STATISTICAL ANALYSIS PLAN

PROTOCOL: ESPERARE_RIM_001

A phase Ib, open label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending oral doses of Rimeporide in patients with Duchenne Muscular Dystrophy

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

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

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Signature:	
Date of signature:	January 10th 2018 *(DD Mmm YYYY)*

Contents

Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
DMD	Duchenne Muscular Dystrophy
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FVC	Forced Vital Capacity
FEV1	Forced Expiratory Volume at the end of the first second
HPLC	Liquid Chromatography
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MP	Medication Product
NMRI	Nuclear Magnetic Resonance Imaging
NMRS	Nuclear Magnetic Resonance Spectroscopy
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	International System of Units
SMC	Safety Monitoring Committee
SOC	System Organ Class

Revision History

Document Version	Changes Made	Document Date
Draft 0.1	Draft specification based on the following documents: • Study protocol (Version 2.1, 19 February 2016); • CRF (Version 12, 06 June 2016).	28 Jun 2016
Draft 0.2	Version updated after Sponsor's revision.	29 May 2017
Draft 0.3	Version updated after Sponsor's revision.	22 Dec 2017
Final 1.0	Version confirmed without additional comments.	10 Jan 2018

1. Introduction

This document outlines the statistical methods to be implemented in for the analysis of specific type of data of ESPERARE_RIM_001 Clinical Trial that will be managed by CROS NT. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol or electronic Case Report Form (eCRF) may necessitate updates to the Statistical Analysis Plan (SAP). In case of deviations from this updated SAP, explanations will be provided in the clinical study report.
All final study data will be considered for the analysis regulated by this SAP.

2. Study Objectives

2.1 Primary objective

The objective of the study is to assess safety and tolerability of multiple doses of Rimeporide in subjects affected by Duchenne Muscular Dystrophy (DMD).

2.2 Secondary objectives

The secondary objective is to evaluate the pharmacokinetic profile of Rimeporide in pediatric patients with Duchenne Muscular Dystrophy (DMD).

2.3 Exploratory objectives

The exploratory objectives are the following:

- To measure inflammatory and muscular injury biomarkers;
- To explore the PK/PD relationship of a 4-week Rimeporide treatment on those biomarkers;
- To explore the relationship between safety endpoints and pharmacokinetic parameters;
- To explore noninvasively spectroscopy biomarkers (for inflammation, oedema, fat fraction, muscle composition) using Nuclear Magnetic Resonance (NMR) imaging after a 4-week treatment with Rimeporide (for all patients);
- To explore noninvasively spectroscopy biomarkers including intracellular pH and intracellular Na using Nuclear Magnetic Resonance (NMR) Spectroscopy after a 4-week treatment with Rimeporide (for patients recruited in Paris only).

