, Black or African American, Other)
- Pregnancy test result (Positive or Negative), if appropriate
- Disease-specific information:
  - Auto-antibodies results to confirm T1D diagnosis: quantitative (IAA (U/mL), GAD (IU/mL), IA-2 (U/mL), ZnT8 (U/mL)) and qualitative, i.e. positive or negative. Quantitative results at Screening visit can be considered as “Baseline values” if sample is taken within 3 weeks prior of randomization. In case of missing values then auto-antibodies non-missing values reported at CRF page 7 will be considered as “Baseline values”.
  - Baseline Auto-antibodies quantitative results (IAA (U/mL), GAD (IU/mL), IA-2 (U/mL), ZnT8 (U/mL)),
  - Baseline insulin (IU/kg/day) and HbA1c (%) results
- Vital Signs:
  - Height (cm)
  - Weight (Kg)
  - Systolic Blood Pressure (mmHg)
  - Diastolic Blood Pressure (mmHg)
  - Heart Rate (bpm)
- Baseline 12-Lead ECG:
  - ECG Result (Normal, Abnormal not clinically significant, Abnormal clinically significant)
  - QT corrected for HR with Fridericia’s formula (QTcF) (msec)
- Baseline Mixed Meal Tolerance Test: glucose, C-peptide and glucagon (time course 0-180 min, i.e. levels at the following timepoints: Basal 1, Basal 2, 15 min, 30 min, 60 min, 90 min, 120 min, 180 min). Cmax (Maximum Plasma Concentration) and Tmax (Time to reach Maximum Plasma Concentration) of the MMTT will be provided. Individual plots will be presented. Based on the observed trends, additional analyses might be performed. Cmax and Tmax will be calculated up to 180 minutes after mixed meal administration (time interval ranging from 15 min. to 180 min.).
  Furthermore, the 2-hour AUC of C-peptide response calculation will be based on actual rather than scheduled timings and will be calculated using the trapezoidal rule. If the actual time is not recorded, the scheduled time will be used instead. Missing C-peptide values will be imputed with the average of the C-peptide value that precedes and follows the missing value. Missing data in C-peptide at 180 minutes (final) will be replaced by the last non-missing value, and the last available basal sample (time and value) will be used as the first sample in the computation of the AUC.

- Baseline MicroRNA-375 expression level (Copies/mL)
- T-cells response (T-cell proliferation (CD4) and rate of precursor (CD8)).
- Renal Reserve: Creatinine Clearance (CLcr) (mL/min) – calculated in the CRF. The formula that will be used to verify the calculation is reported in section 11.1.
- Time since first insulin injection (days) – calculated as specified in section 11.1.

Default frequency tabulations will be provided for categorical variables and descriptive summary statistics will be provided for continuous parameters.

11.1. DERIVATIONS

The following variables will be derived:

- "Basal" Mixed Meal Tolerance Test measurement = (Basal 1 measurement + Basal 2 measurement) / 2
- CLcr (mL/min):
  - MALE patients = [[140 – age (years)] x Weight (kg)] / [Serum Creatinine (µmol/L) x 0.815]
  - FEMALE patients = [[140 – age (years)] x Weight (kg)] / [Serum Creatinine (µmol/L) x 0.815] x 0.85
- Time since first insulin injection (days) = Date of randomization – Date of first insulin injection +1

12. SIGNIFICANT MEDICAL HISTORY

Significant medical history information will be tabulated for the ITT population.

All verbatim terms will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to MedDRA dictionary version 19.1 or higher.

Medical conditions which are not ongoing at Screening will be considered as previous diseases while those reported as "*ongoing*" in CRF will be considered as concomitant diseases.

Previous and concomitant diseases will be analyzed separately with frequency tables reporting the number of patients who exhibited at least one disease and showing diseases by primary System Organ Class and Preferred term.

13. MEDICATIONS

Medications will be tabulated for the ITT population and coded using WHO-DRL dictionary version 2016 or higher.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

Prior medications are those which stopped prior to the date of informed consent.

