STATISTICAL ANALYSIS PLAN

SARIZOTAN/001/II/2015

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SIX-MONTH STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF SARIZOTAN IN PATIENTS WITH RETT SYNDROME WITH RESPIRATORY SYMPTOMS

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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MODIFICATION HISTORY

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1.0	26NOV2019	Ayushi Chaturvedi	Not Applicable – First Version
2.0	30March2020	Ayushi Chaturvedi	Analysis related to primary, key secondary and other secondary endpoints have been updated as per protocol amendment 14.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	adverse drug reaction
AE	adverse event
ALT	alanine-aminotransferase
ANCOVA	analysis of covariance
AST	aspartic-aminotransferase
AUC	area under the plasma drug concentration vs. time curve
bid	twice daily
BUN	blood urea nitrogen
CGI-C	Clinical Global Impression – Change from baseline
CIC	Caregiver-rated Impression of Change from baseline
CI	confidence intervals
C_{max}	maximum post-dose plasma drug concentration
CNS	Central Nervous System
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
γGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
HDL	high density lipoprotein
HBV	Hepatitis-B Virus
HCV	Hepatitis-C Virus
hERG	human *Ether-a-go-go* Related Gene
HIV	human immunodeficiency virus
HR	heart rate
HPA	hypothalamic – pituitary – adrenal

IMP	Investigational Medicinal Product
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LC-MS/MS	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LDL	low density lipoprotein
LOCF	Last Observation Carried Forward
LS Mean	Least Squares Mean
MTD	Maximum tolerated dose
Min	Minimum
Max	Maximum
MMRM	Mixed Model Repeated Measures
PK	Pharmacokinetics
PRL	Prolactin
RBC	red blood cells
RCSS	Rett syndrome Clinical Severity Scale
RTT	Rett syndrome
SAE	Serious Adverse Event
SBP	systolic blood pressure
SE	Standard Error
SD	standard deviation
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings and figures
TSH	Thyroid Stimulating Hormone
VLDL	very low-density lipoprotein
WBC	white blood cells

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and tolerability data for Protocol Sarizotan/001/II/2015. It describes the data to be summarized and analyzed, including the specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 15.0, dated 17 March 2020. This statistical analysis plan is for the double-blind phase only. A separate SAP will be created for the open-label phase, Separate SAPs have been created for both the ECG and PK analyses.

The study was designed to demonstrate the efficacy of sarizotan 10 mg bid ("high" dose) compared to placebo on improvement in respiratory symptoms (primarily reduction of episodes of apnea) in patients with Rett syndrome (RTT) who were at least 13 years old and weighing at least 25 kg (protocol version 1.0, dated 27 October 2015). A lower dose of 5 mg bid was also evaluated to assess dose response. The 10 mg bid dose was selected, as it would be associated with plasma exposures (Cmax) exceeding 269 ng/mL (acute study) or 753 ng/mL (long-term study) that had been shown to be efficacious in reducing apnea episodes in a MeCP2 knockout mouse model of Rett syndrome (SN 0002, 7 May 2015).

Subsequently, based on regulatory requests, toxicology studies to enable treatment of younger patients were completed and the protocol was amended (Amendment 5) to allow enrollment of patients at least 6 years of age who weighed 10 kg or more (protocol version 6.0, dated 29 March 2017). As the body weight of these patients was lower than the originally envisaged population, the doses of sarizotan had to be reduced accordingly to ensure tolerability and achieve exposures comparable to the older patients. As a first step, data from the NIH Natural History study (Tarquinio et al, 2012) were reviewed to determine body weights that Rett patients between the ages of 6 and 13 years were likely to have. As a result the patients between the ages of 6 and 13 received a "high" dose of 5 mg bid or a "low" dose of 2 mg bid, as these doses in these younger patients were expected to achieve the same exposures as older patients greater than 13 years who were receiving doses of 10 mg ("high") bid or 5 mg ("low") bid.
Based on potential concerns for the safety of younger patients with low body weight (<18 kg) the randomization was amended to assign these patients only to the 2 mg bid or placebo groups, while younger patients with body weight of at least 18 kg were assigned to doses of 5 mg bid or placebo.

Based on the emerging data that did not detect any signs of intolerance in the patients treated in this study, and the feedback from Health Authorities who identified that this amended randomization would create imbalance in the treatment groups, the randomization was readjusted to revert to the original plan and randomize all patients equally to the three treatment groups (protocol version 8.0, Amendment 7dated 02 October 2017). Based on this, all younger patients were randomized equally to doses of 5 mg bid, 2 mg bid or placebo.
The protocol was further amended (Amendment 9) to allow inclusion of patients as young as

4 years of age (protocol version 10.0, dated 11 February 2018). However, no further adjustments to the doses administered were required as a result of this amendment.

Despite all these changes, the original intent of the study design to randomize patients equally (1:1:1) to "high" dose sarizotan, "low" dose sarizotan or placebo was maintained. In summary, the definition of the sarizotan "High Dose" group includes RTT patients whose dose was age-weight adjusted to either 10 mg bid or 5 mg bid. The sarizotan "Low Dose" group includes RTT patients whose dose was age-weight adjusted to either 5 mg bid or 2 mg bid.

As a result, the patients who received "High Dose" sarizotan include:

- 10 mg bid in patients ≥ 13 years with weight ≥ 25 kg,
- 5 mg bid in patients ≥13 years with weight < 25 kg,
- 5 mg bid in patients 4 to < 13 years with weight ≥10 kg.

The patients who received "Low Dose" sarizotan include:

- 5 mg bid in patients ≥13 years with weight ≥ 25 kg,
- 2 mg bid in patients ≥13 years with weight < 25 kg,
- 2 mg bid in patients 4 to < 13 years with weight ≥10 kg.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

To evaluate the effect of sarizotan (high dose), compared to placebo, on reducing the number of apnea episodes, during awake time, in patients with RTT with respiratory abnormalities.

2.2. SECONDARY OBJECTIVES

- Key Secondary efficacy: To evaluate the effect of sarizotan (high dose), compared to placebo, on the Caregiver-rated Impression of Change (CIC) from baseline.
- Safety: To evaluate the safety and tolerability of sarizotan in patients with Rett syndrome (RTT) with respiratory abnormalities.
- Efficacy: To evaluate the efficacy of sarizotan, compared to placebo, on the following:
    - Severity of patient symptoms based on evaluation of Caregiver Top 3 Concerns (Visual Analogue Scale [VAS]); Global change from baseline, assessed by the Clinical Global Impression of Change (CGI-C);
    - Motor behavior, assessed by the Motor-Behavioral Assessment Scale;

- Other respiratory symptoms of Rett syndrome, assessed during awake time, including:
  - Percent time spent with breathing dysrhythmia (% time apnea + % time hyperventilation) per hour
  - Number of hyperventilation episodes (≥10 seconds each) per hour
  - Oxygen saturation (number of episodes of oxygen desaturation below 90% per hour).
  - *Respiratory Distress Index* - The sum of the following parameters calculated per hour of wakefulness: 1) number of breath-holding episodes, 2) number of episodes of hyperventilation [1 and 2 are as defined in inclusion criteria; each would have to be ≥10 seconds in duration], and 3) number of drops in oxygen values to < 90%.