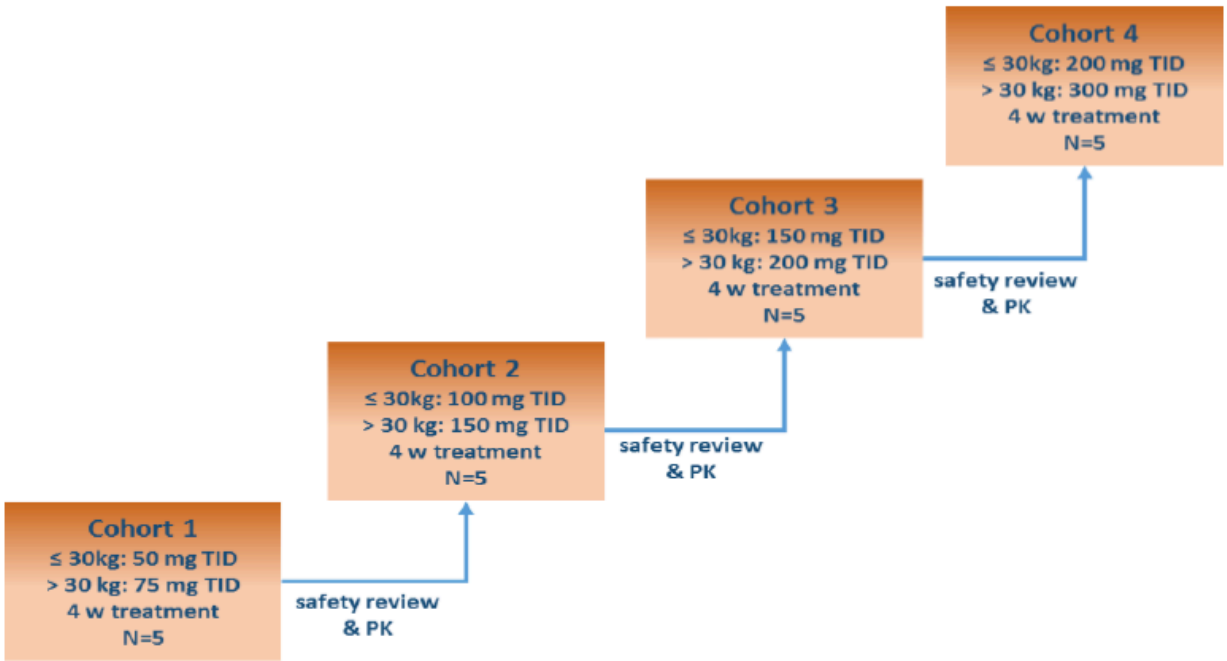
3. Study Design

3.1 General design and plan

The EspeRare RIM 001 is a phase Ib, open label, sequential-group study of ascending oral doses of Rimeporide administered three-times daily (TID) for 28 days to patients with DMD.
The study foresees a screening, a treatment and a follow-up period.
There will be 4 dose levels:

- Patients with a body weight less than or equal to 30kg at baseline will be administered 50 or, 100, or 150 or 200-mg TID;
- Patients with a body weight more than 30kg at baseline will be administered 75 or 150 or 200 or 300-mg TID.

Each subject will participate in only 1 dose cohort and will receive Rimeporide for a total of 4 weeks. Five (5) patients are expected to be recruited in each cohort through all participating sites.
Safety assessments will be made in the clinic at baseline, and after one, two and four weeks of treatment as well as 1-2 weeks following the end of treatment period or withdrawal of the study medication.
After the screening visit and if eligibility criteria are confirmed, patients will return to hospital for 4 study visits during the 4 week treatment period. The first 2 doses of study treatment will be taken in the clinic as well as the last dose 28 days later. In between, 2 safety visits at hospital are scheduled at weekly intervals during the 2 first weeks of study treatment. A phone call is also planned 3 weeks after the first dose to discuss the clinical condition of the patient, and note any possible adverse events reported by the patient or his parents.
Safety assessments will also be made in the clinic 1- 2 weeks following the end of treatment period or after any premature withdrawal of the study medication. The details of examinations and tests that must be performed at study visits are provided in table 1 “Schedule of Assessments” and also in the subsequent sections of this protocol.
The decision to progress to the next higher dose will be made after safety and tolerability data are reviewed for the preceding dose for 5 patients by a data Safety Monitoring Committee (SMC) and determined that it is safe to proceed to the next dose level.