Concomitant medications are those which:

- started prior to, on or after the date of informed consent and started no later than date of end study,
- AND ended on or after the date of informed consent or were ongoing at the end of the study.

The classification of medications into prior or concomitant medications as above was done for statistical purposes.

The following tables will be presented:

- A frequency tables of prior medications by primary therapeutic subgroup (3rd level ATC level subgroup) and generic name.
- A frequency tables of concomitant medications by primary therapeutic subgroup (3rd level ATC level subgroup) and generic name.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication (total duration of exposure and during each treatment cycle) in days will be summarized with descriptive statistics for the SAF by treatment group.

The date of first study medication administration will be taken from the "Diary Card" form (Treatment Cycle No.1, Day 1).

In case of treatment discontinuation, the date of last study medication will be taken from the last available "Diary Card" form.

In case of 3-cycle treatment completion, the date of last study medication will be taken from the "Diary Card" Form taking the date of Treatment Cycle No. 3 Day 14.

14.1. DERIVATIONS

- Duration of exposure (days) for each treatment cycle = (date of last IMP dose intake – date of first IMP dose intake) +1
- Total duration of exposure (days) = sum of the duration of exposure of each treatment cycle.

15. STUDY MEDICATION COMPLIANCE

Data will be summarized by treatment group for SAF population with descriptive statistics.

Descriptive analyses will be presented separately by treatment group for the total number of capsules dispensed, returned and taken, the dose administered (by treatment cycle and overall) as well as the overall compliance to study medication and the compliance by treatment cycle.

Compliance will be calculated from the derived variable "*calculated number of capsules taken*".

15.1. DERIVATIONS

- Overall study medication compliance = Calculated number of capsules taken / 168 capsules (theoretical no. of capsules to be taken over the study).
- Study medication compliance by cycle = Calculated number of capsules taken in each cycle / 56 capsules (theoretical no. of capsules to be taken in each treatment cycle).
- Overall dose of ladarixin administered (mg) = Calculated number of capsules taken * 200 mg
- Dose of ladarixin administered by cycle (mg) = Calculated number of capsules taken in each cycle * 200 mg

16. ANALYSIS OF EFFICACY AND SAFETY VARIABLES

All the efficacy analyses will be performed for the ITT set.

All the AUC analyses (2-hour and 15-120) will be based on actual rather than scheduled timings and will be calculated using the trapezoidal rule. If the actual time is not recorded, the scheduled time will be used instead.

C-peptide AUC values will be transformed to the log(x+1) [selected by TrialNet as the appropriate transformation for MMTT C-peptide AUC].

C-peptide 2-hour AUC values will be calculated from 0-120 C-peptide values of the MMTT. C-peptide (15-120) above fasting AUC will be calculated on the changes from Basal in C-peptide values of the MMTT. Basal value is the average

of Basal #1 and Basal #2 C-peptide values in MMTT. The last non-missing time of Basal #1 and Basal #2 values will be used to calculate the time differences in the AUC.

16.1. PRIMARY EFFICACY ANALYSIS

16.1.1. PRIMARY EFFICACY VARIABLE

The primary variable is the 2-hour C-peptide AUC after the MMTT [Time point: week 13±1].

16.1.2. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The 2-hour C-peptide AUC after the MMTT at week 13 ± 1 will be transformed as log(x+1) values; transformed AUC will be analyzed with Student t-test for unpaired data using PROC TTEST within SAS® to compare Ladarixin and placebo groups. The estimated treatment difference between Ladarixin and placebo will be also presented together with the corresponding 95% confidence interval.