- Overall assessment of symptoms of RTT using the Rett syndrome Clinical Severity Scale (RCSS);

- To determine the efficacy of sarizotan in patients who attain a minimum plasma exposure of 400 ng /ml on Day 15 (expected efficacious concentration based on the knockout mouse model);
- To determine the PK profile of sarizotan at the doses tested and compare with the PK profile in adults.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase II/III, prospective, 24-week, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and efficacy of multiple oral doses of sarizotan in patients with RTT with respiratory abnormalities. This 24-week double-blind treatment period is followed by an open-label extension treatment period of up to 168 weeks, which is ongoing. Patients ≥ 4 years of age were randomized to the low or high dose groups of sarizotan or placebo, with the dose of sarizotan determined based on the patient's age and body weight (refer to *Appendix 5*).

Trial Duration:

The possible duration of the trial is up to 196 weeks, which includes:

- Screening Period (4 Weeks)
- Randomized, double blind treatment period (24 Weeks)

- Open-label extension period (168 Weeks)
- Safety Follow-up Period after final dose of study medication (2 Weeks)

Number of Subjects:

A minimum of 129 patients with RTT were to be included in this study, with approximately equal numbers of patients randomly being assigned to each of the following three treatment groups:

- low dose sarizotan [sarizotan 2 mg *bid* (age 4 to <13 years; or age ≥13 years, weight <25 kg) or 5 mg *bid* (age ≥13 years, weight ≥25 kg)],
- high dose sarizotan [sarizotan 5 mg *bid* (age 4 to <13 years; or age ≥13 years, weight <25 kg), or 10 mg *bid* (age ≥13 years, weight ≥25 kg)],
- or placebo *bid*.

The sample size estimate was based on the following assumptions:

- 3 treatment groups (2 active + placebo)
- Primary endpoint: Percent reduction in the number of apnea episodes (≥10 sec each) per hour
- H_0: Percent reduction in apnea episodes in placebo and active groups is the same
- H_A: There is a difference in the percent reduction in apnea episodes between high dose sarizotan and placebo.

The assumptions for the estimated standard deviation (SD) are based on limited data from a study by Khwaja et al. (2014), in RTT patients. There were only 5 patients with data reported for apnea index (for apnea episodes > 10 seconds). Pilot observational data collected using the BioRadio™ device in 26 patients with RTT indicated that the number of episodes of apnea may approach 60 per hour. Based on the range of 10-60 episodes per hour, ranges of 10-30, 10-45 and 10-60 apnea episodes per hour indicate SDs of 5.0, 8.75 and 12.5, respectively.

Sample sizes were computed to determine the number of patients required to detect a minimum difference in mean percent reduction of 20% (high dose sarizotan 30%, placebo 10%; see Table 1) and 10% (high dose sarizotan 20%, placebo 10%; see Table 2), based on differences between high dose sarizotan and placebo.

Table 1. Sample Size Estimates Assuming 90% Power and – 20% Difference

Parameter	1	2	3	4
Test significance level, α	0.050	0.050	**0.050**	0.050
1 or 2 sided test?	2	2	**2**	2
High Dose mean % Chg, μ_1	-30.00	- 30.00	**- 30.00**	-30.00
Placebo mean % Chg, μ_2	-10.00	-10.00	**-10.00**	-10.00
Difference, $\mu_1 - \mu_2$	-20.00	-20.00	**-20.00**	-20.00
Common St. Dev., σ	12.50	15.00	**20.00**	25.00
Effect size, $\delta = \lvert \mu_1 - \mu_2 \rvert / \sigma$	1.60	1.33	**1.00**	0.80
Power (%)	90	90	**90**	90
n per group	10	13	**23**	34

Table 2. Sample Size Estimates Assuming 90% Power and – 10% Difference

Parameter	1	2	3	4
Test significance level, α	0.050	**0.050**	0.050	0.050
1 or 2 sided test?	2	**2**	2	2
High Dose mean % Chg, μ_1	-20.00	**- 20.00**	- 20.00	-20.00
Placebo mean % Chg, μ_2	-10.00	**-10.00**	-10.00	-10.00
Difference, $\mu_1 - \mu_2$	-10.00	**-10.00**	-10.00	-10.00
Common St. Dev., σ	20.00	**12.50**	8.75	5.00
Effect size, $\delta = \lvert \mu_1 - \mu_2 \rvert / \sigma$	0.50	**0.80**	1.14	2.00
Power (%)	90	**90**	90	90
n per group	86	**34**	18	7

Sample sizes of 23 or 34 in each treatment group would have 90% power to detect a difference in mean percent reduction of -20% or -10%, respectively, assuming a common SD of 20 (for the 20% reduction) and 12.5 (for the 10% reduction), using a two group t-test with a 0.050 two-sided significance level. Assuming an attrition rate of 25% (7 or 9 patients) per group, a total of 30 or 43 patients would need to be enrolled in each group to get 23 or 34 patients completing the study. As this is the first large-scale study evaluating the effect of sarizotan on respiratory symptoms in patients with RTT, a conservative estimate of 10% reduction in apnea episodes was used to estimate the sample size required, i.e. approximately 43 patients per group.

Mode of dose: Oral (capsules), or as a solution either orally (for patients with swallowing difficulties) or through a gastrostomy tube (G-tube)

Blinding:

A randomization number corresponding to the treatment assignment was assigned to each randomized subject using an Interactive Web Response System (IWRS), and was registered in the subject's files for identification. If it was necessary to break the blind during the double-blind period for reasons of safety, the Investigator was able to break the blind using the IWRS. The Investigator was asked to inform the Sponsor and their representative of this as soon as possible and to provide a reason for the unblinding.

3.2. SCHEDULE OF EVENTS

The schedule of events for the 24-week, double-blind, treatment period can be found below, and in Section 11.3 of the study protocol.