3.2 Visit Schedule and Visit Windows

Assessments and study visits will be performed as listed in the table below:

Visit number	**VS**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**Unscheduled**
Time point	**SCR**	**D1**	**W1**	**W2**	**W3**	**W4**	**EOS**	**Visit**
Site Visit	x	x	x	x		x	x	x
Phone call					x			
Inclusion								
Informed consent	x							
Review and confirmation of eligibility criteria	x	x						
Medical History	x							
Demographic data	x							
6-Minute Walk Test	x							
Pulmonary Function Tests by Spirometry	x							
Echocardiography	x							
Local Safety Evaluation								
Physical and neurological examination, Weight, Vital Signs, Heart Rate, Respiratory Rate, Blood Pressure	x	x	x	x		x	x	x
12 lead ECG, including QTc	x	x	x	x		x	x	x
Local Biochemistry, Hematology, Urinalysis	x	x	x	x		x	x	x
Gastrin levels		x				x		
AEs/SAEs review	x	x	x	x	x	x	x	x
PK sampling profile allocation								
PK Blood collection		x				x		
Local NMRI (NMRS if applicable)		x[a]				x[b]		
Blood Samples (for central analysis: CK total, CK isoenzymes, TNFa and TGFβ-1 and other biomarkers)	x					x		
Treatment delivery		x[c]	x[c]	x[c]				
Treatment compliance			x	x	x	x	x	x
Concomitant treatments	x	x	x	x	x	x	x	x

(a) The day before the SD1
(b) Day 27+/- 2 days, just before the end of treatment period.
(c) See section 5.1.4.2 drug dispensing of the study protocol.

Paragraph no. 7 “Outline of study procedures” of Study Protocol contains additional details about procedures of each scheduled visit and visit time windows.

3.3 Sample size justification

A sample size of 20 evaluable patients has been selected for this phase 1b study, based on practical considerations, since this was an exploratory study and not a confirmatory trial. Additional 5 patients might be included in case safety allows furthering escalating the dosage.
Due to the rarity of DMD patients the recruitment was competitive across all sites in order to gather data in a reasonable timeframe, anticipated to be about 12 months.

3.4 Randomization and blinding

Since this is an open label study, this paragraph is not applicable.

3.5 Efficacy endpoints

No efficacy endpoints were foreseen for this study.

3.6 Safety endpoints

The safety endpoints (which are also the primary ones) are the following:

- Adverse Events (AEs);
- Vital Signs, diastolic and systolic blood pressure in supine and standing position, heart rate in same position (supine and standing) and respiratory rate;
- Electrocardiogram (ECG);
- Laboratory parameters (from blood and urine samples);
- Patients withdrawn for safety issues.

3.7 Other endpoints

3.7.1 PK endpoints

The PK endpoints are the secondary endpoints. They consists in the determination of PK profile of Rimeporide in plasma derived from modelling using sparse sampling in paediatric patients with DMD.

3.7.2 Exploratory endpoints

The exploratory endpoints are the following:

- Changes of plasma / serum levels of the inflammation markers after a 4 week treatment with Rimeporide, such as:
  - C - reactive protein (CRP),
  - Tumor Necrosis Factor alfa (TNFα),
  - Transforming Growth Factor beta (TGFβ-1),
  - Other exploratory biomarkers to monitor muscle damages (cytokine panels and specific RNA targeting).
- Changes in NMRI indices for all patients:

- Muscle Water T2,
- Muscle with elevated T2 which selectively measures muscle inflammation,
- Heterogeneity of T2 within the muscle which reflects tissue disorganization,
- Fat fraction in the muscle.

- Changes in 31P NMRS indices and 23Na NMRS indices for patients recruited in Paris.

4. Statistical Analysis

4.1 General

Descriptive statistics will be provided for all variables in the summary tables by cohort according to the type of variable summarized.
Quantitative variables will be summarised by using n, arithmetic mean, SD, median and range (minimum and maximum).
Categorical variables will be summarised by using frequency distributions and percentages.
The baseline used in the analysis for each variable is reported in the table below:

Endpoint	**Baseline**
Vital Signs	Visit 1 - pre-dose
ECG	Visit 1 - pre-dose
Laboratories	Visit 1 (except for C-reactive protein for which Screening value will be used instead)
Gastrin	Visit 1

All data collected in the eCRF, concerning CROS NT analysis, will be presented in the listings.

Separate reports regarding PK, PD and NMRI/NMRS will be produced from external vendors.