16.2. SECONDARY EFFICACY ANALYSES

16.2.1. SECONDARY EFFICACY VARIABLES

The secondary efficacy variables are:

1. 2-hour AUC of C-peptide response to the MMTT [Time points: baseline, weeks 13±1, 26±2 and 52±2].
2. Percent change from baseline of 2-hour AUC of C-peptide response to the MMTT [Time points: weeks 13±1, 26±2 and 52±2].
3. Average (previous 3 days) insulin requirement (IU/kg/day) [Time points: baseline, weeks 13±1, 26±2 and 52±2].
   For the patients reporting "off insulin" response in the CRF the daily insulin requirement value will be conventionally set to zero in the statistical analysis.
4. HbA1c levels [Time points: baseline, weeks 13±1, 26±2 and 52±2].
5. Number of severe hypoglycemic events occurring from randomization [Time points: weeks 13±1, 26±2 and 52±2].
   A severe hypoglycemic event is defined as an event with one of the following symptoms: "Memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness, or visual symptoms", in which the patient was unable to treat him/herself and which was associated with either a blood glucose level < 54 mg/dL or prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration.
6. Basal (2 basal samples in the range between -20 to 0 min) to 180 min time course of C-peptide and glucose derived from the MMTT [Time points: baseline, weeks 13±1, 26±2 and 52±2].
7. Proportion of patients maintaining a residual β-cell function [Time points: baseline, weeks 13±1, 26±2 and 52±2].
   Maintenance of a residual β-cell function is defined as at least one MMTT C-peptide value > 0.2 nmol/L.
8. Proportion of patients with HbA1c < 7% and absence of episodes of severe hypoglycemia from the previous visit [Time points: weeks 13±1, 26±2 and 52+2].
9. C-peptide AUC (15-120 minutes) above fasting value [Time points: baseline, weeks 13±1, 26±2 and 52±2].

16.2.2. ANALYSIS OF SECONDARY EFFICACY VARIABLES

The following analyses of secondary efficacy variables will be performed:

1. The comparisons between groups on 2-hour AUC C-peptide efficacy endpoint will be carried-out using a mixed linear model where the log(x+1) transformed 2-hour AUC C-peptide will be the dependent variable, while treatment group, visit, treatment by visit interaction will be the fixed factors of the model and patient will be the random effect. An unstructured covariance matrix for each patient is considered and the Kenward-Roger adjustment is used for the degrees of freedom.
2. The comparisons between groups on the percent change from baseline of 2-hour AUC C-peptide will be carried-out using a mixed linear model with percent change from baseline of 2-hour AUC C-peptide as dependent variable, treatment group, visit, treatment by visit interaction as fixed factors of the model and patient as random effect. The baseline value of 2-hour AUC C-peptide will be considered as a covariate of the model. An unstructured covariance matrix for each patient is considered and the Kenward-Roger adjustment is used for the degrees of freedom.
3. The comparisons between groups on insulin requirement secondary efficacy endpoint will be carried-out using a mixed linear model with average daily insulin requirement as dependent variable, treatment group, visit, treatment by visit interaction 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.
4. The comparisons between groups on HbA1c secondary efficacy endpoint will be carried-out using a mixed linear model with HbA1c value as dependent variable, treatment group, visit, treatment by visit interaction 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.
5. The effect of treatment on the cumulative number of severe hypoglycemic events will be evaluated by means of a Cox proportional hazards model with sandwich variance estimate. The Andersen-Gill intensity model with model-based variance will be utilized.
6. The comparisons between groups on the C-peptide and glucose in terms of basal to 180 min time course will be carried-out using a mixed linear model with C-peptide and glucose derived from the MMTT as dependent variables, treatment group, visit, time, treatment by visit interaction, time by visit interaction and treatment by time by visit interaction 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. Furthermore, default summary statistics of Cmax and Tmax of the MMTT at each visit will be provided. Cmax and Tmax will be calculated up to 180 minutes after mixed meal administration (time interval ranging from 15 min. to 180 min.). Individual plots will be presented. Based on the observed trends, additional analyses might be performed.
7. Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients maintaining a residual β-cell function at the single time points will be calculated. 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.
8. Number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients with HbA1c < 7% and absence of episodes of severe hypoglycemia from the previous visit 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.
9. The comparisons between groups on C-peptide AUC (15-120) above fasting value will be carried-out using a mixed linear model where the log(x+1) transformed C-peptide AUC above fasting value will be the dependent variable, while treatment group, visit, treatment by visit interaction will be the fixed factors of the model and patient will be the random effect. An unstructured covariance matrix for each patient is considered and the Kenward-Roger adjustment is used for the degrees of freedom.

