Shire is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Statistical Analysis Plan

Protocol No.:	SHP615-301
Protocol Title:	A Phase 3, Multicenter, Open-label Study to Determine the Efficacy, Safety, and Pharmacokinetics of Buccally Administered MHOS/SHP615 in Pediatric Patients with Status Epilepticus (Convulsive) in the Hospital or Emergency Room
Drug:	Midazolam hydrochloride oromucosal solution MHOS/SHP615
Sponsor:	Shire 300 Shire Way, Lexington, MA 02421 USA
Version No. and Date	Final 1.0, Date 11 Sep 2019

Version No:	Document History Description of Update	Author(s)	Effective Date
Final	Not Applicable – First Version	[redacted]	11Sep2019

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CI	confidence interval
CIF	cumulative incidence function
CTMS	clinical trial management system
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
KM	Kaplan-Meier
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MHOS/SHP615	midazolam hydrochloride oromucosal solution
PD	pharmacodynamic
pH	potential of hydrogen
PK	pharmacokinetic
PopPK	population pharmacokinetic
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
SD	standard deviation
SE	status epilepticus
SEM	standard error of the mean

SI	international system of units
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
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. Specifications for tables, figures, and listings are included in a separate document.

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

SHP615-301 is a Phase 3, multicenter, interventional, nonrandomized, open-label study of buccally administered MHOS/SHP615 to pediatric subjects who present with status epilepticus (SE) in the healthcare setting.

Approximately 25 subjects will be enrolled in this study. Children whose corrected gestational age is ≥52 weeks (gestational weeks plus the number of weeks after birth) and <18 years (and weight >5 kg) who arrive at the healthcare setting in full seizure, have not received immediate treatment, and have parent, guardian, or legally authorized representative informed consent/assent (when applicable, per Shire policy and country regulations), are eligible to participate 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. Upon entry in the SHP615-301 study, subjects will receive a single open-label MHOS/SHP615 treatment, dosing stratified by age (2.5, 5, 7.5, or 10 mg buccally).

The efficacy of MHOS/SHP615 in stopping convulsive seizures will be assessed by measuring the percentage of subjects whose initial seizure stops 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 after a single dose of MHOS/SHP615, the subject will be treated according to the participating healthcare setting protocol or guideline. The safety and pharmacokinetics of MHOS/SHP615 will also be assessed.

Subjects will be monitored by assessment of treatment-emergent adverse events (TEAEs), vital signs, laboratory tests, oxygen saturation, physical examination, and electrocardiogram (ECGs) for safety evaluations. All subjects treated in this study will be followed for 1 week after dosing for safety evaluations.

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	Treatment Period - Time from SHP615 Administration									Follow-up
	Screening/Baseline	0 min	10 min	30 (± 5min)	1 h (± 10min)	3h (± 30min)	4 h (± 30min)	6 h[a] (± 30min)	24h[b] (± 30min)	1 week (± 1 day)
Informed consent/assent	X[c]									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical/procedural history	X									
Confirmation of status epilepticus	X									
Evaluation of seizure symptoms[d]	X	X	X	X	X		X	X	X	X
Riker Sedation-Agitation Scale	X	X		X	X		X	X	X	
Laboratory evaluations[e]	X[f]						X		X	
SHP615 administration		X								
PK collection[g]					X	X		X		
Buccal cavity assessment[h]					X		X	X		
Vital signs[i]	X		X	X			X	X	X	
Oxygen saturation[j]	X		X	X			X	X	X	
12-Lead ECG	X[k]			X	X		X	X	X	
Supportive care		X							X	
Physical examination[l]		X								X
Concomitant medications	X	X		X[a]					X	X

Table 1 Schedule of Assessments

Assessment	Treatment Period - Time from SHP615 Administration									Follow-up
	Screening/Baseline	0 min	10 min	30 (± 5min)	1 h (± 10min)	3h (± 30min)	4 h (± 30min)	6 h[a] (± 30min)	24h[b] (± 30min)	1 week (± 1 day)
Adverse event monitoring		X		X[a]					X	X

ECG=electrocardiogram; h=hour; MHOS=midazolam hydrochloride oromucosal solution; min=minute; PK=pharmacokinetic.