No multiplicity adjustment nor hypothesis testing will be implemented due to the nature of this study.

4.2 Analysis sets

4.2.1 Intent-to-treat set

All patients who received at least one dose of study drug will be included in the ITT set.
The PK and exploratory variables will be analysed on the ITT.

4.2.2 Safety set

All patients who received at least one dose of study drug will be included in the Safety set.
This set is defined as the ITT one. As for the safety data presentation, it will be referenced as Safety set.

4.2.3 Incorrect treatment allocations

Not applicable.

4.3 Sub-group analyses

No subgroup analysis will be performed.

4.4 Covariates

Not foreseen.

4.5 Pooling of sites

Not foreseen.

4.6 Interim analyses

No formal interim analysis is planned for the study.

4.7 Handling of missing and incomplete data

Missing values will be included in the denominator count when computing percentages. The number of patients with missing data will be presented under the "Missing" category, if present.
Only the non-missing values will be evaluated for computing summary statistics.
Missing or incomplete data will be treated as described in chapters 5, 6, 7 and 8.

4.8 Changes in the planned analysis

The following changes were implemented in this SAP with respect to the analyses planned in the protocol:

- Other exploratory analysis of safety data, such as summaries for different subsets of patients will not be performed according to the Sponsor decision.
- For binary data, no 95% CI will be calculated and presented.

4.9 Data Review Meeting

Not foreseen.

4.10 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.4) on a Windows 7 operating system.

5. Evaluation of Demographic and Baseline Characteristics

5.1 Subject enrolment and disposition

Definitions and data conventions

Date of first study drug intake
The date of first study drug intake is assumed to be the date of Visit 1.

Completer/discontinued Patient
A patient will be considered as completer if the answer to the question "Did the subject complete the study?" will be equal to "Yes".

A patient will be considered as discontinued if the answer to the question "Did the subject complete the study?" will be equal to "No".

Statistical analysis
Disposition of patients will be presented by cohort and overall for the Safety set.

5.2 Protocol violations

Definitions and data conventions
All the protocol deviations will be evaluated internally case by case from the Sponsor after the database soft lock. The Sponsor is expected to provide CROS NT with a list of major/minor protocol deviations.

Statistical analysis
Major protocol deviations will also be summarised for each cohort and overall in the Safety set.
All protocol deviations will also be listed.

5.3 Study discontinuations

Statistical analysis
Patients who discontinued from the study prematurely will also be presented with a breakdown of the reasons for discontinuation by cohort and overall for the Safety set.

5.4 Demographics and baseline characteristics

Definitions and data conventions
Age (years)
Age as already provided in the eCRF will be used for this analysis.

Body Mass Index (BMI) (kg/m^2)
BMI as already provided in the eCRF will be used for this analysis.

Time since DMD diagnosis (years)
Time since DMD diagnosis (years) will be calculated using the following formula:

Time since DMD diagnosis (years) = (Date of Visit 1 – Date of DMD molecular diagnosis + 1)/365.25

Statistical analysis

Baseline and demographic characteristics will be summarised by cohort and overall by means of descriptive statistics.

The following characteristics will be provided for the Safety set:

- Age (years)
- Ethinicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Time since DMD diagnosis (years)

5.5 Medical and surgical history

Definitions and data conventions

Past disease

A disease is considered as past disease if it is not ongoing at screening visit ("ongoing" box is not ticked).

Concomitant disease

A disease is considered as concomitant disease if it is ongoing at screening visit ("ongoing" box is ticked).

Statistical analysis

Past disease and concomitant diseases will be coded using Medical Dictionary for regulatory activities (MedDRA) dictionary (version 18.1) and frequency distributions and percentages will be summarised by cohort and overall for the Safety by System Organ Class (SOC) and Preferred Term (PT).

Counts will be given for both SOC and PT by subject. Subjects experiencing more than one past/concomitant disease event will be counted only once within each SOC and PT.