Visit Assessment	Screening	Baseline[A]	Day 1	Day 2	Day 7	Day 14	Day 15	Week 8	Week 16	Final (Week 24)[H]	Safety follow-up[J]
Study day(s)	**-28 to -1**	**0**	**1**	**2**	**3-7**	**8-14**	**15**	**16-56**	**57-112**	**113-168**	**169-182**
Informed consent (before any study procedure)	X										
Inclusion/Exclusion Criteria	X	X									
Demography/Background Information	X										
MECP2 gene mutation confirmation	X[P]										
Medical History and Current Medical Conditions	X										
Vital Signs	X	X[C]	X[C]	X		X	X	X	X	X	X
ECG (12-lead)	X	X[D]	X[D]	X		X	X	X	X	X	
Physical Examination	X	X[B]		X		X		X	X	X	
Neurological Examination	X	X[B]		X		X		X	X	X	
Ophthalmological Examination		X							X	X	
Laboratory Evaluation (Hematology, Biochemistry, Urinalysis)	X	X[B]				X		X	X	X	
Thyroid Function Tests (TSH, T3, T4)	X										
Virology (Hepatitis B/C, HIV)	X										
Plasma ACTH and cortisol		X		X					X	X	
Serum prolactin		X							X	X	
Serum pregnancy test [O]	X	X								X	
Tanner Staging		X								X	
Suicidality assessment		X						X		X	
Dosage administration and drug label record			X	X	X	X	X	X	X	X[K]	

Assessment \ Visit	Screening	Baseline[A]	Day 1	Day 2	Day 7	Day 14	Day 15	Week 8	Week 16	Final (Week 24)[H]	Safety follow-up[J]
Prior/Concomitant Medications and Significant Non-Drug Therapies	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X[E]	X
Respiratory monitoring (in clinic) [M]		X							X	X	
Respiratory monitoring (at home) [N]	X					X		X	X	X	
CGI-C						X		X	X	X	
CIC						X		X	X	X	
RCSS		X								X	
Motor-Behavioral Assessment Scale		X						X	X	X	
Caregiver Top 3 Concerns		X						X	X	X	
Telephone contact [G]					X						
Pharmacokinetic blood sample			X[F]				X[F]				
Overnight stay (hotel/housing) required		X	X	X[L]		X	X[L]				
Study Completion										X[I]	X

[A] Patients meeting all entry criteria will report to the hospital/clinic on Day 0. Baseline evaluations may be started on Day 0 and continued on Day 1 pre-dose. Following completion of baseline evaluations, subjects will be randomized and dosed on Day 1.

[B] This evaluation does not need to be performed at baseline unless the screening assessment was done more than 28 days beforehand or there were abnormalities noted that require follow-up.

[C] Vital signs to be performed at baseline must be repeated 3 times, with an interval of at least 10 minutes between readings, on Day 0 or at least 1 hr prior to dosing on Day 1, and at 1 and 4 hr post-dose, just prior to taking blood samples for PK measurements.

[D] 12-lead ECG will be performed at baseline and repeated 3 times, with an interval of at least 10 minutes between readings, on Day 0 or at least 1 hr prior to dosing on Day 1, and at 1 and 4 hr post-dose, just prior to taking blood samples for PK measurements.

[E] Patients will be contacted 30 days after their final dose of study medication to follow up on the occurrence of any SAEs.

[F] A pre-dose PK sample will be taken, and samples will be collected at 1 and 4 hr post dose (window ± 15 min).

[G] Telephone contact with patient/caregiver will be done on Day 7 to assess tolerability of current dose of study medication, before the increase to Dose Level 3 and Dose Level 4 on Days 8 and 9, respectively; adverse events and concomitant medication use will be assessed.

[H] All Week 24 (Final) evaluations should be performed when a subject discontinues from the study prematurely.

[I] Patients completing 168 days (+/- 7 days) of treatment will be considered to have completed the initial 6-month period of the study.

[J] Safety follow-up assessments to be performed 14 days after the final dose of study medication, if the patient is not continuing in the open-label extension

treatment period, or if the patient discontinues prematurely.

[K] Record dosing from last 8-week period. Dose administration will be done only for patients continuing in the open-label extension treatment period.

[L] Patient will be released from the hospital on Day 2 and Day 15, approximately 4 hr after the morning dose, if there are no tolerability issues.

[M] During outpatient treatment, patients will undergo cardio-respiratory monitoring using a specialized ambulatory data acquisition system (BioRadio). In addition, respiratory function will be assessed in the clinic using a similar device (SOMNOtouch).

[N] During outpatient treatment, patients will undergo cardio-respiratory monitoring using a specialized ambulatory data acquisition system (BioRadio). Respiratory monitoring will be attempted at home for 6 hours each day during the time awake at Screening (three 3-day periods during the first, second and third week), and on any 3 days in the week preceding each subsequent scheduled office visit. Data recorded using this system will be downloaded from the device at home using the Internet/WiFi or a dedicated laptop provided by the Sponsor, if Internet access is not available; data collected during the screening test period will be verified for accuracy by Vivonoetics.

[O] To be performed for all post-pubertal females.

[P] MECP2 genetic mutation testing will be performed only if the patient has not had the test performed previously, or does not have adequate documentation of the test results from an accredited laboratory.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

None.

4. PLANNED ANALYSES

One analysis is planned for the 24-week, double-blind treatment period, and a separate analysis will be performed for the open-label extension period, once it is completed. The analysis of the data from the open-label period will be described in a separate SAP. The analysis for PK parameters and analysis for ECG data will also be described in separate SAPs.

4.1. INTERIM ANALYSIS

No interim analysis was planned for this study.

4.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics team following Sponsor authorization of this SAP and Database Lock.

5. ANALYSIS POPULATIONS AND STUDY PERIOD

Subjects to be included/excluded from each analysis population set will be determined before unblinding

5.1. ITT POPULATION

The Intent-to-Treat (ITT) population will include all patients who were randomized to treatment.,.

This population will be used for all efficacy analyses.

5.2. PER PROTOCOL POPULATION

The Per Protocol population will include all patients in the ITT population who also meet the

following criteria:

- Have no critical protocol deviations during the study, including meeting critical study entry criteria.
- Have been compliant with study medication administration, as evident from a "Yes" response to the CRF question "Was the IP taken Per Protocol (PP) (two times a day)?" on the drug accountability form at the Week 24 (final) visit. In patients with a "No" response, a further review of the compliance data at Week 24 was performed to identify those to be excluded from the Per Protocol population.
- Have no major efficacy data missing.

Patients who meet the above criteria will be identified prior to database lock and unblinding.

This population will be used for supportive efficacy analyses.

5.3. SAFETY POPULATION

The Safety population will include all patients who took at least one dose of study medication. The safety analyses are based on the actual treatment received.