16.3. EXPLORATORY AND POST-HOC ANALYSES

16.3.1. EXPLORATORY VARIABLES

The exploratory variables are:

1. Basal (2 basal samples in the range between -20 to 0 min) to 180 min time course of glucagon derived from the MMTT [Time frame: baseline, weeks 13±1, 26±2 and 52±2].
2. Auto-antibodies (GAD, IA-2, IAA, ZnT8), [Time frame: baseline, weeks 13±1, 26±2 and 52±2].
3. MicroRNA-375 expression level (miR-375) [Time frame: baseline, weeks 13±1, 26±2 and 52±2].
4. T-cell response ex vivo to major β-cell antigens (e.g. pro-insulin, GAD65) - selected sites only [Time frame: baseline, weeks 13±1, 26±2 and 52±2].
5. 2-hour AUC of C-peptide response to the MMTT stratified by the number of positivity in auto-antibodies (1, 2, 3, and 4) at Screening visit.
6. Proportion of responders at week 52, defined as patients with percent decrease from baseline in 2-hour AUC of C-peptide above the median percent decrease from baseline to Week 52.

16.3.2. ANALYSIS OF EXPLORATORY VARIABLES

Data will be summarized for all patients in the ITT population, by treatment group.

For the endpoint #1, the comparisons between groups on glucagon in terms of basal to 180 min time course will be carried-out using a mixed linear model with glucagon derived from the MMTT as dependent variables, treatment group, visit, time, treatment by visit interaction, time by visit interaction and treatment by time by visit interaction 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. Furthermore, default summary statistics of Cmax and Tmax of the MMTT at each visit will be provided. Cmax and Tmax will be calculated up to 180 minutes after mixed meal administration (time interval ranging from 15 min. to 180 min.).

For the endpoints from #2 to #4 default summary statistics of the values over time and the changes from baseline will be provided.

For the endpoint #5, the comparisons between groups will be carried-out using a mixed linear model with 2-hour AUC of C-peptide response to the MMTT as dependent variable, treatment group, visit, number of positivity in auto-antibodies at Screening visit, treatment by visit interaction, treatment by number of positivity interaction 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.

Analysis of endpoint #6 will be performed calculating the number and proportion along the 95% confidence interval (Clopper-Pearson's formula) of patients responder. 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.

16.3.3. POST-HOC AND SUBGROUPS ANALYSES

Post-hoc and subgroups analyses aiming to compare the two treatment groups might be considered for all the efficacy endpoints. Such analyses might include, but may not be limited to, calculation of additional endpoints (e.g., Igls score and/or beta2 score), subgroup analysis of efficacy variables by time from first insulin dose to randomization, i.e. ≤6 weeks and ≤10 weeks). Descriptive and appropriate inferential statistical tests will be used. The reason to perform such post-hoc and subgroups analyses will be presented and justified in an appropriate document before to perform the analysis.

16.4. SAFETY ANALYSES

16.4.1. SAFETY VARIABLES

The safety analyses will include the following variables:

1. Vital signs (SBP, DBP and heart rate)
2. Routine laboratory tests (hematology, clinical chemistry)
3. Incidence of Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

16.4.2. ANALYSIS OF SAFETY VARIABLES

Data will be summarized for SAF set with descriptive statistics, by treatment group.

Default summary statistics of vital signs and results for routine laboratory tests over time and the changes from baseline will be provided. Vital signs (SBP, DBP and heart rate) will be recorded at baseline, at pre-dose visit of 2nd cycle and at week 13±1 follow-up visit. Routine laboratory tests will be performed at baseline, pre-dose visit of 2nd cycle and at week 13 ±1 follow-up visit only.

Moreover, results for routine laboratory tests will be assessed as being below the lower limit of the normal range, within the normal range or above the upper limit of the normal range and will be summarized with a frequency table for each visit.