5.6 Prior and concomitant medications

Definitions and data conventions

The following categories of medications will be identified:

- previous medication (stop date ≤ date of first study medication intake);
- concomitant medication (stop date > date of first study medication intake or stop date ongoing/missing).

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

- concomitant medication;
- previous medication.

Statistical analysis
Previous and Concomitant medications
Medications will be coded using WHO Drug Dictionary (WHO-DD), version March 1st2015, using the following Anatomical Therapeutic Chemical Classification (ATC) codes:

- Anatomical Main Group (ATC 1st level code);
- Chemical subgroup (ATC 4th level code);
- Preferred name.

Previous and concomitant medications will be summarized separately for Safety set by anatomical main group, chemical subgroup and preferred name by cohort and overall.
Subjects experiencing more than one previous (or concomitant) medication within the same anatomical main group, chemical subgroup and preferred name will be counted only once.

5.7 Other baseline characteristics

6-Minute Walk Test, spirometry (predicted FEV1 and FVC) and echocardiography (in particular, LVEF) at the screening visit will be summarised by cohort and overall by means of descriptive statistics.

6. Evaluation of Treatment Compliance and Exposure

6.1 Compliance to study drug and treatment

Definitions and data conventions
Date of first study drug intake
The date of first study drug intake is assumed to be the date of Visit 1.

Date of last study medication intake
The date of last study medication intake is the date of last study drug intake recorded on the study termination form of the eCRF.

Compliance to study medication
Compliance to study medication will be evaluated on the basis of the information recorded on the eCRF.

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

$$\text{Compliance}(\%) = \frac{\text{Total number of study medications taken during the treatment period}}{\text{Total number of scheduled study medications during the treatment period}} \times 100$$

Total number of	
Study medications taken	Scheduled study medications
Sum of actual study medications taken from the day of first study medication intake to the day of last visit	Sum of expected study medications taken from the day of first study medication intake to the day of last visit performed

performed during of treatment period.	during of treatment period.

Statistical analysis
Compliance to study medication will be summarised by cohort and overall using descriptive statistics on the Safety set. An additional summary displaying the number and percentage of patients in the following categories will also be presented by cohort and overall: [0%-10%], (10%-20%], (20%-30%], (xx%-xx%], (90%-100%], >100%.

6.2 Exposure to study drug

Definitions and data conventions
The extent of exposure (days) will be calculated using the following formula:

Extent of exposure (days) = Date of last study medication intake - Date of first study medication intake +1.

Statistical analysis
Extent of exposure will be summarised by cohort and overall using descriptive statistics on Safety set.

6.3 Evaluation of pharmacokinetics

Statistical analysis
A separate PK report including the details on the statistical analysis of PK data will be produced by Calvagone Sarl.

7. Evaluation of Efficacy

7.1 Analysis of primary endpoint

Not foreseen.

7.2 Analysis of secondary efficacy endpoints

Not foreseen.

7.3 Analysis of exploratory efficacy endpoints

Not foreseen.

7.4 Evaluation of pharmacodynamics

Statistical analysis
A separate PD report including the details on the statistical analysis of PD data will be produced by Eurofins Scientific.

8. Evaluation of Safety

8.1 Adverse events

Definitions and data conventions

Pre-treatment adverse events

An adverse event (AE) will be classified as pre-treatment AE if it starts before the date/time of first study medication intake (AE onset date/time < date/time of first study medication intake).

Treatment-emergent adverse event (TEAE)

An AE will be classified as a TEAE if it starts on or after the date/time of first study medication intake (AE onset date/time ≥ date/time of first study medication intake).

In case of missing or incomplete dates/times 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/times. The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE
- Pre-treatment.

Serious adverse event (SAE)

A SAE is an AE judged as serious.

Adverse drug reaction (ADR)

An ADR is an AE judged as "Probably related" or "Possibly related".