This population will be used for all safety analyses.

5.4. 24-WEEK DOUBLE-BLIND TREATMENT PERIOD

The 24-week, double-blind, treatment period included all patients who provided informed consent, or the patient's parent, legal guardian, or representative provided written informed consent, prior to the patient's participation in the trial, met all of the selection criteria, including diagnostic and respiratory criteria, for enrolment in the study, and were randomized to treatment.

5.5. INITIAL 24-WEEK OPEN-LABEL EXTENSION TREATMENT PERIOD

Patients were eligible for the 24-week Initial open-label treatment period if they completed the final evaluations at Week 24 (Day 168), and met the following criteria:

1. Had no safety or tolerability issues that would have precluded continuing the study medication.
2. Had been compliant with the trial requirements.
3. Had not worsened to the extent that they were considered at an increased risk for

morbidity or mortality, as judged by the Investigator.

5.6. THREE ADDITIONAL 48-WEEK OPEN-LABEL EXTENSION TREATMENT PERIODS

Three additional 48-week open-label treatment periods were added to the study and will include all patients who provided informed consent at Weeks 48, 96 and 144, and for whom the investigators believe the patients are benefitting from treatment with sarizotan and are not experiencing any significant adverse events.

6. GENERAL CONSIDERATIONS

Descriptive statistics for continuous variables will be summarized by treatment group with n, mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Descriptive statistics for categorical variables will be summarized by treatment group with count and percentages. All percentages should use the total number of subjects with data available in the relevant analysis set as the denominator, unless otherwise specified. Categories for missing data will be presented as appropriate.

Decimal places format

In general, the number of decimal places displayed for each statistic will be determined as follows, unless otherwise specified:

Descriptive Summaries	
Range (Min, Max)	Recorded decimal places
Mean, Median, Geometric Mean	Recorded decimal places + 1
Standard Deviation, Standard Error	Recorded decimal places + 2
Inferential Statistics	
LS Means, Difference in LS Means	Recorded decimal places + 1
CI's corresponding to LS Means and Difference in LS Means	Recorded decimal places + 2
Odds Ratio	Recorded decimal places + 3
Listings	Recorded decimal places

Percentages: All percentages between 0 and 99 will be rounded to one decimal unless there is a need to report more than one decimal for percentages (e.g., AEs).

P-values, if any, shall be reported to four decimal places or as <0.0001.

Data from subjects excluded from an analysis set will be included in the data listings, but not in the summaries.

6.1. REFERENCE START DATE AND STUDY DAY

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

Reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

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 durations will be presented based on the imputations specified in Appendix 1; Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data will be reported by the protocol-defined nominal visit. For each nominal visit a pre-specified analysis window has been defined (Section 8). These analysis windows will define the visit at which the data are reported. Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. STATISTICAL TESTS

All statistical tests of treatment effects will be conducted to compare sarizotan (high dose group and low dose group) versus placebo at a two-sided alpha level of 0.05, unless otherwise specified.

6.5. COMMON CALCULATIONS

For quantitative measurements, change from baseline at Visit X will be calculated as:

Value at Post-baseline Visit X – Baseline Value

For quantitative measurements, percentage change from baseline at Visit X will be calculated as:

((Value at Post-baseline Visit X – Baseline Value)/Baseline value)*100

Age will be calculated as following:

Age = (Date of informed consent - Date of Birth + 1) / 365.25

6.6. SOFTWARE VERSION

All analyses will be conducted using SAS Enterprise Guide7.13 (64-bit).

7. STATISTICAL CONSIDERATIONS

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

Baseline value and age will be adjusted as covariates, and treatment as fixed factor will be included in the analyses wherever applicable.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers. Randomization to treatment arms was not stratified by country/ center. Centers will be grouped in regions for purposes of the analyses as follows:

- Europe (United Kingdom and Italy)
- India
- US and Australia.

7.3. MISSING DATA

All data obtained for the ITT population will be used in the analysis. Missing efficacy data for the primary endpoint will not be imputed. Last observation carried forward (LOCF) method will be adopted as imputation for the secondary quantitative endpoints (wherever required). Details of which endpoint will be imputed using LOCF approach can be found in the respective endpoint's section description.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

The study level error rate will be controlled by following a sequential multiple testing procedure, where testing will begin with the primary efficacy endpoint. The effects of the high dose sarizotan versus placebo will be analyzed first for all parameters in a pre-specified sequence.

The sequence of testing will be as presented below:

- Percentage reduction (change) from baseline in the number of apnea episodes,
- Mean rating of CIC
- Mean change from baseline in the Top Three Concerns Total Score.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be performed for patients dichotomized by age groups of less than 13 years of age, and 13 years of age and older.. No inferential statistics will be performed for these sub-groups.

8. OUTPUT PRESENTATIONS

In tables, the order and naming of the treatment groups will be as follows:

- Sarizotan Low Dose
- Sarizotan High Dose
- Placebo

In addition to the above treatment groups, the outputs will also be presented for Sarizotan threshold plasma concentration for the primary efficacy and demographics as follows

- Sarizotan (>400 ng/ml)
- Placebo

In addition to above treatment groups, the outputs will also be presented for Sarizotan pooled dose as follows:

- Sarizotan (all doses)
- Placebo

In listings, the order and naming of the treatment groups will be as follows:

- Sarizotan Low 2 mg dose
- Sarizotan Low 5 mg dose
- Sarizotan High 5 mg dose
- Sarizotan High 10 mg dose

Placebo

For visit presentations, the naming of the visit will be as follows:

Screening
Day 0 (Baseline)
Day 1
Day 2
Day 7
Day 14
Day 15
Week 8
Week 16
Week 24
Safety Follow-up

8.1. DATA SELECTION FOR DOUBLE BLIND TREATMENT PERIOD (24 WEEKS)

For patients who enter the open-label extension treatment period, all data up to and including the date of the first dose in the open-label extension phase will be considered as part of the double-blind treatment period (24 weeks). For patients who do not enter the open-label extension, all data will be included in the double-blind treatment period (24 weeks).

8.2. VISIT WINDOWS:

The following visit windows will be used for analyses of efficacy endpoints:

Visit	**Window**
Screening (day - 28)	Day - ∞ to day -1
Baseline (day 0)	Day -28 to day 0 (last value before first dose of study drug) [Baseline for the BioRadio™ data will be the last value prior to Day 1 (no cutoff at Day -28)]
Day 1	No window (day of the first dose taken)
Day 2	No window (immediately after day 1)
Week 2 (day 14)	Day 1 to day 35
Day 15	No window (immediately after day 14)
Week 8 (day 56)	Day 36 to day 84
Week 16 (day 112)	Day 85 to day 140
Week 24 (day 168)	Day 141 to day 196
Safety follow - up	Day 1 – Day 30 where Day 0 Is the day when the patient discontinues the study. This Is likely to be a scheduled visit day – but possibly an unscheduled visit. Operationally it might be identified by being the previous day that a vital sign was measured (or any other measurement that is done when a patient either reaches Week 24 or discontinues prematurely – as per the protocol schedule of evaluations). Importantly the patient is no longer on drug during this entire window.