The frequency of patients reporting an abnormal (not clinically significant or clinically significant) laboratory value at Screening and at subsequent visits will be presented for each laboratory variable.

TEAEs will be presented in terms of the number of TEAEs, the incidence, severity and relationship to the study drug, overall and by System Organ Class and Preferred Term. TESAEs will be presented in the same way.

16.4.3. ADVERSE EVENTS

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 version 19.1 or higher.

Any AE which started at or after the first administration of study treatment will be considered a Treatment Emergent Adverse Event (TEAE).

Each AE will be graded according to severity definitions as “Mild”, “Moderate” or “Severe”.

Summary of TEAEs will be presented for the SAF set by treatment group.

If the start date is missing for an AE, the AE will be considered to be treatment emergent (See Appendix 2 for more details about how to handle with partial or missing start/stop dates).

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

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

The following tables and listings will be presented:

1) An overview of TEAEs including the number of patients who exhibited at least one TEAE, at least one serious TEAE, at least one non-serious TEAE, at least one ADR, at least one serious ADR, number of TEAEs, number of non-serious

TEAEs, number of TESAEs, number of ADRs, number of serious ADRs, number of deaths, number of patients who discontinued study drug due to a TEAE;

2) Summary of TEAEs by primary System Organ Class and Preferred Term;

3) Summary of TEAEs by primary System Organ Class, Preferred Term and Severity;

4) Summary of Serious TEAEs by Primary System Organ Class and Preferred Term;

5) Summary of ADRs by Primary System Organ Class and Preferred Term;

6) Summary of TEAEs leading to Study Drug Discontinuation by Primary System Organ Class and Preferred Term;

7) Summary of TEAEs leading to Death by Primary System Organ Class and Preferred Term;

8) Line Listing of all AEs by Patient;

9) Line Listing of SAEs by Patient;

10) Line Listing of Adverse Drug Reactions by Patient;

12) Line Listing of Deaths;

16.4.4. SAFETY LABORATORY EVALUATIONS

Results from the local laboratories will be included in the reporting of this study for Hematology and Blood Chemistry. Data will be summarized for the SAF set.

Presentations will use SI Units.

The following summaries will be provided for Hematology and Blood Chemistry laboratory data:

1) A summary table showing for all laboratory tests the values and changes from baseline to each subsequent visit by treatment group;
2) A summary table showing for all laboratory tests the frequency of patients reporting an out-of-range (below LLN or above ULN) laboratory value at Screening and at subsequent visits by treatment group.
3) A summary table showing for all laboratory tests the frequency of patients reporting an abnormal (clinically or not clinically significant) laboratory value at Screening and at subsequent visits by treatment group.

A listing showing values, the reference ranges and the clinical significance according to investigators' opinion will be produced. Laboratory data will be presented by-patient and within-patient by laboratory test and visit.

16.4.4.1. Conversion of Laboratory Values Units

To convert from the conventional unit to the SI unit, multiply by the conversion factor:

Parameter	Conventional Unit	Conversion Factor	SI Unit
Hematology			
Hemoglobin	g/dL	10	g/L
Hematocrit	%	0.01	Proportion of 1.0
RBC count	x 10^6/µL	0.1	x 10^{12}/L
	x 10^6/mm^3	1	
	x 10^3/µL	1	
WBC count	x 10^3/mm^3	1	x 10^9/L
Neutrophils	x 10^3/µL	1	x 10^9/L