[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 postdose time point will be made if the subject has not been discharged from the healthcare setting; 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] If more than 3 months have elapsed between initial informed consent and seizure, parent, guardian, or legally authorized representative should re-sign the latest at the time of admission prior to treatment.

[d] Seizure symptoms will be assessed based on physician's clinical judgment and healthcare setting protocol.

[e] Laboratory evaluations include serum biochemistry and urinalysis (including a urine pregnancy test in women of childbearing potential at screening/baseline).

[f] Blood glucose can be measured by local lab or testing kit.

[g] The PK samples will be collected at 1, 3, and 6 hours after administration of MHOS/SHP615.

[h] 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.

[i] Vital signs will include single supine blood pressure, pulse rate, respiratory rate, and body temperature.

[j] Oxygen saturation at baseline will be measured and recorded (on room air, if feasible), in the emergency room. 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.

[k] If subject is stable enough for ECG.

[l] Physical examination will be performed at some point between 0 min (dosing) and 6 hours postdose, when possible.

2.5 Determination of Sample Size

The target sample size (approximately 25 subjects; minimum 3 subjects per age group) is estimated based on the expected response rate which is assumed to be 58.5% compared with the threshold of 30% with at least 80% of statistical power at the 2-sided 5% level.

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 MHOS/SHP615 administered buccally in pediatric patients with SE (convulsive) in a healthcare setting.

3.2 Secondary Objectives

The secondary objectives of this study are to assess the safety and pharmacokinetics of MHOS/SHP615 administered buccally to pediatric patients with SE (convulsive) in a healthcare setting.

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

4.5 Pharmacokinetic Set

The Pharmacokinetic Set (PK Set) will consist of all subjects who receive a single dose of MHOS/SHP615 and for whom at least 1 post-dose PK blood sample was collected.

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 number of subjects included in each subject population set (i.e., Screened, Safety, FAS, PPS and PK Set) will be summarized. In addition, the reason for exclusion from the PPS will be summarized.

The number and percentage of subjects who completed or prematurely discontinued the study will be presented for the Safety Set. Reasons for premature discontinuation from the study as recorded on the disposition page of the eCRF will be summarized (number and percentage) for the Safety Set. 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 table of major protocol deviations and a listing of all protocol deviations by subject will be presented for the Safety Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of demographic and baseline characteristics will be presented for the Safety Set and FAS overall and by 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 summarized in the following order in the tables:

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

History of epilepsy and confirmation of SE pre-dose will also be summarized 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. Epilepsy history will be presented by System Organ Class (SOC) and Preferred Term (PT). SOC will be sorted alphabetically and PT within SOC will be sorted by descending incidence.

Similar summaries by SOC and PT will be presented for medical history other than epilepsy.

All medical history will be listed for the Safety Set.

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: 3 months (52 weeks corrected gestational age) 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

Exposure to investigational product for the Safety Set will be summarized in terms of actual dose received. Actual dose is the planned dose when the drug administration was documented to be complete on the study drug administration eCRF form. Descriptive statistics (n, mean, standard deviation (SD), minimum, median, and maximum) for the actual dose received will be presented overall and by age group (age at the time of investigational product administration). The number and percentage of subjects who had a complete or incomplete study drug administration will also be presented.

A listing will be created by subject number giving the date and time of study drug administration.

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.

Prior and concomitant medication usage will be summarized by the number and proportion of subjects receiving medication within each therapeutic class (level 3) and preferred name for the Safety Set. Multiple medication usage by a subject in the same category (i.e., therapeutic class or preferred name) will be counted only once. These summaries of prior and concomitant medication usage will be presented separately by indication as follows:

- Anticonvulsant medication for ongoing SE (rescue treatment)
- Anticonvulsant medication (prophylaxis treatment)
- Any other indication

Prior and concomitant therapies will be summarized similarly except that MedDRA SOC and PT will be used instead of therapeutic class and preferred name and there will be no summary by indication.

All prior and concomitant medications (therapies) will be listed.

10. EFFICACY ANALYSES

All efficacy analyses will be based on the FAS. All confidence intervals will be 2-sided 95% confidence intervals (CI), unless stated otherwise.

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.