Note: Day 1 = first dosing day of study drug

If there is more than one record within the same window, the non-missing value closest to the scheduled visit study day will be used for analyses. If two values are equidistant from the scheduled visit day, the earliest non-missing value will be used.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be summarized.

Disposition summary will be provided by study period separately for all randomized subjects.

The frequency and percentage of randomized subjects who complete the study or discontinue early will be summarized by treatment group and overall. Reasons for discontinuation from the study will also be summarized.

The number of subjects in each population will be presented by treatment groups and overall.

A list of critical protocol deviations will be provided for the randomized population. A summary of critical or major protocol deviations with reason for the deviation will be provided as counts and percentages.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented and summarized for all randomized subjects.

No statistical testing will be carried out for any demographic or baseline characteristics. Patient characteristics will be recorded at the screening visit and will be listed by patients and summarized by treatment groups. Overall summaries will include descriptive statistics for continuous measures (n, mean, SD, median, minimum, and maximum) and for categorical measures (n, count, and percent). Missing categories will be represented as appropriate.

Rett syndrome history will be summarized by treatment and overall for the following:

- Duration of Rett syndrome (in months) defined as:

(Date of Informed Consent – Date of Diagnosis of Rett syndrome)/30.25

- Count and percentages of all responses for “Respiratory abnormalities”

11. MEDICAL HISTORY

Medical History information will be presented and summarized for the safety population and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 22.0.

Medical History will be recorded at the Screening visit.

Counts and percentages of Medical History conditions will be presented by treatment groups, SOC and preferred term. Also a list of medical history findings will be provided.

12. MEDICATIONS

Medications will be presented and summarized for the safety population and coded using World Health Organization (WHO) DRUG dictionary of medical code.

Prior and concomitant medications during the study will be summarized using ATC level 3 coding.

- 'Prior' medications are medications which started and stopped prior to first dose of study medication.
- 'Concomitant' medications are medications which ended on or after first dose of randomized study medication or ongoing at the end of the study.

The number of patients with concomitant medications will be summarized using count and percentages by therapeutic class, preferred term, treatment group and overall. Patients are counted only once in each therapeutic class category, and only once in each preferred term category.

A list of prior and concomitant medications (includes procedures) will be provided separately.

Concomitant medication (includes procedures) summary will be provided period-wise separately.

See Appendix 1 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.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be summarized for the Safety Population.

The total duration of study medication administration will be taken from the "Study medication administration" form of the eCRF.

Duration of exposure (in Days) will be summarized descriptively.

Duration of exposure (in Days) = Date of Last dose – Date of First Dose +1

Interruptions and compliance are not taken into account for duration of exposure.

14. STUDY TREATMENT NON-COMPLIANCE

List of the treatment non-compliance (<80%) will be provided for the Safety population based on the data from DB period.

15. EFFICACY OUTCOMES

Summaries will include descriptive statistics for continuous measures (n, mean, SD, median, minimum and maximum) and for categorical measures (n, frequency and percentage).

15.1. PRIMARY EFFICACY

15.1.1 PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy outcome in the double-blind period will be the percent reduction (change) from baseline in the number of apnea episodes (each ≥10 seconds in duration) per hour, during awake time. The data was obtained from the vendor Vivonoetics. Assessment of the respiratory outcomes was performed at home on any 3 days in each of the first 3 weeks of the screening period, and in the week prior to each of the visits at Weeks 2, 8, 16, and 24.

15.1.2 MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

Primary efficacy variable will not be imputed.

15.1.3 ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary efficacy analysis for the 24-week, double-blind, treatment period will be performed on the Intent-to-Treat (ITT) population, consisting of all patients who were randomized to treatment.

Primary efficacy variable is percent reduction (change) from baseline in the number of apnea episodes (each ≥10 seconds in duration) per hour, during awake time, obtained from the BioRadio™.

The primary efficacy test of hypothesis is as below:

H_0: There is no difference in mean percent reduction (change) from baseline in number of apnea episodes in placebo and Sarizotan high dose group.

H_A: There is a difference in the mean percent reduction (change) from baseline in number of apnea episodes in placebo and Sarizotan high dose group..

Descriptive statistics will be presented for actual value, change from baseline and percentage change from baseline in apnea episodes by visit and treatment groups.

Prior to analyzing the primary efficacy data, a blinded data review will be performed to identify outliers. The potential outliers would be examined and determined if the value is clinically plausible and removed from the analysis if not. The primary inferential comparison between treatment groups will be done using a restricted maximum likelihood (REML)-based, mixed-effects repeated measures model approach (MMRM) along with 95% confidence interval for the difference between treatment groups for percent change from baseline in the number of apnea episodes. The MMRM model will include percent change from baseline as response, the fixed, categorical effects of treatment group, visit, treatment group-by-visit interaction, and the continuous terms age and baseline value as covariate. The data collected at Baseline, Week 2, Week 8, Week 16 and Week 24 will be used in the MMRM model.

An unstructured covariance matrix will be used to model the within-subject correlation. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the model for unstructured covariance matrix fails to converge, other covariance structures will be considered using Akaike information criterion/Bayesian information criterion method to find appropriate covariance structure, for e.g. a heterogeneous autoregressive covariance structure.

The differences in LS means will be calculated along with associated standard errors, 2-sided 95% confidence intervals and p-values.

The above analysis will also be repeated on the PP population.

A sensitivity analysis will be performed for the ITT population to include all data (including outliers) to check the robustness of the primary analysis to potential outliers.

Additionally, graphical presentations will be provided.

15.1.4 KEY SECONDARY EFFICACY VARIABLE

The key secondary efficacy outcome was the difference between sarizotan and placebo on the Caregiver-rated Impression of Change (CIC) from baseline, a 7-point Likert-type scale for which ratings range from 1 = very much improved to 7 = very much worse, with 4 = no change. The key secondary efficacy analysis will be performed for the ITT population.

Summary statistics for CIC mean rating scores will be provided by visit and treatment group.

The mean rating of the caregiver-rated CIC at Week 24 LOCF will be compared between treatment groups using the Van Elteren test (a stratified Cochran Mantel Haenszel test with modified ridit scores). The following age strata will be considered in the analysis:

<13 years

>=13 years

Improvement on the CIC (i.e. Responder) will be defined as a Likert scale score of 1 (very

much improved), 2 (much improved) or 3 (minimally improved). The proportion of patients with a rating of improvement in the CIC (n, count, and percent) will be presented at post-baseline visits by treatment group.

In addition to the above analysis, comparisons between treatments for the proportion of responders at Week 24 LOCF will be done using logistic regression. The logistic regression model will include treatment group and age. For the treatment comparison, an estimate of the odds ratio, corresponding Wald 95% CI and chi-square p-value will be presented.

Additionally, graphical presentation will be provided for the proportion of responders at Week 24.

In accordance with the original protocol (dated 27 October 2015, Section, page 70, Section 15.2.6) and the amended protocol (version 11.0, incorporating protocol Amendment 10, dated 29 November 2018, page 100, Section 15.2.6) as referred to in the FDA minutes of the meeting of February 5, 2020 issued by the FDA March 4, 2020, the Sponsor has reverted to using the "win" criteria referred to in these sections, as directed by FDA. A statistical "Win" will be claimed if the following results are obtained in the primary and key secondary efficacy analyses:

- Statistically significant difference between high dose sarizotan (5 or 10 mg bid) and placebo in the percent reduction (change) from baseline in the number of apnea episodes (each ≥10 seconds in duration) per hour, during awake time;
- Directional change on the CIC in favor of high dose sarizotan (5 or 10 mg bid) group compared to placebo.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses described in SAP section 15.2.1.1 will be performed for the ITT population with LOCF imputation. Efficacy analyses described in SAP section 15.2.1.2, 15.2.1.3, 15.2.1.4, 2 and 15.2.1.5 will be performed for the ITT population.

15.2.1 SECONDARY EFFICACY VARIABLES & DERIVATIONS

Change from baseline calculation will be done as defined in section 6.5.

15.2.1.1 Change from Baseline in Total Score of Caregiver Top 3 Concerns at Week 24

The severity of patient symptoms will be assessed using the Caregiver Top 3 Concerns scale, which uses a 100-mm visual analogue scale (VAS). The caregiver will select the 3 symptoms that are most problematic at baseline from a list of 12 possible concerns, and will rate each one using the VAS to indicate the severity on a scale of 0 to 100. The

same 3 symptoms will be rated using the VAS at the scheduled visits at Weeks 8, 16, and 24 in the double-blind treatment period. The Top 3 Concerns Total Score for each patient is calculated as the sum of the score for the 3 concerns rated. This total score can range from 0 to 300.

15.2.1.2 Mean rating of Clinical Global Impression of Change (CGI-C) at Week 24

The CGI-C rating scale permits a global evaluation of the subject's improvement or worsening over time. At each post-baseline visit, the rater will assess the change in the subject's symptoms of RTT relative to the symptoms at baseline using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. The CGI-C assessment will be conducted on Day 14, and at Weeks 8, 16 and 24 (or at early discontinuation) during the initial double-blind treatment period, and will be based on the patient's condition at the Baseline visit.

Improvement on CGI-C (i.e. Responder) will be defined as a Likert scale score of 1 (very much improved) or 2 (much improved) or 3 (minimally improved).

15.2.1.3 Change from baseline to Week 24 in Motor-Behavioral Assessment Scale (MBAS)

The MBAS is comprised of three sub-scales i.e. Behavioral/Social Assessment (included 16 items), Orofacial/Respiratory Assessment (included 7 items) and Motor Assessment/Physical Signs (included 14 items).

Each item is rated on a scale from 0 to 4, with '0' indicating normal or never, and '4' indicating very severe or constant.

To see the change in Motor-Behavioral Assessment Scale, change from baseline will be calculated at Week 24, considering the grand total score (all 3 sub-scales), as well as the total score on each of the three sub-scales.

Day 0 will be considered as baseline for this endpoint.

15.2.1.4 Change from baseline to Week 24 in other respiratory symptoms of RTT

The following additional respiratory parameters will be analyzed:

- Percent time spent with breathing dysrhythmia (% time apnea + % time hyperventilation) per hour;
- Number of hyperventilation episodes (≥10 seconds each) per hour;
- Oxygen saturation (# of episodes of oxygen desaturation below 90% per hour).
- Respiratory Distress Index - The sum of the following parameters calculated per hour of

wakefulness: 1) number of breath-holding episodes, 2) number of episodes of hyperventilation [1 and 2 are as defined in inclusion criteria; each would have to be ≥10 seconds in duration], and 3) number of drops in oxygen values to < 90%.

- Apnea episodes collected parallel at the hospital/clinic at Baseline and at Weeks 16 and 24, using a stretch-sensitive resistance plethysmograph (SOMNOtouch)

Data from the Bio-Radio and the SOMNOtouch will not be pooled and will be analyzed separately.

Data for determination of these additional respiratory outcome parameters was collected during home cardiorespiratory recording using the BioRadio™ and in parallel at the hospital/clinic at Baseline and at Weeks 16 and 24, using a stretch-sensitive resistance plethysmograph (SOMNOtouch) and was obtained from the vendor Vivonoetics.

To see the change in other respiratory symptoms of RTT, change from baseline will be calculated at Week 24.

15.2.1.5 Change from baseline to Week 24 in Rett syndrome Clinical Severity Scale (RCSS)

The RCSS scale will assess the severity of symptoms of RTT. This scale contain 13 items which measure and provide a clinician rating of core symptoms of Rett syndrome on a Likert scale of either 0 to 4 or 0 to 5, with a maximum total score of 58.

The change in RCSS, will be determined by calculating the difference between baseline and Week 24 for the total score of RCSS . Day 0 will be considered as baseline for this endpoint.

15.2.2 Missing Data Methods for Secondary Efficacy Variables

Last observation carried forward (LOCF) method will be adopted as imputation in the presence of at least one post-baseline observation if data is collected at multiple visits post baseline and is missing. Missing items in, Top 3 concerns score at baseline will be imputed with the mean baseline value of that item of all patients in the analysis population. There will be no imputation for MBAS, RCSS and Other Respiratory symptoms of RTT since only descriptive summary is presented.

15.2.3 Analysis of Secondary Efficacy Variables

15.2.3.1 Analysis of Caregiver Top 3 Concerns Total Score at Week 24

Descriptive statistics will be presented for actual value, change from baseline and percentage change from baseline in Top 3 Concerns total score by visit and treatment groups.