Adverse event leading to drug discontinuation

An AE leading to discontinuation is an AE with action taken equal to "Study drug withdrawn".

Adverse event leading to death

An AE leading to death is an AE with outcome equal to "Death: patient died".

Count of adverse events

Two AEs with the same Preferred Term (PT) and classified in the same category (pre-treatment AE or TEAE) will be considered as two different events when calculating the "number of events" in the tables.

Statistical analysis

Pre-treatment AEs and TEAEs will be presented separately. Pre-treatment AEs will be presented in the listings only.

The number of treatment-emergent AEs, SAEs, ADRs, AEs leading to drug discontinuation and AEs leading to death, and the number and the percentage of patients experiencing treatment-emergent AEs, SAEs, ADRs, AEs leading to drug discontinuation and AEs leading to death will be summarised by cohort and overall.

AEs will be coded using the MedDRA dictionary (version 18.1). The SOCs and PTs will be used for tabulation. The number of AEs and the number and the percentage of patients with at least one

AE will be presented by SOC and PT for treatment-emergent AEs, SAEs, ADRs, serious ADRs, severe AEs, AEs leading to drug discontinuation and AEs leading to death by cohort and overall.

8.2 Clinical laboratory evaluation

Statistical analysis
Haematology parameters, biochemistry parameters, gastrin levels and the change from baseline will be summarised by cohort at each timepoint by means of descriptive statistics.
In order to perform the above described summaries, different units need to be standardized according to SI units. The Sponsor agreed to support CROS NT in the conversion process before the DB hard lock.

The following figures will be displayed graphically:

- Haematology and biochemistry patient profiles during the study for each parameter as well as for Gastrin levels;
- Haematology and biochemistry median values per cohort during the study for each parameter as well as for Gastrin levels.

8.3 Vital signs

Statistical analysis
Weight (kg), Systolic Blood Pressure – Supine (mmHg), Diastolic Blood Pressure - Supine (mmHg), Heart Rate – Supine (bpm), Systolic Blood Pressure Standing (mmHg), Diastolic Blood Pressure – Standing (mmHg), Heart Rate – Standing (bpm), Respiratory Rate (breaths/min), Temperature (Celsius) will be summarised by cohort at each timepoint by means of descriptive statistics.

The following figures will be displayed graphically:

- Vital signs patient profiles during the study for each parameter;
- Vital signs median values per cohort during the study for each parameter.

8.4 ECGs

Statistical analysis
Heart Rate (bpm), PR interval (msec), QRS duration (msec), QTc interval (msec), QTcB interval (msec), QTcF interval (msec), QRS Axis (degree) and the change from baseline will be summarised by cohort at each timepoint by means of descriptive statistics.

The following figures will be displayed graphically:

- 12-lead ECG patient profiles during the study for each parameter;
- 12-lead ECG median values per cohort during the study for each parameter.

8.5 Physical examination

Statistical analysis
Physical examinations will be listed only.

8.6 Other safety evaluations

NMRI/NMRS

Statistical analysis

A separate NMRI/NMRS report will be produced including the details on the statistical analysis of NMRI/NMRS data by CRIS scrl.

Neurological examination

Statistical analysis

Neurological examinations will be listed only.

9. Tables, Figures and Listings

9.1 Programs and tables quality control

The statistician-programmer of the tables, listings and figures will carefully review the programs and will verify that no error message is highlighted in the 'LOG' file.
Moreover, a second statistician-programmer will verify the internal consistency of each table and figure by checking the results using different SAS programs.

The following level of validation will be implemented:

- Validation of statistical datasets: via validation of tables.
- Validation of statistical output:
  - tables: Independent programming and comparison of main results;
  - listings: Peer review of the program code used to create the output;
  - figures: Peer review of the program code used to create the output.

9.2 Programming conventions

All tables/figures/listings will be presented in landscape format.
The standard font size is 9 points Arial 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: Percentages are calculated on the number of patients (N).
Note 2: A serious adverse event is an ....
Note 3: …….