The primary efficacy analysis will be conducted on the FAS by constructing the 2-sided, 95% Wald CI for the percentage of subjects reaching therapeutic success. The lower limit of the 95% CI will be compared with the threshold of 30%, which is equivalent to comparing the percentage of success to the threshold at the 2-sided 5% level of significance. The 2-sided p-value of the Wald test will also be provided. A sample SAS code for the primary efficacy analysis is provided in the Appendix.

In addition, the primary efficacy endpoint, response rate, will be evaluated using descriptive statistics for the following subgroups:

- Age group (age at the time of investigational product administration):
  - <1 year
  - 1 to <5 years
  - 5 to <10 years
  - 10 to <18 years
- Gender: male and female
- Epilepsy etiology (based on the underlying etiology of their epilepsy):
  - Genetic
  - Idiopathic

- Metabolic
- Symptomatic (Structural)

The number and percentage of subjects achieving therapeutic success will be presented along with the corresponding exact 95% Clopper-Pearson CI for each subgroup category. The exact Clopper-Pearson CI will be used because the sample size could be small in some subgroups.

10.2 Secondary Efficacy Endpoints and Analysis

The secondary efficacy endpoints will include:

- Percentage of subjects whose seizure event(s) stopped within 10 minutes of single dose 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 of single dose 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 of single dose 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 a single dose 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 according to the participating healthcare setting protocol or guideline, 10 minutes after a single dose of MHOS/SHP615.

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

In addition, the secondary efficacy endpoints will be evaluated for the following subgroups defined in Section 10.1: Age group, gender, epilepsy etiology.

10.2.1 Percentage of Subjects Whose Seizure Event(s) Stopped Within 10 Minutes of Single Dose 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 a single dose of MHOS/SHP615.

Two-sided, 95% Wald CI for the percentage of subjects reaching therapeutic success will be constructed on 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. Administration of rescue anticonvulsant medication for ongoing initial seizure will be treated as a competing event.

Cumulative incidence function (CIF) of resolution of seizures will be estimated and a plot will be provided. In addition, CIF estimates and 95% CI will be provided at several time points post dose.

A supporting data listing detailing each subject's contribution to the analysis will also be provided.

A sample SAS code for this analysis is provided in the Appendix.

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. Administration of rescue anticonvulsant medication prior to recovery of consciousness will be treated as a competing event. 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 or PK sample collection, ECG or time the subject was discharged from the hospital.

CIF of recovery of consciousness will be estimated and a plot will be provided. In addition, CIF estimates and 95% CI will be provided at several time points post dose.

A supporting data listing detailing each subject's contribution to the analysis will also be provided.

The sample SAS code provided in the Appendix for time to resolution of seizures (see Section 10.2.2) can be used as reference for this analysis.

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

Anticonvulsant medication for ongoing SE (rescue treatment) are captured on the "prior and concomitant medications" eCRF form. The percentage of 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 presented along with the corresponding 95% Wald CI.

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 a single dose of MHOS/SHP615. A Treatment failure/Non-responder is defined as a subject with continuing seizure activity 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.

The percentage of subjects who fail to respond to treatment will be presented along with the corresponding 95% Wald CI.

10.3 Exploratory Efficacy Endpoint(s) and Analyses

No exploratory efficacy endpoints are defined.

10.4 Sensitivity Analyses

Analyses of the primary efficacy endpoint and secondary efficacy endpoints will be repeated for subjects in the Per Protocol Set.

The analyses will be the same as specified in Sections 10.1 and 10.2 for the primary and secondary efficacy endpoints, respectively. The 2-sided nominal p-value of the Wald test will be presented for the analysis of therapeutic success based on the PPS and no multiplicity adjustment will be performed for this sensitivity analysis. If the PPS and the FAS are identical, these sensitivity analyses will not be performed.

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 definition of baseline and 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 within the 4-24 hours after MHOS/SHP615 administration:

- Persistent decrease in oxygen saturation to <92% measured at 10 minutes, 30 minutes, and 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.

The number and percentage of subjects with respiratory depression will be presented along with the corresponding 95% Wald CI.

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 TEAEs, vital sign measurements, laboratory tests, oxygen saturation, and ECG
- 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.