Parameter	Conventional Unit	Conversion Factor	SI Unit
	x 10^3/mm^3	1	
	%	x WBC/100	
	x 10^3/µL	1	
Lymphocytes	x 10^3/mm^3	1	x 10^9/L
	%	x WBC/100	
Monocytes	x 10^3/µL	1	x 10^9/L
	x 10^3/mm^3	1	
	%	x WBC/100	
Basophils	x 10^3/µL	1	x 10^9/L
	x 10^3/mm^3	1	
	%	x WBC/100	
Eosinophils	x 10^3/µL	1	x 10^9/L
	x 10^3/mm^3	1	
	%	x WBC/100	
Platelets	x 10^3/µL	1	
	x 10^3/mm^3	1	x 10^9/L
Blood chemistry			
Total Bilirubin	mg/dL	17.104	µmol/L
	g/dL	17104	
	g/L	171.04	
Aspartate aminotransferase (AST)	units/L	1	U/L
Alanine aminotransferase (ALT)	units/L	1	U/L
	g/dL	10	g/L
Serum Albumin	%	1	%
Urea	mg/dL	0.357	mmol/L
Sodium	mEq/L	1.0	mmol/L
Potassium	mEq/L	1.0	mmol/L
Serum Creatinine	mg/dL	88.4	µmol/L

16.4.5. VITAL SIGNS ANALYSIS

Data will be summarized for the SAF Set.

The following vital sign measurements will be reported for this study as part of safety endpoints:

1. Systolic Blood Pressure (mmHg) – at Screening, pre-dose visit of 2nd cycle, Follow-up visit week 13
2. Diastolic Blood Pressure (mmHg) – at Screening, pre-dose visit of 2nd cycle, Follow-up visit week 13
3. Heart Rate (bpm) – at Screening, pre-dose visit of 2nd cycle, Follow-up visit week 13

Vital sign measurements performed at Day 3 to 5 of 1st treatment cycle for German investigational sites only will also be reported, even if they are not protocol-defined safety endpoints.

For SBP, DBP and heart rate, the change from Screening to each subsequent visit after Screening will be calculated as follows: Absolute Change (unit) = (Absolute Value at Visit X – Baseline Value).

Default summary statistics for SBP, DBP and heart rate at each visit and changes form baseline to each visit will be produced by treatment group.

16.5. ECG EVALUATIONS

Data will be summarized for the SAF set.

ECG will be performed at Screening, at pre-dose visit of 2nd cycle and at pre-dose visit of 3rd cycle.

For German investigational sites only: an ECG will be performed at Day 3 to 5 of 1st treatment cycle.

If QTcF value at subsequent visit after Screening is either > 500 msec or has increased by > 60 msec from screening value, the ECG evaluation will be repeated and the repeated QTcF value will be considered as the only evaluation value for that visit.

A summary table showing for QTcF the values and changes from baseline to each subsequent evaluation will be produced by treatment group.

A summary table showing the Investigator's judgement on ECG evaluation (Normal/Abnormal NCS/Abnormal CS) will be produced at Screening and at subsequent visits by treatment group.

16.6. PREGNANCY TEST OVER THE STUDY

Data will be summarized for the SAF set.

Pregnancy tests will be performed at Screening, at pre-dose visit of 2nd cycle and at pre-dose visit of 3rd cycle.

For Belgian investigational sites only: a pregnancy test will be performed at Follow-up Visit at 3 months.

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

16.7. PERMANENT TREATMENT DISCONTINUATION CRITERIA

Data will be summarized for the Safety Analysis Set (SAF).

The following measurements will be reported:

- IMP treatment completed (Yes/No)
- If No: total number of capsules administered
- If No: reason for permanent discontinuation of IMP:
    - QTcF > 500 msec or increased by 60 msec from Screening measurement on two consecutive ECG reading (1 hour apart)
    - Complete Left Bundle Branch Block (LBBB), atrio-ventricular block, complete heart block
    - Significant cardiovascular disease
    - Renal Dysfunction
    - Hepatic Dysfunction

- Hypoalbuminemia
- Pregnancy
- Other AE
- Other

The following listings of discontinuation criteria will be presented:

- Laboratory test results: Serum Creatinine, Serum Albumin, Total Bilirubin, ALT, AST (Screening, Pre-dose visit 2nd and 3rd cycle, for German Investigational sites only also Day 3-5 of 1st cycle).
- Creatinine Clearance (Screening, Pre-dose visit 2nd and 3rd cycle, for German Investigational sites only also Day 3-5 of 1st cycle).