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.

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.

In the tables, listing and figures the treatment under comparison will be labelled as "Cohort 1", "Cohort 2", "Cohort 3" and "Cohort 4".

Unless otherwise stated, listings will be presented by cohort, and sorted by the patient number.

All the listings will be based on the Safety set.

The derived variables will be identified in the listings with a flag (*).

In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes. Numeric variables will be listed generally with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered in the listings for the derived variables (in the analyses approximations will not be performed):

- Age (years), extent of exposure (days): 0 decimal place;
- BMI (kg/m^2), time since disease diagnosis (years), compliance to study medication: 1 decimal place;
- change from baseline: same as the variable considered.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- Min, max: same as actual data;
- Mean and its confidence limits (unadjusted and adjusted), adjusted difference between means and its confidence limits, SD, median: actual data + 1 decimal;
- Percentage: 1 decimal place;

9.3 Tables

The list of tables is provided here below:

TABLE	TITLE
TABLE T14.1-1	DISPOSITION OF PATIENTS / SUMMARY OF ALL PATIENTS
TABLE T14.1-2.1	PRIMARY REASONS FOR DISCONTINUATION FROM THE STUDY / SAFETY SET
TABLE T14.1-3.1	SUMMARY OF MAJOR PROTOCOL DEVIATIONS / SAFETY SET
TABLE T14.1-4.1	DEMOGRAPHIC CHARACTERISTICS

TABLE	TITLE
TABLE T14.1-5.1	PAST DISEASES / SAFETY SET
TABLE T14.1-5.2	CONCOMITANT DISEASES / SAFETY SET
TABLE T14.1-6.1	PREVIOUS MEDICATIONS / SAFETY SET
TABLE T14.1-6.2	CONCOMITANT MEDICATIONS / SAFETY SET
TABLE T14.1-7	ECHOCARDIOGRAPHY, 6-MINUTE WALK TEST AND SPIROMETRY AT SCREENING / SAFETY SET
TABLE T14.1-8	COMPLIANCE TO STUDY MEDICATION / SAFETY SET
TABLE T14.1-9	EXTENT OF EXPOSURE / SAFETY SET
TABLE T14.3.1-1	SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS / SAFETY SET
TABLE T14.3.1-2	TREATMENT-EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE T14.3.1-3	SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE T14.3.1-4	TREATMENT-EMERGENT ADVERSE DRUG REACTIONS BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE T14.3.1-5	TREATMENT-EMERGENT ADVERSE EVENTS LEADING TO DRUG DISCONTINUATION BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE T14.3.1-6	TREATMENT-EMERGENT ADVERSE EVENTS LEADING TO DEATH BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY SET
TABLE T14.3.4-1.1	VITAL SIGNS DURING THE STUDY AND CHANGE FROM BASELINE / SAFETY SET
TABLE T14.3.4-2.1	12-LEAD ELECTROCARDIOGRAM PARAMETERS DURING THE STUDY AND CHANGE FROM BASELINE / SAFETY SET
TABLE T14.3.4-3.1	HEMATOLOGY LABORATORY PARAMETERS DURING THE STUDY AND CHANGE FROM BASELINE / SAFETY POPULATION
TABLE T14.3.4-3.2	BIOCHEMISTRY LABORATORY PARAMETERS AND GASTRIN LEVELS DURING THE STUDY AND CHANGE FROM BASELINE / SAFETY POPULATION

9.4 Figures

The list of figures is provided here below:

FIGURE	TITLE
FIGURE F14.3.4-1.1.1	HEMATOLOGY PATIENT PROFILES DURING THE STUDY / <PARAMETER X> / SAFETY SET
FIGURE F14.3.4-1.1.2	HEMATOLOGY DURING THE STUDY / <PARAMETER X> / SAFETY SET
FIGURE F14.3.4-1.2.1	BIOCHEMISTRY AND GASTRIN PATIENT PROFILES DURING THE STUDY / <PARAMETER X> / SAFETY SET
FIGURE F14.3.4-1.2.2	BIOCHEMISTRY AND GASTRIN DURING THE STUDY / <PARAMETER X> / SAFETY SET
FIGURE F14.3.4-2.1	12-LEAD ECG PATIENT PROFILES DURING THE STUDY / <PARAMETER X> / SAFETY SET
FIGURE F14.3.4-2.2	12-LEAD ECG DURING THE STUDY / <PARAMETER X> / SAFETY SET

FIGURE	TITLE
FIGURE F14.3.4-3.1	VITAL SIGNS PATIENT PROFILES DURING THE STUDY / <PARAMETER X> / SAFETY SET
FIGURE F14.3.4-3.2	VITAL SIGNS DURING THE STUDY / <PARAMETER X> / SAFETY SET

9.5 Listings

The list of listings is provided here below:

LISTING	TITLE
LISTING 16.2.1-1	DISPOSITION OF PATIENTS / SAFETY SET
LISTING 16.2.1-2	STUDY TERMINATION / SAFETY SET
LISTING 16.2.2-1	PROTOCOL DEVIATIONS / SAFETY SET
LISTING 16.2.2-2	VIOLATIONS OF INCLUSION/EXCLUSION CRITERIA / SAFETY SET
LISTING 16.2.3-1	POPULATIONS FOR ANALYSIS / SAFETY SET
LISTING 16.2.4-1	DEMOGRAPHICS AND BASELINE CHARACTERISTICS / SAFETY SET
LISTING 16.2.4-2	PHYSICAL EXAMINATIONS / SAFETY SET
LISTING 16.2.4-3	NEUROLOGICAL EXAMINATION / SAFETY SET
LISTING 16.2.4-4	6-MINUTE WALK TEST / SAFETY SET
LISTING 16.2.4-5	ECHOCARDIOGRAPHY / SAFETY SET
LISTING 16.2.4-6	SPIROMETRY / SAFETY SET
LISTING 16.2.4-7	PAST-CONCOMITANT DISEASES / SAFETY SET
LISTING 16.2.5-1	MEDICATIONS / SAFETY SET
LISTING 16.2.5-2	STUDY DRUG ADMINISTRATION / SAFETY SET
LISTING 16.2.5-3	DISMISSAL / SAFETY SET
LISTING 16.2.5-4	STUDY DRUG COMPLIANCE AND DISPENSATION / SAFETY SET
LISTING 16.2.7-1.1	TREATMENT-EMERGENT ADVERSE EVENTS / SAFETY SET
LISTING 16.2.7-1.2	SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS / SAFETY SET
LISTING 16.2.7-1.3	TREATMENT-EMERGENT ADVERSE DRUG REACTIONS / SAFETY SET
LISTING 16.2.8-1	VITAL SIGNS / SAFETY SET
LISTING 16.2.8-2	LABORATORY PARAMETERS AND GASTRIN LEVELS / SAFETY SET
LISTING 16.2.8-3	ABNORMAL LABORATORY PARAMETERS / SAFETY SET
LISTING 16.2.8-4	12-LEAD ECG / SAFETY SET

10. Literature

- CROS NT Standard Operating Procedure SOP ST03/V01 “Statistical Analysis Plans”;
- European Medicines Agency (EMA), International Conference on Harmonisation (ICH) E3 Harmonised Guideline (1996) “Structure and Content of Clinical Study Reports”;
- EMA, ICH E9 Harmonised Guideline (1998) “Statistical Principles for Clinical Trials”.

11. Appendices

11.1 Table shells

See document “AppendixI_ESPERARE_RIM_001_180110(Final1.0)docx”.

11.2 Figure shells

Not foreseen.

11.3 Listing shells

Not foreseen.