Comparisons between treatments will be done using an ANCOVA model. The model will include treatment group and the baseline value along with age as covariates. Change will be estimated using the least-squares mean derived from the ANCOVA. Comparisons between treatment groups at Week 24 will be made using the difference in least-squares mean, 95% confidence interval (CI) and p-values from the ANCOVA model.

Additional summaries of the Top 3 Concerns will be presented as follows:

i. Frequency and percentage of all Top 3 Concerns reported.

ii. Mean change and percent change from baseline for each Top 3 Concern reported.

iii. The number and percentage of patients with at least a 20% improvement in the Top 3 Concerns Total Score.

Additionally, graphical presentation will be provided.

15.2.3.2 Analysis of mean rating of Clinical Global Impression of Change (CGI-C) at Week 24

Summary statistics for the proportion of responders on the CGI - C (n, count, and percent) will be presented at all available scheduled visits for 24-week double-blind treatment period as per protocol.

Summary statistics will also be presented for the CGI-C mean change score and summarized by visit. Additionally, graphical presentation will be provided.

15.2.3.3 Analysis of change from baseline to Week 24 in Motor-Behavioral Assessment Scale (MBAS)

Descriptive statistics will be presented by treatment group for actual and change from baseline in Motor-Behavioral Assessment scale, both for subtotals and grand total at all available scheduled visits for the 24-week double-blind treatment period, as per protocol.

15.2.3.4 Analysis of change from baseline to Week 24 in other respiratory symptoms of RTT

Descriptive statistics will be presented by treatment group for actual values and change (or percent change) from baseline in other respiratory symptoms of RTT for both BioRadio™ and SOMNOtouch (***Refer to Section 15.2.1.4 for list of other respiratory symptoms***) at all available scheduled visits for the 24-week double-blind treatment period, as per protocol. Data from the Bio-Radio and the SOMNOtouch will not be pooled and will be analyzed separately.

15.2.3.5 Analysis of change from baseline to Week 24 in Rett syndrome Clinical Severity Scale (RCSS)

Descriptive statistics will be presented by treatment group for actual score and change from baseline in the Rett syndrome Clinical Severity Scale (RCSS) at Week 24 of the double-blind treatment period, as per protocol.

15.2.4 EXPLORATORY VARIABLES & DERIVATIONS

Primary efficacy endpoint will also be analyzed for the group of patients who have Sarizotan threshold plasma concentration (>400 ng/ml) vs placebo. The analysis will be analyzed as described in Section 15.1.3. Additional analyses based on exposure and response will be performed.

16. QUALITY OF LIFE ANALYSIS

Not applicable.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety population.

17.1. ADVERSE EVENTS

Adverse Events (AEs) are be coded using MedDRA central coding dictionary version 22.0.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with drug administration, whether or not related to the product.

The above definition covers also cases of

- Exacerbation of pre-existing diseases or conditions.
- Pre-existing diseases or conditions (reported at time of screening in medical history) will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition.
- Events occurring in subjects treated with matching placebo are also considered AEs.

An AE will be defined as a treatment-emergent adverse event (TEAE) if the first onset (or

worsening, in the case of pre-existing disease) is after the first administration of study treatment throughout the study. In addition, any serious adverse events (SAEs) reported in the 30 days following last dose of IMP will be recorded and counted in the final clinical study report.

See Appendix 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates. Listings will include TEAEs and Non-TEAEs. Listings will be provided for TEAEs, SAE and TEAEs leading to discontinuation from study for safety analysis set.

17.1.1 ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum intensity, and by relationship to study medication.

An overview of AE's will be provided with patients experiencing n (%) at least one SAEs, AEs, TEAE, treatment related TEAE, treatment related SAE, Number of patients died and patients discontinuing the study due to AE.

An overview of AE summary will be provided each period wise separately.

17.1.2 INTENSITY

Intensity is classed as mild, moderate, severe. TEAEs starting after the first dose of study medication with a missing intensity will be classified as severe. If a subject reports a TEAE more than once within that SOC/PT, the AE with the greatest intensity will be used in the corresponding intensity summaries.

17.1.3 RELATIONSHIP TO STUDY DRUG

Relationship, as indicated by the Investigator, is classed as " Probable", "Possible", "Unlikely" , "Not related" and "Unknown". A "related" TEAE is defined as a TEAE with a relationship to study medication as " Probable", "Possible" and "Unknown" to study medication. TEAEs with a missing/Unknown relationship to study medication will be regarded as *"probable"* to study medication. The rest of the AEs will be considered as not related ("Unlikely" and "Not related").

If a subject reports the same AE more than once within that SOC/PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

17.1.4 AEs Leading to patient Discontinuation

AEs leading to permanent discontinuation of patient will be identified.

For AEs leading to discontinuation of patient, summaries of incidence rates (count and percentages) by SOC and PT will be prepared.

17.1.5 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.

17.1.6 Adverse Drug reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered as adverse drug reactions. ADR is a related event, so it is a TEAE that is related as defined in Section 17.1.3

A summary of ADR by SOC and PT will be prepared.

Any ADR during the study will be presented in a data listing.

17.1.7 Summary of non-TEAEs

Not applicable. Non-TEAEs will be in the data listing.

17.2. Deaths

Any deaths during the study will be presented in a summary table and a data listing.

17.3. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for hematology, clinical chemistry, urinalysis, thyroid function tests, virology, serum pregnancy test for post-pubertal females, HPA axis and prolactin. A list of laboratory assessments to be included in the outputs is included in the protocol.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries (descriptive statistics for quantitative measurements and count and percentage for qualitative measurements except urinalysis) will be provided for laboratory parameter (i.e. hematology, clinical chemistry, urinalysis, HPA axis, Serum Pregnancy Test and prolactin).

- Actual and change from baseline by visit (for quantitative measurements).
- Shift from baseline to Week 24 and End of Study visits according to standard normal range criteria (for quantitative measurements and categorical measurements).
- Incidence table at Week 24 and End of Study visits according to clinically notable values (for quantitative measurements and categorical measurements).
- Listing of subjects' laboratory evaluations with flagging of abnormal values.

The descriptive statistics for actual measurement and change from baseline by treatment group will be performed at scheduled visits.

17.4. 12-LEAD ECG

ECG analysis related details can be found in ECG SAP.

17.5. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature (^{0}C)

The following summaries will be provided for vital signs data:

- Actual values and change from baseline by visits and timepoints
- Incidence of clinically notable vital signs values at Day 1, Day 15, Week 24 and End of Study visits as defined in Appendix 3 of the SAP
- Listing of patients' vital signs

The descriptive statistics for actual measurement and change from baseline will be presented by treatment group and timepoints at scheduled visits.

17.6. PHYSICAL EXAMINATION

The count and percentage of patients with physical examination assessments will be summarized by body system and treatment group at schedule visit.

A patient-wise listing of physical examination findings will be provided.

17.7. NEUROLOGICAL EXAMINATION

The count and percentage of patients with neurological examination assessments will be summarized by system and treatment group at schedule visit.

A patient-wise listing of neurological examination findings will be provided.

17.8. OPHTHALMOLOGICAL EXAMINATION

The count and percentage of patients with ophthalmological examination assessments will be summarized by each type of assessment and treatment group at schedule visit.

A patient-wise listing of ophthalmological examination findings will be provided.

17.9. STRUCTURED SUICIDALITY ASSESSMENT

The count and percentage of patients with suicidality assessments will be summarized by system and treatment group at schedule visit.

A patient-wise listing of suicidality query will be provided.

17.10. TANNER STAGING

A patient-wise listing of Tanner staging will be provided.

18. DATA NOT SUMMARIZED OR PRESENTED

Not applicable.

19. REFERENCES

Annotated CRF dated 23rd September

Clinical Study Protocol Sarizotan/001/II/2015, V.15.0, dated 17 March 2020.

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APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

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

START DATE	STOP DATE	ACTION
	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 < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	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, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant

START DATE	STOP DATE	ACTION
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 < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	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 < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	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
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	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, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Assign as concomitant

APPENDIX 2. CLINICALLY NOTABLE VALUES FOR LABORATORY PARAMETERS

Parameter	Synonym	S.I. units			Other units		
		Unit	Lower Limit	Upper Limit	Unit	Lower Limit	Upper Limit
Albumin		g/L	≤ 14	≥ 62	g/dL	≤ 1.4	≥ 6.2
Alk. Phosphatase	ALP	U/L	NA	≥ 3.0*URL			
Amylase		U/L	≤ 15	≥ 350			
ALAT, SGPT	ALT,GPT	U/L	NA	≥ 3.0*URL			
ASAT, SGOT	AST,GOT	U/L	NA	≥ 3.0*URL			
Bicarbonate		mmol/L	≤ 10	NA			
Bilirubin total		µmol/L	NA	≥ 34	mg/dL		≥ 2.0
Calcium total		mmol/L	≤ 2.1	≥ 3.0	mg/dL	≤ 8.2	≥ 12
Chloride		mmol/L	≤ 80	≥ 125			
Cholesterol		mmol/L	NA	≥ 7.25	mg/dL		≥ 280
Creatinine kinase	CPK	U/L	NA	≥ 3.0*URL			
Creatinine		µmol/L	NA	≥ 177	mg/dL		≥ 2.0
Gamma-GT Male		U/L	NA	≥ 100			
Female		U/L	NA	≥ 90			
Globulin total		g/L	≤ 10	NA			
Glucose		mmol/L	≤ 1.7	≥ 13.9	mg/dL	≤ 30	≥ 250
LDH		U/L	NA	≥ 3.0*URL			
Phosphate		mmol/l	NA	≥ 2			
Potassium		mmol/L	≤ 2.5	≥ 6.5			
Protein total		g/L	≤ 45	NA			
PTT		sec	NA	≥ 80			
Sodium		mmol/L	≤ 120	≥ 165			
Triglycerides		mmol/L	NA	≥ 5.6	mg/dL		≥ 500
Urea		mmol/L	NA	≥ 16.6	mg/dL		≥ 100
Urea nitrogen	BUN	mmol/L	NA	≥ 84.0	mg/dL		≥ 30
Uric acid Male		µmol/L	NA	≥ 624	mg/dL		≥ 10.5
Female		µmol/L	NA	≥ 505	mg/dL		≥ 8.5

Parameter		Synonym	S.I. units			Other units		
			Unit	Lower Limit	Upper Limit	Unit	Lower Limit	Upper Limit
Basophils			L/L	NA	≥ 0.15	%		≥ 15
Eosinophils			L/L	NA	≥ 0.10	%		≥ 10
Erythocytes	Male	RBC	10^{12}/L	≤ 2.5	NA			
	Female		10^{12}/L	≤ 2.0	NA			
ESR	Male		Mm	NA	≥ 25			
	Female		Mm	NA	≥ 35			
Hematocrit	Male	EVF	L/L	≤ 0.37	NA	%	≤ 37	
	Female		L/L	≤ 0.32	NA	%	≤ 32	
Hemoglobin	Male		g/L	≤ 115	NA	g/dL	≤ 11.5	
	Female		g/L	≤ 95	NA	g/dL	≤ 9.5	
Leukocytes		WBC	10^{9}/L	≤ 2.8	≥ 16.0			
Lymphocytes			L/L	NA	≥ 0.80	%		≥ 80
MCHC			mmol/L	≤ 12.4	≥ 27.9	g/dL	≤ 20	≥ 45
MCV			10^{-15}L	≤ 60	≥ 120			
Monocytes			L/L	NA	≥ 0.40	%		≥ 40
Neutrophils			L/L	≤ 0.15	NA	%	≤15	
Thrombocytes		Platelets	10^{9}/L	≤ 75	≥ 700			

CLINICALLY NOTABLE URINALYSIS VALUES

Variable	Clinically Notable Values
Protein	Increase of 2 units
Glucose	Increase of 2 units

APPENDIX 3. CLINICALLY NOTABLE VITAL SIGNS VALUES

Parameter	Unit	Decrease	Increase
Sitting/Supine SBP	mmHg	Value ≤ 90 and ≥ 20 decrease from Baseline.	Value ≥ 180 and ≥ 20 increase from Baseline
Sitting/Supine DBP	mmHg	Value ≤ 50 and ≥ 15 decrease from Baseline.	Value ≥ 105 and ≥ 15 increase from Baseline
Orthostatic Hypotension (based on standing SBP/DBP)	mmHg	Decrease in SBP/DBP from Supine to Standing position exceeding > 30mmHg	NA
Sitting pulse rate	bpm	Value ≤ 50 and ≥ 15 decrease from Baseline	Value ≥ 120 and ≥ 15 increase from Baseline
Weight	kg	≥ 7% decrease from Baseline.	≥ 7% increase from Baseline.
Respiration rates*	Breaths/ minute	< 12	> 25
Temperature	°C	NA	Value ≥ 38.3 and ≥ 1.1 increase from Baseline.
Temperature	°F	NA	Value ≥ 101.0 and ≥ 2.0 increase from baseline

APPENDIX 4. AGE CATEGORIZATION

Age Group 1	< 13 years
Age Group 2	>= 13 years

APPENDIX 5. RANDOMIZATION OF PATIENTS ACCORDING TO AGE AND BODY WEIGHT CRITERIA