16.8. PRE-VISIT PHONE CALLS

Pre-visit phone calls will be performed at Week 11/12, at Week 24/25 and at Week 50/51.

Listings will be presented and will include: Date of call, glucose data checked (Yes/No), Insulin intake (Confirmed /Adjusted).

17. ANALYSIS OF PHARMACOKINETIC DATA

Not applicable for this study.

18. TABLE SHELLS AND SPECIFICATIONS

18.1. TABLE SPECIFICATIONS

Tables will be provided as defined by the table shells.

Similar tables based on different populations will have the same number, except for the last digit.

All output will be generated by SAS and exported into a Microsoft Word document in RTF format. All output will be in landscape orientation. Left and right margins will be 2 cm from the side; the top and bottom margins will be 2.5 cm. Font size will be Courier New 7 pt.

The header containing the sponsor name (Dompé farmaceutici S.p.A) and protocol number will appear on the top left corner of each page of the output. The page number, in the format of “Page x of y”, will appear on the top right corner of the output, where y = last page of corresponding output.

Column headers in tables include the total possible numbers to be included in summaries for that table, designated as “(N=XX)”.

The SAS program name, and the date of the creation of the output (run date) will appear on the bottom left corner as follows:

Source: [program name].sas, Run on ddmmmyyyy

Table Format Specification:

Maximum and minimum values will be reported with the same number of decimal places as collected. Means and medians will be reported to one additional decimal place. Standard deviations and standard errors will be reported to two decimal places more than the collected data. Percentages will be reported with one decimal place.

Data in the tables are formatted as follows:

- Text fields in the body of the tables and listings will be left-justified.
- When no data are available for a table, an empty page with the title will be produced with suitable text. Example: THERE WERE NO SERIOUS ADVERSE EVENTS.

18.2. LINE LISTINGS SPECIFICATIONS

Individual line listings will be provided as defined by the listing shells.

All output will be generated by SAS and exported into a Microsoft Word document in RTF format. All output will be in landscape orientation. Left and right margins will be 2 cm from the side; the top and bottom margins will be 2.5 cm. Font size will be Courier New 7 pt.

The header containing the sponsor name (Dompé farmaceutici S.p.A) and protocol number will appear on the top left corner of each page of the output. The page number, in the format of “Page x of y”, will appear on the top right corner of the output, where y = last page of corresponding output.

The SAS program name, and the date of the creation of the output (run date), the reference to CRF page or diary card will appear on the bottom left corner as follows:

CRF source: Form “<Form Name>”, Section “<Section Name>”, Page <nn>.

Source: [program name].sas, Run on ddmmmyyyy.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Quintiles Output Conventions:

Outputs will be presented according to the standard Quintiles' (now IQVIA) layout of tables and line listings.

Dates & Times:

Depending on data available, dates and times will take the form ddmmmyyyy hh:mm:ss (i.e. 01JAN2017 10:20:15)

Spelling Format:

English US.

Listings:

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output) with active IMP first and then placebo
- Randomization number
- Date (where applicable)
- For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labelled 'Not Randomized'.

In all listings missing data will be reported, according to the variable type, as follows:

- Character variables and dates will be presented as empty fields
- Numerical variables will be presented with a "-"

APPENDIX 2. PARTIAL DATE CONVENTIONS

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < date of informed consent, assign as prior If stop date >= date of informed consent and start date <= end of treatment, assign as concomitant If stop date >= date of informed consent and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < date of informed consent, assign as prior If stop date >= date of informed consent and start date <= end of treatment, assign as concomitant If stop date >= date of informed consent and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < date of informed consent, assign as prior If stop date >= date of informed consent and start date <= end of treatment, assign as concomitant If stop date >= date of informed consent date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < date of informed consent, assign as prior If stop date >= date of informed consent and start date <= end of treatment, assign as concomitant If stop date >= date of informed consent and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < date of informed consent, assign as prior If stop date >= date of informed consent, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < date of informed consent, assign as prior If stop date >= date of informed consent, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant