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STATISTICAL ANALYSIS PLAN

SERENDEM

MD1003 in patients suffering from demyelinating neuropathies, an open label pilot study

Version 1.0

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomic Therapeutic Chemical
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CMT	Charcot-Marie-Tooth
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Boards
FAS	Full analysis set
GGT	Gamma glutamyl transferase
HCG	Human chorionic gonadotropin
HR	Heart Rate
IEC	Independent Ethics Committee
IgM	Immunoglobin M
INCAT	Inflammatory Neuropathy Cause and Treatment
INR	International Normalised Ratio
IRB	Institutional Review Board
IS	Included Set
ISS	INCAT Sensory Sum
ITT	Intent To Treat
LLN	Lower Limits of Normal
LOCF	Last observation carried forward
MAG	Myelin-Associated Glycoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
ONLS	Overall Neuropathy Limitation Scale
PPS	Per Protocol set
PT	Preferred Term

RBC	Red blood cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SBP	Systolic Blood Pressure
SCR	Screened Set
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limits of Normal
W	Week
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

The objective of this Statistical Analysis Plan (SAP) is to ensure the maximum credibility of all study findings. This plan will not repeat all the definitions given in the protocol, but will provide further details of the analyses planned therein.

This Statistical Analysis Plan was prepared and signed prior to the database lock after all patients had completed the study.

This SAP has been written in agreement with:

- The Study Protocol version 4.0 dated 10FEB2017
- The Case Report Form (CRF) version 1.0 dated 16MAY2019.

1.1 Study objective

The primary objective of the study is to assess the effect of MD1003 on motor and sensory conduction, in patients suffering from demyelinating polyneuropathies.

The secondary objective is to evaluate safety of MD1003 in this patient population.

This pilot study is not controlled by a placebo. It is aiming to evaluate the acceptability of the treatment in this population, to assess the intra and inter-individual variability of the neurophysiological procedures proposed in this study protocol, and to assess the robustness of the evaluation criteria. The results will serve as hypothesis for the sample size calculation of a larger placebo controlled trial.

1.2 Study design

This is a pilot, open label, uncontrolled monocentric study in 3 distinct groups of patients suffering from a specific aetiology pattern of peripheral neuropathy:

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Demyelinating neuropathy associated with immunoglobin M (IgM) monoclonal gammopathy and antibodies against myelin-associated glycoprotein (anti-MAG)
- Charcot-Marie-Tooth 1a and 1b (CMT1a and CMT1b) neuropathy

The total study duration is expected to be 52 weeks: 4 weeks for baseline period and 48 weeks for treatment period. The study flow-chart is presented below:

	Week -4	Week 0	Week 12	Week 24	Week 36	Week 48
	Selection	Inclusion	Follow-up			End
STUDY WINDOWS		+/-5 days	+/-10 days			+/- 15 days
Informed consent	X					
Inclusion criteria	X	X				
Non-inclusion criteria	X	X				
Medical history	X					
Clinical examination	X	X	X	X	X	X
Neurophysiological examination		X		X		X
MRC sum score		X	X	X	X	X
INCAT sensory Score		X	X	X	X	X
Posturography score		X		X		X
ONLS score		X	X	X	X	X
Timed 10-meter walk test		X	X	X	X	X
6-min walk test		X	X	X	X	X
Excitability testing		X		X		X
AEs reporting		X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X
Biological test [1]	X [2]					X
Serum sample	X			X		X
Study drug dispensation		X	X	X	X	
Compliance check			X	X	X	X

[1] *Biological safety panel includes: RBC, hemoglobin, mean corpuscular volume, WBC, platelets, electrolytes (Na, K, HCO3, Ca), protein, creatinine, glomerular filtration rate, fasting blood glucose, AST, ALT, total and free bilirubin, gamma glutamyl transferase, alkaline phosphatase, triglyceride, cholesterol, PT, aPTT, INR*

[2] *Biological aetiology additional panel: Serum protein electrophoresis, IgA measurement, HbA1c, HBsAg, HIV, HCV tests, fibrinogen*

Six visits were planned:

- Visit 1: Selection visit at W-4
- Visit 2: Inclusion visit at W0
- Visit 3 at W12 ± 10 days
- Visit 4 at W24 ± 10 days
- Visit 5 at W36 ± 10 days
- Visit 6: last visit at W48 ± 15 days

Actually, a unique visit was performed for visit 1 and visit 2 (see section 2.1).

1.3 Sample size

This pilot study is exploratory. The various clinical and electrophysiological endpoints allowed to define which of them would be the most relevant in a larger randomized controlled trial.

It was assumed that 15 patients was a sufficient sample size to 1) detect a signal of clinical efficacy of MD1003 in demyelinating peripheral neuropathies, and 2) rank clinically the best

endpoints for confirmatory studies in the three most common demyelinating peripheral neuropathies.

The study included 15 patients in total divided into 3 subgroups of 5 patients suffering from either CIDP, anti-MAG or CMT1a/CMT1b.

2 SUMMARY OF CHANGES TO THE PROTOCOL

2.1 Changes to the conduct of the study

Classical MRC sum score with 6 muscles was planned in the protocol for the assessment of muscle strength. In the context of peripheral neuropathies an extended version of this MRC involving 19 muscles was used.

Safety data were to be reviewed on a regular basis by the Data Safety Monitoring Boards (DSMB) (see protocol section 11.8.2). It was the Sponsor decision not to implement a DSMB in this open labelled non-controlled study based on FDA's guidance for clinical Sponsor "Establishment and Operation of Clinical Trial Data Monitoring Committees".

Weight measurement is not in the investigator day to day practice and was omitted.

Posturography was not performed in the same conditions as described in the protocol as the equipment available on site (dynamometric platforms Bertec 400*600mm (Bertec Corporation, Columbus, OH, USA) with a recording frequency of 1000 Hz) is different.

Data related to the center of pressure of the Posturography parameters were collected instead of data related to center of gravity.

Additionally, in agreement with the sponsor, the trial site has merged the selection visit with the inclusion visit for all the patients, leading to a single one-day visit.

2.2 Changes to the conduct of the analysis

The name of "ITT population" has been replaced by "FAS population" to be compliant with the ICH guidelines.

As sensitivity analysis of the efficacy endpoints, a Wilcoxon signed rank test will be performed to assess if the changes from baseline at week 48 in the efficacy criteria are statistically significant considering an alpha level of 5%.

Regarding secondary efficacy criteria, missing data at week 48 will be imputed considering LOCF approach.

3 GENERAL STATISTICAL CONSIDERATIONS

3.1 Hypothesis and significance level

Statistical tests will be conducted two-sided with a significance level of 5%. A resultant probability value of $p<0.05$ will be judged as being of statistical significance.

3.2 Handling of missing data

To calculate age of the patients, if the month and year of the birth are available, the day of birth will be imputed to the 15th of the month of the birth.

The last observation carried forward (LOCF) approach will be used to handle missingness on the primary evaluation criteria at week 48 (Motor nerve conduction velocity, Distal latency, F wave latency and Length of motor nerve potential). Missing data at week 48 will be replaced by the last available post-baseline value.

Other missing or inconsistency data, especially for the secondary criteria, could be reviewed before the database lock, during the data review meeting, and the management of their imputation will be discussed. Following data review meeting, an imputation considering LOCF approach will be performed regarding missing data of secondary criteria at week 48.

Missing or incomplete dates will be managed as below:

To define Treatment Emergent Adverse Events, missing dates of study drug intake or adverse events will be replaced.

- Missing dates of the first study drug intake

In case of completely missing dates of the first study drug intake, it will be considered equal to the day of the inclusion visit + 1 day at the morning.

If the day and the month are missing:

- If the year is the same as the year of the first study drug intake, it will be estimated by the day of the inclusion visit + 1 day at the morning
- If the year is after the year of the inclusion visit, it will be estimated by the 1st January at the morning

If only the day is missing:

- If the month/year are the same as the month/year of the inclusion visit, it will be estimated by the day of the inclusion visit + 1 day at the morning.
- If the month/year are after to the month/year of the inclusion visit, it will be estimated by the first day of the month at the morning.

If only the time of first study drug intake is missing, it will be considered at the morning.

- Missing dates of the last study drug intake

In case of completely missing dates of the last study drug intake, it will be considered as the date of study completion/discontinuation – 1 day at the evening.

If the day and the month are missing:

- If the year is the same as the year of date of study completion/discontinuation, it will be estimated by the study completion/discontinuation date – 1 day at the evening

- If the year is before the year of the study completion/discontinuation date, it will be estimated by the 31 December at the evening.

If only the day is missing:

- If the month/year are the same as the month/year of the study completion/discontinuation, it will be estimated by the date of study completion/discontinuation – 1 day at the evening.
- If the month/year are prior to the month/year of the study completion/discontinuation, it will be estimated by the last day of the month at the evening.

If only the time of the last study drug intake is missing, it will be considered at the evening.

- Missing start dates of adverse events

In case of completely missing date, it will be estimated by the date of the first study drug intake.

If the day and the month are missing:

- If the year is the same as the year of the first study drug intake, it will be estimated by the date of the first study drug intake
- If the year is prior to the year of the first study drug intake, it will be estimated by the 31 December
- If the year is after the year of the first study drug intake, it will be estimated by the 1st January

If only the day is missing:

- If the month/year are the same as the month/year of the first study drug intake, it will be estimated by the date of the first study drug intake
- If the month/year are prior to the month/year of the first study drug intake, it will be estimated by the last day of the month
- If the month/year are after the month/year of the first study drug intake, it will be estimated by the first day of the month

If after imputation, the estimated start date is after the end date of the adverse event, it will be replaced by the end date of the adverse event.

- Missing end dates of adverse events

In case of adverse event not "ongoing" (i.e. 'Recovered/Resolved', 'Recovered/Resolved with sequelae' or 'Fatal' in the CRF) at the end of the study and end date completely missing, it will be estimated by the last available date (last visit, last examination, date of completion/discontinuation or last study drug intake).

If the day and the month are missing:

- If the year is the same as the year of last available date, it will be estimated by the last available date
- If the year is not the same as the year of last available date, it will be estimated by the 31 December

If only the day is missing:

- If the month/year are the same as the month/year of last available date, it will be estimated by the last available date
- If the month/year are not the same as the month/year of last available date, it will be estimated by the last day of the month

If after imputation, the estimated end date is before the start date of the adverse event, it will be replaced by the start date of the adverse event.

- Missing start/end dates of concomitant treatments

When the start or end date is partially or completely missing, the same rules as for start and end date of adverse events will be applied.

To calculate the time since the first appearance of symptoms and the time since the progression, if the date of the first appearance of symptoms or date of the progression is incomplete, it will be replaced as below:

If the day and the month are missing, it will be estimated by the 15th June

If only the day is missing, the day will be estimated by the 15th of the corresponding month.

3.3 Subgroups, interactions and covariates

The following disease groups will be considered for analyses:

- CMT
- CIDP
- Anti-MAG

All efficacy analyses performed on the three disease groups will be descriptive only due to the sample size of each group. Statistical test will be performed on all patients and not by disease group.

No subgroup analysis is planned.

3.4 Baseline data

Baseline data will be defined as the last non missing value available before the first administration of study treatment.

For all data collected both at selection visit (Visit 1) and inclusion visit (Visit 2), the baseline value will be defined as the assessment closest to and before the start of study medication, *i.e.* visit 2. The selection visit (visit 1) will be taken if the value is not available at inclusion visit.

3.5 Interim analyses

No interim statistical analysis is planned.

3.6 Handling of multiple testing

Not applicable.

3.7 Statistical computer software

For statistical analyses performed by ATLANSTAT, SAS® Enterprise Guide software version 7.1 (SAS® for Windows version 9.4) or higher will be used.

4 ANALYSIS SETS

The following populations will be defined:

- Screened Set (SCR)

All patients who signed the informed consent.

- Included Set (IS)

All patients for whom the study drug is dispensed.

- Safety Set (SS)

All patients who received at least one dose of study medication will be included in the Safety Set.

- Full Analysis Set (FAS)

All patients who received at least one dose of study medication and with at least one assessment at baseline and during the study will be included in Full Analysis Set.

- Per Protocol Set (PPS)

All patients of the FAS and without major protocol deviations will be included in Per Protocol Set.

A table displaying all analysis populations will be presented by disease group and overall. A listing will be also provided.

5 PROTOCOL DEVIATIONS

A protocol deviation is defined as any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

A major protocol deviation is defined as a deviation which may affect the subject's rights, safety or well-being or the completeness, accuracy and reliability of the study data and so likely to bias significantly the interpretation of the primary efficacy criterion results.

All protocol deviations will be reviewed, in particular but not limited to:

- Deviations in inclusion and exclusion criteria
- Study treatment duration different from 48 weeks (336 days) ± 15 days (considering interruption periods if applicable)
- Study treatment interruption > 10 consecutive days
- Deviations in study drug intake/compliance (see section 10, compliance < 80% and > 120% on 48 weeks period)
- Non respect of visit schedule (see section 1.2)
- Intake of concomitant prohibited treatments (See protocol section 5.5),
- Missing or incomplete evaluation of the primary efficacy criterion.

All protocol deviations will be reviewed before study database lock and their grade (minor / major) will be classified before the statistical analysis, during the data review meeting.

The number and percentage of patients having at least one protocol deviation (minor and/or major) and at least one major protocol deviation will be described on the Included Set by disease group and overall.

All deviations will be also listed.

6 DESCRIPTIVE STATISTICS

Data will be summarized depending on the nature of variables:

- Continuous variables: number of patients with observed values, arithmetic mean, standard deviation (SD), minimum, Q1, median, Q3 and maximum. Mean, SD, Q1, median and Q3 will be given with an additional decimal than the reported variable itself.
- Categorical data: number and percentage (%) of patients per class. Regarding the percentage calculation, unless otherwise is specified, missing values will not be considered and one decimal will be provided.

Descriptive statistics will be given by disease group (CIDP, anti-MAG and CMT1) and overall if needed.

7 DISPOSITION OF PATIENTS

The number of screened and included patients should be provided by disease group and overall.

The number and percentage of included patients who completed or withdrew prematurely the study will be tabulated by disease group and overall. Study withdrawal reasons will be also given.

The study duration (weeks) will be provided by disease group and overall and calculated as [(Date of completion/discontinuation of the study – date of selection visit +1) / 7].

A listing will be also provided.

8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics at baseline (see definition in section 3.5) will be produced by disease group and overall on the FAS population.

If more than 10.0% of the FAS population are excluded from the PPS population, the demographic data and history of the disease will be repeated on the PPS population.

- Demographic data: age (years), sex, number of women with childbearing potential at baseline and for the women with childbearing potential, pregnancy test (HCG) at baseline.

  Age will be calculated as integer [(date of selection visit – date of birth)/ 365.25] with day of birth imputed as defined in section 3.2.

  A listing will be provided.

- History of the disease: Time since the first appearance of symptoms (years), progression (yes/no), if yes, time since the progression (years)

  Time since the first appearance of symptoms will be calculated as [(date of selection visit – date of the first appearance of symptoms + 1) / 365.25]

  Time since progression will be calculated as [(date of selection visit – date of progression + 1) / 365.25]

  In case of incomplete dates for the first appearance of symptoms or for progression, an imputation will be considered (see section 3.2).

  A listing will be provided.

- Medical history: The number and percentage of patients with at least one medical history at selection visit V1 will be described by disease group and overall using the MedDRA codes (version 22.0) of System Organ Classes (SOC) and preferred terms (PT).

Descriptive statistics at baseline for clinical examination and biological testing (except aetiology additional panel) will be included in safety analyses (see section 12).

Descriptive statistics at baseline for MRC sum score, INCAT sensory score, posturography parameters (analysis of walking: all parameters in the condition spontaneous speed; analysis of balance: center of pressure on anterior/posterior axis and center of pressure covered area in the four conditions - open/closed eyes and spread feet (60s)/feet together (60s)), ONLS score, timed

10-meter walk test, 6-min walk test, neurophysiological examination and excitability test will be included in efficacy analyses (see section 10).

9 PREVIOUS AND CONCOMITANT TREATMENTS

Previous and concomitant treatment reported names will be coded in Anatomic Therapeutic Chemical (ATC) codes with WHO-DD Type B3 Mars 2019.

Previous treatments will be defined as treatments stopped strictly before the first administration of study drug.

Concomitant treatments will be defined as treatments stopped the day or after the first administration of study drug or ongoing treatments at the end of study.

The number and percentage of patients with at least one previous treatment will be described according to the ATC1 and ATC2 by disease group and overall on Safety Set population.

In the same way, the number and percentage of patients with at least one concomitant treatment will be summarized according to the ATC1 and ATC2, by disease group and overall on Safety Set population.

In case of missing start/end date of treatment, imputation will be considered to define if previous or concomitant treatment (see section 3.2).

A listing of all previous and concomitant treatments will be provided.

10 ANALYSIS OF EFFICACY

10.1 Main criterion

10.1.1 Main criterion – primary analysis

The primary endpoint will be evaluated using the relative change from baseline to week 48 of the following criteria of demyelination:

- Motor nerve conduction velocity (m/s),
- Distal latency (ms),
- F wave latency (ms),
- Length of motor nerve potential (ms).

A maximum of eight nerves will be assessed for those four criteria:

- Right/left median,
- Right/left ulnar,
- Right/left peroneal,
- Right/left tibial.

Relative change from baseline will be considered as clinically significant for the patient when the value at week 48 is at least 10% improved compared to the baseline value at least for two out of these four criteria in at least three nerves out of eight investigated nerves.

Relative change from baseline will be calculated as [(value at week 48 – value at baseline) / value at baseline] * 100.

An improve is defined as an increase for the motor nerve conduction velocity, and as a decrease for distal latency, F wave latency and length of motor nerve potential.

Missing values at week 48 for the four criteria will be imputed as LOCF method (see section 3.2).

The primary endpoint, for the primary analysis, will be summarized as the number and percentage of patients with a clinical significant relative change (at least 10%) for at least two out of the four criteria in at least three nerves out of the eight investigated by disease group and overall on the FAS population.
For each of those four criteria, number and percentage of patients with at least 10% improved value at week 48 compared to baseline for at least three nerves out of eight will be summarized by disease group and overall on the FAS population, as well as the number and percentage of patients with a clinical significant change.

As sensitivity analysis, if more than 10.0% of the FAS population are excluded from the PPS population, same analysis will be performed on the PPS population.

10.1.2 Main criterion – secondary analysis

As secondary analysis of the primary endpoint, a description of the four criteria of demyelination will be provided at baseline and week 48, as well as the relative change from baseline at week 48 (as defined in section 10.1.1), by disease group and overall on the FAS population, considering all nerves pooled per patient and parameter. A Wilcoxon signed rank test will be performed overall for each parameter to assess if the relative change from baseline is statistically significant at week 48.
In the same as the primary analysis, missing values at week 48 will be imputed as LOCF method (see section 3.2).

A listing of relative changes for each nerve for each patient and for each criterion of demyelination (motor nerve conduction velocity, distal latency, F wave latency, length of motor nerve potential) will be provided as well as the results of primary criterion (success/failed).

10.2 Secondary criteria

The secondary endpoints are changes from baseline to week 48 in:

- ONLS score,
- MRC subscore (total muscle) and total score,
- INCAT Sensory Sum (ISS) Score,
- Posturography parameters:
    - Analysis of Walking: all parameters in the condition spontaneous speed
    - Analysis of Balance: center of pressure on anterior/posterior axis and center of pressure covered area in the four conditions (Open/Closed eyes and Spread Feet (60s)/Feet together (60s))
- Timed 10-meter walk test (s) (whatever the assistance),
- Distance 6-min walk test (m) (whatever the assistance),
- Supernormality (%),
- Strength-duration time constant (ms),
- Rheobase (mA),
- Refractoriness (%),
- Minimal absolute refractory period (ms),
- Maximal absolute refractory period (ms).

ONLS score, MRC score, INCAT Sensory Sum score, timed 10-meter walk test and distance 6-min walk test will be described at baseline and each post-baseline visit by disease group and overall on the FAS population. The absolute changes from baseline will be provided at week 48.

Posturography parameters and excitability testing (Supernormality, Strength-duration time constant, Rheobase, Refractoriness, Minimum and maximum absolute refractory period) will be described at baseline, week 24 and week 48 by disease group and overall on the FAS population. The absolute changes from baseline to week 48 will be also produced. Regarding the posturography parameters of the analysis of balance, the absolute changes from baseline to week 48 will be also produced only if 'orthostatic position, bare foot on a force platform' is reported and not when the test was conducted in a different condition specified under "other". A Wilcoxon signed rank test will be performed overall for each secondary criterion to assess if the absolute change from baseline is statistically significant at week 48.

In addition, a boxplot will be provided for each parameter displaying Q1, median and Q3 values at each visit by disease group.

Absolute change from baseline will be calculated as (value at week 48 – value at baseline).

Listings of secondary criteria will be provided.

11 COMPLIANCE

All patients should receive active drug 300mg/day, one capsule in the morning, one capsule at noon and one capsule in the evening (capsule of 100mg).

Three bottles, each containing 90 capsules, are dispensed to the patient at each post-baseline visit for three months. The patient is asked to use only one bottle per month. All unused investigational products are returned and checked by the investigator. The number of returned capsules and interruption periods (if applicable) are reported on the CRF at each visit.

The cumulative number of interrupted days per patient will be calculated as the sum of number of days of each interruption, with the number of days of an interruption = date restarted – date of last dose intake - 1

The actual treatment duration (weeks) will be calculated as the [extent of exposure in weeks – (cumulative number of interrupted days/7)], with extent of exposure calculated as defined in section 12.1.

The global compliance (%) will be calculated as (Actual number of capsules taken / Theoretical number of capsules taken during the actual extent of exposure) x 100

With:

- Actual number of capsules taken = Sum of number of capsules dispensed at each visit (V2 to V5) – Sum of number of returned capsules at each post-baseline visit (V3 to V6).
- Theoretical number of capsules taken will be calculated as follows:
    - If the time of the first study drug intake is morning:
        - if the time of the last study drug intake is evening, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake + 1) * 3]
        - if the time of the last study drug intake is noon, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake) * 3] + 2
        - the time of the last study drug intake is morning, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake) * 3] + 1
    - If the time of the first study drug intake is noon:
        - if the time of the last study drug intake is evening, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake) * 3] + 2
        - if the time of the last study drug intake is noon, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake) * 3] + 1
        - if the time of the last study drug intake is morning, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake) * 3]
    - If the time of the first study drug intake is evening:
        - if the time of the last study drug intake is evening, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake) * 3] + 1

- if the time of the last study drug intake is noon, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake) * 3]
- if the time of the last study drug intake is morning, then theoretical number of capsules taken = [(date of last study drug intake – date of first study drug intake) * 3] - 1

Descriptive summaries will be produced on the Safety Set population by disease group and overall for the following parameters: cumulative number of interrupted days per patient, actual treatment duration (weeks) and global compliance (%). A listing will be also provided.

12 SAFETY ANALYSIS

All safety analyses will be performed on Safety Set population.

12.1 Extent of exposure

The extent of exposure (weeks) will be calculated as (date of last study drug intake – date of first study drug intake + 1) / 7

The cumulative dose per patient (g) will be calculated as (actual number of capsules taken x 100mg) / 1000, with actual number of capsules taken calculated as defined in section 11.

Descriptive statistics will be tabulated by disease group and overall on Safety Set population and a listing will be given.

12.2 Adverse events

Any adverse event (AE) having been reported during the study for a given patient, will be classified by Preferred Term (PT) and corresponding System Organ Class (SOC) using the MedDRA terminology version 22.0.

Any AE recorded in the Adverse Events section of the CRF will be regarded as Treatment Emergent (TEAE) if it occurs during study drug period, or worsens after the first study drug intake.

The study drug period is defined as period from the day of the first study drug intake until 30 days (included) after the last study drug intake.

AEs occurring before the first study drug intake and worsening after the first study drug intake are reported as new AEs in the CRF with start date = worsening date.

Other AEs occurring during study and before the first study drug intake will be defined as pre-TEAEs (different from medical history).

AEs occurring beyond 30 days after the last study drug intake will be assigned as post-TEAEs.

In case of missing start/end date of AEs, imputation will be considered (see section 3.2) to define the emergence of AEs.

An AE will be defined as study drug related if the causality recorded in the CRF is "Definite", "Probable", “Likely”, "Possible", “Conditional” or missing. The AE will be defined as "Not Related" if the causality is "Unlikely" or “Not related”.

An AE will be defined as leading to a study drug discontinuation if “Drug withdrawn” is reported in the CRF.

AE duration will be computed in days as (end date – start date + 1).

A summary table describing an overview of the incidence of AEs in terms of the number and percentage of patients with at least one AE and number of events will be provided by disease group and overall with:

- Pre-TEAEs
- TEAEs
- TEAEs according to the intensity (Mild, Moderate, Severe)
- Serious TEAEs
- Study drug related TEAEs
- TEAEs leading to study drug discontinuation
- TEAEs leading to death
- Study drug related serious TEAEs
- Serious TEAEs leading to study drug discontinuation
- Study drug related serious TEAEs leading to study drug discontinuation
- Post-TEAEs

The number and percentage of patients with at least one AE and the number of events will be summarized according to SOC and PT for:

- All Pre-TEAEs
- TEAEs
- Serious TEAEs
- Study drug related TEAEs
- TEAEs leading to a study drug discontinuation
- TEAEs leading to death
- Post-TEAEs

A listing of all AEs will be performed, as well as SAEs.

12.3 Vital signs and clinical examination

Vital signs (temperature in °C, heart rate per minute and SBP/DBP in mmHg) will be summarized at baseline and each post-baseline visit by disease group and overall.

Clinical examination results (normal / abnormal) will be also tabulated by disease group and overall.

A listing of patients with abnormal clinical examination results will be given.

12.4 Laboratory evaluation

Following laboratory parameters will be described at baseline and week 48 by disease group and overall: RBC, hemoglobin, WBC, platelets, electrolytes (Na, K and Cl), protein, creatinine, glomerular filtration rate, fasting blood glucose, AST, ALT, total bilirubin, gamma glutamyl transferase (GGT), alkaline phosphatase, triglyceride, cholesterol and INR). In addition, a scatterplot displaying values at baseline and at week 48 per patient will be provided for the following same parameters, except glomerular filtration rate.

Number of abnormal values (< LLN or > ULN) will be summarized for each parameter by disease group and overall.

A listing of patients with abnormal laboratory results will be provided.

13 TABLES, FIGURES AND LISTINGS SHELLS

Shell tables are available in a separate document (See ShellTables_SERENDEM_version1.0_04NOV2019.docx).

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14 REFERENCE

The references are provided in the protocol.