STATISTICAL ANALYSIS PLAN

NCT Number: NCT03336450

Study Title: A Phase 3, Multicenter, Open-label Extension Study of Buccally Administered MHOS/SHP615 in Pediatric Patients with Status Epilepticus (Convulsive) in Community Settings

Study Number: SHP615-302

SAP Version and Date:

Version 1: 12 Sep 2019

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Statistical Analysis Plan

Protocol No.:	SHP615-302
Protocol Title:	A Phase 3, Multicenter, Open-label Extension Study of Buccally Administered MHOS/SHP615 in Pediatric Patients with Status Epilepticus (Convulsive) in Community Settings
Drug:	Midazolam hydrochloride oromucosal solution MHOS/SHP615
Sponsor:	Shire 300 Shire Way, Lexington, MA 02421 USA
Version No. and Date	Final 1.0, Date 12 Sep 2019

Version No:	Document History Description of Update	Author(s)	Effective Date
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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CTMS	clinical trial management system
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
MHOS/SHP615	midazolam hydrochloride oromucosal solution
pH	potential of hydrogen
PT	preferred term
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
Riker SAS	Riker sedation-agitation scale
SAP	statistical analysis plan
SAS	statistical analysis system
SE	status epilepticus
SI	international system of units
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the final study protocol version (amendment #3) dated 18Dec2017. In addition, the administrative letter #3 noted subject enrollment to the study continues after the Japan New Drug Application (JNDA) and supporting analysis for JNDA.

Currently, only 2 subjects have been enrolled in this study. With the limit of the enrolment to subjects from its parent study, SHP615-301, Shire anticipates that the enrollment of 6 patients may not be possible or may only be possible with an extended study duration.

Shire also intends to provide a clinical study report for SHP615-302, that will include the analysis results from all study data up to the approximately same data lock date as study SHP615-301 (data cut-off date for this analysis is 31 August 2019). Due to the expected small number of subjects, only subject data listings will be produced to support the JNDA for this study. Specifications for listings are included in a separate document.

When study SHP615-302 is closed, all cumulative data including any additional data obtained during the study extension period will be analyzed, evaluated and reported as appropriate.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

2. STUDY DESIGN

2.1 General Study Design

Study SHP615-302 is a Phase 3, multicenter, interventional, nonrandomized, open-label extension study of MHOS/SHP615 administered buccally by caregivers to pediatric subjects who present with status epilepticus (SE) (convulsive) in community settings. Children who are >6 months and <18 years of age and completed the antecedent Phase 3 pivotal SHP615-301 study, tolerated and responded to treatment with MHOS/SHP615, subsequently experience full seizure in the community setting, have not received immediate treatment, and have parent, guardian, or legal representative consent/assent, are eligible to participate in this extension study providing all eligibility criteria are met. The seizure event(s) must be accompanied by loss of consciousness and can be either generalized tonic clonic or start focally and then generalize.

This study consists of a 24-hour, open-label treatment period followed by a 1-week safety follow-up period. After completing Study SHP615-301, the subject's parent, guardian, or legal representative will be dispensed a single oral, prefilled syringe of MHOS/SHP615 stratified by age (2.5, 5, 7.5, 10 mg buccally) along with a diary and training on how to administer the drug and record details associated with the seizure. Upon the onset of the next seizure in the home, school, or community setting, the parent, guardian, or legal representative will administer the single MHOS/SHP615 treatment as trained.

The efficacy of MHOS/SHP615 in treating SE will be assessed by measuring the percentage of subjects whose initial seizure stopped within 10 minutes, with a sustained absence of visible seizure activity for 30 minutes following a single, age-based dose of MHOS/SHP615. If the seizures have not stopped within 10 minutes, and/or if a serious adverse event emerges, the subject should be treated according to the participating hospital protocol or guideline. The caregiver/parent and subject must visit the study site for examination as soon as possible following MHOS/SHP615 administration, even if the seizure has stopped. All subjects will be followed up at study sites even if the seizure resolves. The safety of MHOS will also be assessed.

Subjects will be monitored by vital signs, laboratory tests, and electrocardiograms (ECGs) for safety evaluations. All subjects treated in this study will be followed for 1 week after the administration of MHOS/SHP615 for safety evaluations. The caregiver will record observations on seizure activity, timing of the seizure(s), and dosing relating errors in a study diary.