An overall summary of TEAEs will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs (and serious categories), TEAEs related to investigational product, severe TEAEs and TEAEs leading to discontinuation from the study. The overall summary of TEAEs will be repeated for the following age groups (age at the time of investigational product administration):

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

The number/percentage of subjects reporting TEAEs and number of events will be tabulated by SOC and PT overall and by age group. A similar summary will be presented by PT only (sorted by descending frequency of PT). Serious TEAEs, TEAEs considered related to investigational product, TEAEs leading to discontinuation from the study and TEAEs leading to death will also be summarized by SOC and PT.

A summary of the number and percentage of subjects with TEAEs by SOC, PT and highest severity will also be provided. If more than one TEAE occurs with the same SOC/PT for the same subject, then the subject will be counted only once for that SOC/PT using the highest severity category.

A summary of the number and percentage of subjects with the following TEAEs of special interest will be provided by SOC and PT overall, by age group and by highest severity:

- 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.

The summaries of TEAEs described above (overall summary and TEAEs by SOC and PT) will be repeated by study period as follows:

- TEAEs which started before hospital discharge
- TEAEs which started after hospital discharge

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

11.2.2 Clinical Laboratory Variables

The following clinical laboratory variables are assessed in this study and will be presented in the tables and 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, amylase total 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 only except for blood glucose at baseline. For blood glucose, if central laboratory result is not available at baseline, the local laboratory value will be used instead.

Descriptive statistics of clinical laboratory actual values (in SI units) and changes from baseline will be presented at each scheduled time point for quantitative variables overall and by age group. If more than one laboratory result is reported per study time point per parameter, the last non-missing result will be selected for analysis.

Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. The number of subjects with a non-missing result,

and the number and percentage of subjects with a clinically significant result less than the lower limit of normal (LLN), non-clinically significant result less than the LLN, within the normal range, non-clinically significant result more than the upper limit of normal (ULN), and clinically significant result more than the ULN will be summarized by study time point. If more than one laboratory result is reported per study time point per parameter, the result yielding the most severe classification will be selected for analysis.

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable (e.g., "<X"), a coded value will be used in the analysis instead as specified in Section 18.9. However, the actual values as reported in the database will be presented in data listings.

For quantitative urinalysis results, the number and percentage of subjects in each category will be presented by scheduled time point overall and by age group. If more than one laboratory result is reported per study time point per parameter, the result yielding the most severe classification will be selected for analysis.

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 for a subject across study time points to identify any trends.

11.2.3 Vital Signs

Descriptive statistics for vital signs actual values and their changes from baseline will be presented at each scheduled time point overall and by age group for the following parameters:

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

If more than one vital sign result is reported per study time point per parameter, the last non-missing result will be selected for analysis.

In addition, spaghetti plots of individual subject's actual values will be presented by scheduled time point for each vital sign parameter.

Vital sign values will be classified according to clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a non-clinically significant result and clinically significant result will be summarized by study time point. If more than 1 vital sign result is reported per study time point per parameter, the result yielding the most severe classification will be selected for analysis.

All vital sign data will be presented in subject listings. 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)

Descriptive statistics for ECG variables and their changes from baseline will be presented at each scheduled assessment time point overall and by age group 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.

For the analysis of quantitative ECG parameters, if more than one ECG result is reported per study time point per parameter, the last non-missing result will be selected for analysis.

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, as assessed by the investigator, or ECG not performed, will be summarized at each scheduled assessment time point. For the analysis of qualitative ECG parameters, if more than one ECG result is reported per study time point per parameter, the result yielding the most severe classification will be selected for analysis. Subjects with clinically significant ECG results will be listed. 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)

Descriptive statistics for Riker SAS score actual value and change from baseline will be presented at each scheduled time point.

The Riker SAS score actual value will also be treated as a qualitative variable and the number and percentage of subjects in each score category will be summarized by scheduled time point.

If more than one Riker SAS score is reported per study time point per parameter, the last non-missing result will be selected for analysis.

11.2.6 Oxygen Saturation

Descriptive statistics for oxygen saturation (%) actual value and change from baseline will be presented at each scheduled time point for measurements performed on room air.

In addition, the number and percentage of subjects with oxygen saturation <92% on room air for 2 minutes or more will be presented by scheduled time point.

If more than one oxygen saturation result is reported per study time point per parameter, the last non-missing result will be selected for analysis.

A spaghetti plot of individual subject's oxygen saturation actual values will be presented by scheduled time point for measurements performed on room air.

11.2.7 Buccal Irritation

The number and percentage of subjects with normal and abnormal buccal cavity assessment result or assessment not performed will be summarized at each scheduled assessment time point.

In addition, the number and percentage of subjects with redness/inflammation, ulceration or other abnormality will be presented at each scheduled time point.

If more than one buccal cavity assessment is reported per study time point per parameter, the last non-missing result will be selected for analysis.

Details of the buccal cavity assessments for each subject, including the specification of other abnormality 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

All PK analyses will be performed by Certara (the PK vendor).

Plasma midazolam, its active metabolite (1-hydroxymidazolam), and potential additional metabolite(s) concentrations will be evaluated using the PK set defined in Section 4.5 from blood samples collected at 1, 3, and 6 hours (or time of discharge, if earlier than 6 hours) after administration of MHOS/SHP615.

Concentration data will be summarized by dose (2.5, 5, 7.5, and 10 mg) and nominal sample time (1, 3, and 6 hours). Descriptive summary statistics including n, minimum, maximum, mean, median, SD, % coefficient of variation (CV), and standard error of the mean (SEM) will be presented. A listing for PK concentration data will be provided. Plots of the concentration-time data by dose will be provided.

No noncompartmental or compartmental analyses are planned.

Population pharmacokinetic (PopPK) analysis may also be considered and consideration will depend on assessment of data collected and likely incremental informative value to the program. Should additional PopPK analyses be considered further, a PopPK-specific analysis plan will be written then.

No pharmacokinetic/pharmacodynamic (PK/PD) analyses are planned.

13. OTHER ANALYSES

No other analyses are planned for this study.

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

There is no major change compared to analyses specified in the protocol.

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

For continuous variables, the number of subjects (n), mean, median, SD, minimum, and maximum values will be presented. For the by-time-point summaries, the number of subjects at each timepoint (n) represents the number of subjects who had a non-missing result for a given parameter at that timepoint.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. Unless otherwise stated, the denominator for percentages is N (the number of subjects in the analysis set). Note that for any summary by subgroup (e.g. by age group), the denominator is the number of subjects in that subgroup within that analysis set.

18.1.2 Decimal Places and Rounding Rules

- For measures of median and mean, use 1 decimal place beyond those used for the measurement.
- For measures of SD and SEM, use 2 decimal places beyond those used for the measurement.
- For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
- Percentages shall be reported to 1 decimal place, except when the percentage equals exactly 100 where it shall be displayed as an integer (100). For zero, only count and no percentage will be displayed. This rule also applies to %CV.
- BMI, age, duration of SE history and years since epilepsy diagnosis should be rounded to 1 decimal place for reporting.
- For p-values use 3 decimal places. Display p-values that would round to 0.000 as <0.001.

18.1.3 Format of Tables/Listings

The compound name and study number shall appear in the top left corner of the page in the format of SHP615-301. 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; frequency counts are aligned centrally within a cell and lined up by decimal point; statistical summaries for continuous variables are centrally aligned. Column headers shall follow the alignment of their data.

For cases in which there are no observations contributing to a table, the table 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. For each cross reference, the listing number shall be preceded by the word "Listing".

Final tables 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

For each safety variable, the last value collected before the date/time of the investigational product administration (including unscheduled assessments if any) will be used as baseline for all analyses of that safety variable.

In general, for by-time point summaries, data recorded at the nominal time point will be presented. Unscheduled measurements will not be included in by-time point summaries. Listings will include all scheduled and unscheduled assessments.

Rules for handling safety parameters with more than one assessment reported per study time point are given in the corresponding safety parameter subsections of Section 11.

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

If the severity is missing for an AE starting on or after the date of investigational product administration, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.8 Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of investigational product administration, a causality of "Related" will be assigned. The imputed

values for relationship to investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

18.9 Character Values of Clinical Laboratory Variables

In general, 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 converted to X for quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. Exceptions to this rule are provided in Table 2.

Table 2 Coding of Special Character Values for Clinical Laboratory Variables

Clinical Laboratory Test	Possible Results (in SI units)	Coded Value for Analysis
Chemistry: Total Bilirubin	<2	1

19. REFERENCES

Not applicable.

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

See separate file with Tables, figures and listings specifications.

21. APPENDIX: SAMPLE SAS CODES

21.1 Sample SAS Code for the Primary Endpoint Analysis

The analysis of the primary endpoint, response rate, is described in Section 10.1. The following sample SAS code can be used to perform this analysis.
Consider the subject level dataset SUCCESS which contains the variable RESP indicating response status for each patient. RESP=1 if response is achieved and RESP=2 if response is not achieved. PROC FREQ can be used as follows to obtain the response rate, Wald 95% CI and 2-sided p-value needed for the primary endpoint analysis.

```
ods output BinomialCLs=PropCI BinomialTest=Pval (where=(Name1="P2_BIN"));
proc freq data=SUCCESS;
   table RESP / binomial (CL=wald p=0.3 VAR=SAMPLE) alpha=.05;
run;
```

The response rate is contained in variable PROPORTION of dataset PROPCI. The associated lower limit and upper limit of the 95% CI are contained in variables LOWERCL and UPPERCL, respectively, of dataset PROPCI. Note that the response rate, lower limit and upper limit are given as rates and need to be converted to percentages in the analysis (if R is the rate, the associated percentage P is given as P=R*100).
The 2-sided p-value is contained in variable NVALUE1 of dataset PVAL.
Note that a similar SAS code can be used for secondary endpoint analyses described in Sections 10.2.1, 10.2.4 and 10.2.5 except that the p-value will not be presented:

```
ods output BinomialCLs=PropCI;
proc freq data=SUCCESS;
   table RESP / binomial (CL=wald) alpha=.05;
run;
```

For subgroup analyses of the primary/secondary endpoints, the exact Clopper-Pearson confidence interval will be used and the p-value will not be presented:

```
ods output BinomialCLs=PropCI;
proc freq data=SUCCESS;
   by SUBGROUP;
   table RESP / binomial (CL=exact) alpha=.05;
run;
```

The BY statement of PROC FREQ is used to obtain the results for each category of one subgroup.

21.2 Sample SAS Code for Time to Event Analysis with Competing Events

The analysis of time to resolution of seizures (see Section 10.2.2) is based on time to event analysis with competing events. Resolution of seizures (convulsions) is the event of primary interest. Administration of rescue anticonvulsant medication for ongoing initial seizure is the competing event in these analyses. The following SAS code is proposed for analyses of time to resolution of seizures.

Consider the subject level dataset SEIZEND which contains the variables RESTIME and STATUS. RESTIME is the time in minutes from investigational product administration to the end of the initial seizure or administration of rescue anticonvulsant medication, whichever occurs first. STATUS=1 if the initial seizure resolves without administration of rescue anticonvulsant medication beforehand and STATUS=2 if rescue anticonvulsant medication is administered prior to resolution of the initial seizure. PROC LIFETEST can be used as follows to obtain the CIF plot and CIF estimates at 2, 3, 5, 7, 10, 15, 20 and 30 minutes.

```
ods graphics on;
ods output FailureSummary=Summary CIF=CIFTIME;
proc lifetest data=SEIZEND plots=CIF timelist=2 3 5 7 10 15 20 30;
   time RESTIME*STATUS(0)/eventcode=1;
run;
```

Note that the SAS code above specifies that STATUS=0 is associated with censoring. However, as specified in Section 10.2.2, no subject will be censored in the analysis and this has no impact to the outcome of PROC LIFETEST (but is needed for the SAS code to run properly).

Note also that the timelist=2 3 5 7 10 15 20 30 is given as an example only and the time points will be refined based on the actual data.

Dataset SUMMARY contains the number of events of primary interest and number of competing events in variables EVENT and COMPETE, respectively.

The CIF estimates at the prespecified time points are contained in variable CIF of dataset CIFTIME. The associated lower limit and upper limit of the 95% CIs are contained in variables CIF_LCL and CIF_UCL, respectively, of dataset CIFTIME. Note that CIF estimates, lower and upper limit of the 95% CIs are given as rates and need to be converted to percentages in the analysis (if R is the rate, the associated percentage P is given as P=R*100).

The analyses of time to recovery of consciousness (see Section 10.2.3) will be conducted similarly. Note that in this analysis, censoring can occur and the variable STATUS=0 is used to indicate censored observations. The number of censored observations is given in variable CENSORED of dataset SUMMARY.