2.2 Randomization

Not applicable.

2.3 Blinding

Not applicable.

2.4 Schedule of Assessments

Table 1 below presents the schedule of activities in the study.

Table 1 Schedule of Assessments

Assessment	Screening	Treatment Period - Time from SHP615 Administration								Follow-up
		Community Setting		In Hospital						
		Seizure event onset	5 min after	Time after MHOS/SHP615 administration						1 week (±1day)
				10 min	30 (±5min)	1 h (±10min)	4 h (±30min)	6 h[a] (±30min)	24h[b] (±30min)	
Informed consent/assent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical/procedural history	X									
Provide study diary and educational materials to caregiver	X									
Provide training/education to caregivers	X									
Dispense age-based dose of SHP615 with administration instructions	X									
[redacted]										X
Evaluate seizure symptoms/record diary information		X		X	X	X	X	X	X	X
SHP615 administration in community setting			X							
Riker Sedation-Agitation Scale					X[c]	X[c]	X[c]	X[c]	X	
Vital signs[d]		X[e]		X[c]	X[c]	X[c]	X[c]	X[c]	X	
Oxygen saturation[f]					X[c]	X[c]	X[c]	X[c]	X	
12-Lead ECG[g]					X[c]	X[c]	X[c]	X[c]	X	
Laboratory evaluations[h]								X[c]		
Buccal cavity assessment[i]						X[c]	X[c]	X[c]		

Table 1 Schedule of Assessments

Assessment	Screening	Treatment Period - Time from SHP615 Administration								Follow-up
		Community Setting		In Hospital						
				Time after MHOS/SHP615 administration						1 week (±1day)
		Seizure event onset	5 min after	10 min	30 (±5min)	1 h (±10min)	4 h (±30min)	6 h[a] (±30min)	24h[b] (±30min)	
Physical examination			X[j]						X	
Supportive care		X	X[k]						X	
Concomitant medications/recording	X	X	X[k]						X	X
Adverse event monitoring/recording		X	X[k]						X	X

AE=adverse event; ECG=electrocardiogram; h=hour; MHOS=midazolam hydrochloride oromucosal solution; min=minute.

[a] Minimum 6-hour observation period after dosing for safety monitoring and blood sampling. Otherwise monitored per standard medical healthcare setting procedure.

[b] Assessments at the 24-hour post dose time point will be made if the subject has not been discharged from the hospital; or a telephone follow-up call will be made to assess AEs and concomitant medications. Patients will be asked to return for additional assessment of ongoing AEs, as needed.

[c] Performed if subject has arrived at study site.

[d] Vital signs will include single supine blood pressure, pulse rate, respiratory rate, body temperature; collection of vital signs information will begin as soon as possible in community setting or after transfer to healthcare setting.

[e] Parent, guardian, or legally authorized representative should count respiration rate prior to the administration of investigational product.

[f] Oxygen saturation should be measured from time of arrival in hospital, (on room air, if feasible). If it is not possible for the subject to have an oxygen saturation obtained on room air due to medical concerns, this will be recorded. The investigator will record the oxygen saturation as well as the oxygen delivery system and amount of oxygen administered.

[g] Electrocardiogram should be performed upon arrival at the hospital.

[h] Laboratory evaluations include serum biochemistry and urinalysis. A urine pregnancy test should be administered to female patients of childbearing age.

[i] Buccal cavity where MHOS/SHP615 was administered between cheek and gum line will be examined for redness, inflammation, and ulceration and findings noted on physical examination CRF.

[j] Physical examination will be performed at some point between arrival at the hospital and 6 hours postdose, when possible.

[k] Upon arrival at hospital and across all time periods, as appropriate.

2.5 Determination of Sample Size

The target sample size (≥6 subjects) is estimated based on feasibility analysis rather than based on statistical rationale.

Maximum sample size*: approximately 25 subjects.

Estimated minimum sample size: 25 x 0.585 (expected response rate in hospital**) x 0.4 (60% expected drop-out rate from screening) = approximately 6 subjects.

*Evaluable sample size in this extension study depends on the actual efficacy and safety of MHOS/SHP615 in the Study SHP615-301.

**Based on the reported global clinical studies data outside of Japan, expected response rate in hospital settings is conservatively estimated to be 58.5%. This is close to the lowest response rate reported in worldwide clinical studies.

2.6 Multiplicity Adjustments for Type I Error Control

Not applicable.

3. OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to assess the efficacy of buccally administered MHOS/SHP615 in pediatric subjects with SE (convulsive) in the community setting.

3.2 Secondary Objectives

The secondary objective of this study is to assess the safety of buccally administered MHOS/SHP615 in pediatric patients with SE (convulsive) in the community setting.

3.3 Exploratory Objectives

[redacted]

[redacted]

4. SUBJECT POPULATION SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed an informed consent/assent.

4.2 Safety Set

The Safety Set will consist of all subjects who have received a single dose of MHOS/SHP615, regardless of whether the study drug administration was documented to be complete or not on the study drug administration eCRF form.

4.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the Safety Set who have at least 1 assessment for determination of therapeutic success (cessation of seizure within 10 minutes with sustained absence of seizure for 30 minutes) performed after the administration of MHOS/SHP615, i.e., provided that the following two conditions are met:

1. For all subjects: Date and time of study drug administration and date and time of seizure cessation for the initial seizure are all recorded.
2. For subjects who had initial seizure cessation within 10 minutes post-dose with no recurrence of seizure within 30 minutes but with the documentation of a recurrence of seizure post-dose: Date and time of the first recurrence during the first 6 hours post-dose is recorded.

Refer to Section 10.1 for the definition of therapeutic success.

4.4 Per Protocol Set

The Per Protocol Set (PPS) will consist of subjects who meet all of the following criteria:

- Subject is in the FAS
- Subject met all eligibility criteria
- Subject for whom the study drug administration is documented to be complete on the study drug administration eCRF form
- Within 10 minutes of investigational product administration subject did not receive other anti-seizure rescue medication to treat the initial seizure

5. SUBJECT DISPOSITION

A listing of all Screen Failures, i.e., subjects identified as Trial Screen Failure on the disposition page of the electronic case report form (eCRF), will be presented.

The reason for exclusion from the FAS and PPS will be listed.

All subjects who prematurely discontinued the study will be listed by discontinuation reason for the Safety Set.

6. PROTOCOL DEVIATIONS

Protocol deviations as obtained from a clinical trial management system (CTMS) will be assessed throughout the study. All identified deviations will be reported in the CTMS. Protocol deviations from the CTMS will be coded to severity categories (minor and major) and provided as part of the CTMS transfer to Biostatistics. A listing of all protocol deviations by subject will be presented for the Safety Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

A listing of demographic and baseline characteristics will be presented for the Safety Set. The listing will include age group (age at the time of investigational product administration):

- <1 year
- 1 to <5 years
- 5 to <10 years
- 10 to <18 years

The following demographic characteristics will be listed:

- Age (years) – calculated as [(number of months between date of birth and investigational product administration)/12]
- Sex
- Race
- Ethnicity
- Weight (kg) measured during SHP615-301 study
- Height (cm) measured during SHP615-301 study
- BMI (kg/m^2) – calculated as 10000*weight (kg)/ height $(cm)^2$

History of epilepsy and confirmation of SE pre-dose will also be listed as follows:

- Duration of epilepsy history (years) – calculated as [(number of months between start date of epilepsy history and informed consent/assent)/12]
- Years since epilepsy diagnosis (years) – calculated as [(number of months between date of epilepsy diagnosis and informed consent/assent)/12]
- Major epilepsy etiology (genetic, metabolic, structural or idiopathic)
- Confirmation of SE pre-dose: Loss of consciousness, seizure frequency/duration
- Time between seizure onset pre-dose and investigational product administration (minutes)

If the start date of epilepsy history or date of epilepsy diagnosis is incomplete with only month and year captured, the day will be imputed to the first day of the month for the purpose of calculating duration of epilepsy history and years since epilepsy diagnosis. The imputed dates will not be presented in the listings.

In addition, the epilepsy diagnosis name will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher. The listing of Epilepsy history will include System Organ Class (SOC) and Preferred Term (PT).

Similarly, a listing including SOC and PT will be presented for medical history other than epilepsy.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

Only one administration of the investigational product is planned in this study. All subjects enrolled in the study will receive treatment with the investigational product based on their age as follows:

- 2.5 mg: >6 months to <1 year (and weight >5 kg)
- 5 mg: 1 to <5 years
- 7.5 mg: 5 to <10 years
- 10 mg: 10 to <18 years

A listing will be created by subject number giving the date and time of study drug administration, planned dose as well as drug accountability including study drug lot number.

9. PRIOR AND CONCOMITANT MEDICATION

Version 01Sep2017 or newer of the WHO Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class and preferred name. Prior and concomitant therapies will be coded using MedDRA version 20.0 or newer.

Prior medication (therapy) is defined as any medication (therapy) received within 30 days of and prior to the date of investigational product administration. In particular, medications (therapies) with an end date prior to 30 days before the date of investigational product administration are not considered prior medications (therapies). Concomitant medication (therapy) is defined as any medication (therapy) with a start date prior to the date of investigational product administration and continuing after the investigational product administration or with a start date on or after the date of investigational product administration and before the end of the follow-up period, inclusive.

Considering the protocol allowed assessment window, the end of the follow-up period will be one week plus one day (i.e., 8 days) after the investigational product administration. Any medication (therapy) with a start date after the end of the follow-up period will not be considered a concomitant medication (therapy).

Medications (therapies) can be counted both as prior and concomitant medication (therapy).

For prior or concomitant medications (therapies), including rescue medications, incomplete start/stop dates will be imputed as specified in Section 18.5. Imputed dates will not be presented in the listings.

A listing of prior and concomitant medication usage will be presented for the Safety Set and will include therapeutic class (level 3) and preferred name.

Prior and concomitant therapies will be listed similarly except that MedDRA SOC and PT will be used instead of therapeutic class and preferred name.

10. EFFICACY ANALYSES

All efficacy analyses will be based on the FAS.

10.1 Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is response rate, which is defined as the percentage of subjects with therapeutic success. Therapeutic success will be declared for subjects who meet both of the following conditions:

1. Cessation of visible seizure activity within 10 minutes, i.e., the time from investigational product administration to the end of the initial seizure is less than or equal to 10 minutes. The initial seizure refers to the seizure which triggered the use of the investigational product and which is captured on the "confirmation of status epilepticus" eCRF form.
2. A sustained absence of visible seizure activity for 30 minutes following a single dose of MHOS/SHP615 without the need for additional rescue medication, i.e., subject has no recurrence of seizure within 30 minutes of investigational product administration as documented on the "subject seizure status (recurrence)" eCRF form, and no rescue medication has been administered within 30 minutes of investigational product administration.

A listing will present therapeutic success status for subjects in the FAS.

10.2 Secondary Efficacy Endpoints and Analysis

The secondary efficacy endpoints will include:

- Percentage of subjects whose seizure event(s) stopped within 10 minutes after administration of MHOS/SHP615 and who have sustained absence of seizure activity for at least 1 hour.
- Percentage of subjects whose seizure event(s) stopped within 10 minutes after administration of MHOS/SHP615 and who have sustained absence of seizure activity for at least 4 hours.
- Percentage of subjects whose seizure event(s) stopped within 10 minutes after administration of MHOS/SHP615 and who have sustained absence of seizure activity for at least 6 hours.
- Time to resolution of seizures (convulsions)
- Time to recovery of consciousness
- Percentage of subjects who require additional anticonvulsant medication for ongoing SE according to the participating healthcare setting protocol or guideline, 10 minutes after administration of MHOS/SHP615.
- Percentage of subjects who fail to respond to treatment:
  - Treatment failure/Non-responder is defined as continuing seizure activity and/or the need for any additional rescue medication in the study site (or another emergency medical institution), 10 minutes after administration of MHOS/SHP615.

Details of the statistical analyses used for the secondary efficacy endpoints are provided in the subsections below.

10.2.1 Percentage of Subjects Whose Seizure Event(s) Stopped Within 10 Minutes After Administration of MHOS/SHP615 and who Have Sustained Absence of Seizure Activity for At Least 1 Hour/4 Hours/6 Hours

The same definition of therapeutic success as given in Section 10.1 will be used except that the second condition will be modified to require sustained absence of visible seizure activity without the need for additional rescue medication for 1 hour, 4 hours or 6 hours, respectively, following administration of MHOS/SHP615.

A listing will present the response status for subjects in the FAS.

10.2.2 Time to Resolution of Seizures (Convulsions)

Time to resolution of seizures (convulsions) in minutes will be calculated as time from investigational product administration to the end of the initial seizure or administration of rescue anticonvulsant medication, whichever occurs first. The initial seizure refers to the seizure which triggered the use of the investigational product and which is captured on the "confirmation of status epilepticus" eCRF form. Note that, as per the definition of the FAS, there will be no censoring in this time to event analysis as all subjects will have a date and time captured for the initial seizure cessation.

A listing will present the event type (end of the initial seizure or administration of rescue anticonvulsant medication) and time to resolution of seizures (convulsions).

10.2.3 Time to Recovery of Consciousness

Time to recovery of consciousness in minutes will be calculated only for subjects who lose consciousness pre-dose as time from investigational product administration to recovery of consciousness post-dose or administration of rescue anticonvulsant medication, whichever occurs first. If the time of recovery of consciousness is missing and there is no administration of rescue anticonvulsant medication during the 24 hours treatment period, the time to recovery of consciousness will be censored at the latest time of any assessment captured in the eCRF up to hospital discharge during the 24 hours treatment period, i.e., vital signs, oxygen saturation, Riker SAS, buccal cavity assessment, laboratory, ECG or time the subject was discharged from the hospital.

A listing will present the event type (recovery of consciousness, administration of rescue anticonvulsant medication or censored)) and time to recovery of consciousness.

10.2.4 Percentage of Subjects Who Require Additional Anticonvulsant Medication for Ongoing SE 10 Minutes After Administration of MHOS/SHP615

Anticonvulsant medication for ongoing SE (rescue treatment) are captured on the "prior and concomitant medications" eCRF form. Subjects who require additional anticonvulsant medication for ongoing SE 10 minutes after investigational product administration and before the end of the initial seizure will be listed.

10.2.5 Percentage of Subjects Who Fail to Respond to Treatment

Responder is defined as subject with cessation of visible seizure activity within 10 minutes after administration of MHOS/SHP615. A Treatment failure/Non-responder is defined as a subject with continuing seizure for more than 10 minutes after a single dose of MHOS/SHP615 or the need for any additional anticonvulsant rescue medication to treat the initial seizure any time after the single dose of MHOS/SHP615 according to the participating healthcare setting protocol or guideline. Any of the following events qualifies as a treatment failure:

- The time from investigational product administration to the end of the initial seizure is more than 10 minutes. The initial seizure refers to the seizure which triggered the use of the investigational product and which is captured on the "confirmation of status epilepticus" eCRF form.
- Rescue anticonvulsant medication is administered to treat the initial seizure anytime after MHOS/SHP615 administration.

Subjects who fail to respond to treatment will be listed.

10.3 Exploratory Efficacy Endpoint(s) and Analyses

No exploratory efficacy endpoints are defined.

10.4 Sensitivity Analyses

Not applicable.

11. SAFETY ANALYSES

The safety analysis will be performed using the Safety Set. Safety variables include adverse events (AEs), clinical laboratory variables, vital signs, oxygen saturation, Riker SAS, buccal cavity assessment, and ECG variables.

Section 18.3 provides the way unscheduled assessments will be handled in safety analyses.

11.1 Primary Safety Endpoint and Analysis

The primary safety endpoint will be respiratory depression, which will include the following measures after MHOS/SHP615 administration:

- Persistent decrease in oxygen saturation to <92% measured at 30 minutes, 1, 4, 6, and 24 hours post-dose (i.e., <92% on room air for 2 minutes or more after dosing while monitoring [per healthcare setting protocol and/or the clinical judgment of the physician]).
- Increase in respiratory effort such that assisted ventilation is used (bag-valve-mask ventilation or endotracheal intubation)

In the primary safety analysis, any of the following events will qualify as a respiratory depression:

- An oxygen saturation assessment (including unscheduled) within 24 hours (±30 minutes to account for the protocol allowed assessment window) after the investigational product administration indicates an oxygen saturation <92% on room air for 2 minutes or more after dosing while monitoring.
- An AE with MedDRA preferred term "Respiratory depression" starts within 24 hours after the investigational product administration, i.e., the AE starts on the same day as investigational product administration and is identified as not occurring prior to investigational product administration on the eCRF or the AE starts on the day following investigational product administration. Such adverse event indicates an increase in respiratory effort requiring the use of assisted ventilation.

Subjects with respiratory depression will be listed.

11.2 Secondary Safety Endpoint and Analysis

The secondary safety endpoints include the following:

- Aspiration pneumonia
- Sedation or agitation as measured by the Riker SAS
- Incidences/monitoring of treatment-emergent adverse events (TEAEs), vital sign measurements, laboratory tests, oxygen saturation, and ECGs
- Occurrence of buccal irritation

Details of the statistical analyses of secondary safety endpoints are provided in the subsections below.

11.2.1 Adverse Events

Adverse events will be coded using Version 20.0 or newer of MedDRA.

TEAEs are defined as AEs whose onset occurs, severity worsens or intensity increases on or after the date of investigational product administration. Events which occur more than one week (+1 day to account for the protocol allowed assessment window) after the investigational product administration will not be considered treatment emergent.

For classifying AEs as TEAEs/non-TEAEs, incomplete start dates will be imputed as specified in Section 18.6. Imputed dates will not be presented in the listings.

The following TEAEs of special interest will be listed:

- Aspiration pneumonia
- Respiratory depression
- Buccal irritation

The preferred terms corresponding to these TEAEs of special interest will be identified by Shire based on medical input and be provided to IQVIA for the analysis.

A listing will be presented and will include both TEAEs and Non-TEAEs (unless specified otherwise). Serious AEs, AEs leading to death, and AEs leading to discontinuation from the study will be identified in the listing. Listings will indicate whether an AE is treatment emergent or not and whether it started before hospital admission, after hospital admission and before hospital discharge or after hospital discharge. Separate listings will be presented for AEs of special interest (aspiration pneumonia, respiratory depression, buccal irritation).

11.2.2 Clinical Laboratory Variables

The following clinical laboratory variables are assessed in this study and will be presented in the listings:

Chemistry	BUN, serum creatinine, creatinine clearance determined by the Schwartz method, glucose (fasting if possible), calcium (total), sodium, potassium, chloride, AST, ALT, total bilirubin, direct and indirect bilirubin (if total bilirubin is elevated), alkaline phosphatase, albumin, total protein and bicarbonate.
Urinalysis	pH, glucose (qualitative), protein (qualitative), blood (qualitative), ketones, nitrites, leukocyte esterase, specific gravity and microscopy (if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase).

The summaries of laboratory variables will be based on central laboratory results.

Clinical laboratory sample collection information and test results in SI units will be listed for all subjects in the Safety Set.

Subjects with clinically significant abnormal laboratory test results will be listed. This listing will include all results of the laboratory parameter that was abnormal and determined to be clinically significant by the investigator.

11.2.3 Vital Signs

Vital signs actual values will be presented at each scheduled time point:

Systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min) and body temperature (C).

All vital sign data will be presented in a subject level listing. In addition, subjects with clinically significant vital sign values will be listed. This listing will include all results of the vital sign parameter that was determined by the investigator to be clinically significant for a subject across study time points to identify any trends.

11.2.4 Electrocardiogram (ECG)

ECG variables will be presented at each scheduled assessment time point for the following parameters:

Heart rate (bpm), RR interval (ms), PR interval (ms), QRS interval (ms), QT interval (ms), QTcB interval (ms) and QTcF interval (ms).

QTcB and QTcF corrections will be summarized as provided by central laboratory, i.e., the corrections will not be recalculated for the analysis.

All ECG data will be presented in a subject level listing. This listing will include all results for a subject across study time points to identify any trends.

11.2.5 Riker Sedation-Agitation Scale (SAS)

Riker SAS score will be listed for all subjects in the Safety Set.

11.2.6 Oxygen Saturation

Oxygen saturation results will be listed for all subjects in the Safety Set.

11.2.7 Buccal Irritation

Details of the buccal cavity assessments for each subject, including the abnormalities, will be presented in the listings.

11.3 Other Safety Variables

Information on physical examination (whether performed, reason for not performing the examination and date of assessment) will be presented in the listings.

Urine pregnancy test information and results will also be presented in the listings.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

13. OTHER ANALYSES

[redacted]

14. INTERIM ANALYSIS

There is no formal interim analysis planned for this study.

15. DATA MONITORING/REVIEW COMMITTEE

There is no data monitoring committee for this study.

16. COMPUTER METHODS

All statistical analyses will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, NC, USA 27513).

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

- The protocol defines the secondary efficacy endpoint "Time to recovery of consciousness/baseline mental status". However, no data for baseline mental status is captured in the eCRF and therefore, this endpoint will be analyzed as "Time to recovery of consciousness".
- The free text answers to the [redacted] will not be reported in listings as these may not be interpretable.
- The protocol has text describing aggregated statistical summaries but, in light of the small number of subjects who will receive the investigational product as part of this study, only subject level data listings will be presented.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

All available data will be included in the analysis. In general, no imputation of missing data will be performed except when specified in the subsections below.

Data from all healthcare setting study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

Outputs will be presented according to Shire TFLs Library V8.1. General considerations which are applicable to this study are summarized in the following subsections.

18.1.1 Descriptive Statistics Presentation

No descriptive statistical summaries will be presented.

18.1.2 Decimal Places and Rounding Rules

- BMI, age, duration of SE history and years since epilepsy diagnosis should be rounded to 1 decimal place for reporting.

18.1.3 Format of Listings

The compound name and study number shall appear in the top left corner of the page in the format of SHP615-302. Page numbering, in the format "Page X of Y", shall be presented in all output in the upper right corner of the page for each table.

Output shall be aligned so that the title of the table text is centrally aligned over the data; the body of the table, where applicable, text is left-justified. Column headers shall follow the alignment of their data.

For cases in which there are no observations contributing to a listing, the listing shall be produced with all titles and footnotes as per its shell, but with the text "– No Observations –" in the body of the output.

Footnotes shall be displayed under the table on each page.

Final listings shall be combined into one bookmarked PDF file.

18.2 Derived Efficacy Endpoints

Derivations for efficacy endpoints are described in Section 10.

18.3 Repeated or Unscheduled Assessments of Safety Parameters

Listings will include all scheduled and unscheduled assessments.

18.4 Missing Date of Investigational Product

Not applicable in this single dose study.

18.5 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partially missing) start date/time and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

18.5.1 Incomplete Start Date/Time

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing time

- If the start time of another anti-seizure rescue medication is missing and the start date is equal to the date of study drug administration, then the time of study drug administration will be assigned to the missing time.
- For any other cases, the missing time will not be imputed.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of investigational product administration, then the day and month of the date of investigational product administration will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of investigational product administration, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of investigational product administration, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of investigational product administration, then the day of the date of investigational product administration will be assigned to the missing day
- If either the year is before the year of the date of investigational product administration or if both years are the same but the month is before the month of the date of investigational product administration, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the date of investigational product administration or if both years are the same but the month is after the month of the date of investigational product administration, then the first day of the month will be assigned to the missing day.

18.5.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- 31 December will be assigned to the missing fields

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- The last day of the month will be assigned to the missing day

18.6 Missing Date Information for Adverse Events

For AEs, only incomplete (i.e., partially missing) start dates will be imputed.

18.6.1 Incomplete Start Date

Follow same rules as in Section 18.5.1.

18.6.2 Incomplete Stop Date

Not applicable.

18.7 Missing Severity Assessment for Adverse Events

There will be no imputation, the actual values will be presented in data listings.

18.8 Missing Relationship to Investigation Product for Adverse Events

There will be no imputation, the actual values will be presented in data listings.

18.9 Character Values of Clinical Laboratory Variables

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification, or "> X", i.e. above the upper limit of quantification, will be presented as recorded, i.e. as "< X" or "> X" in the listings.

19. REFERENCES

Not applicable.

20. TABLE OF CONTENTS FOR FIGURES, TABLES, AND LISTINGS

See separate file with listings specifications.