PROTOCOL: SHP615-301

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 [redacted]
MEDICAL MONITOR:	[redacted]
PROTOCOL HISTORY:	Original Protocol: 20 Mar 2017 Protocol Amendment 1: 08 Jul 2017 Protocol Amendment 2: 28 Aug 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

[redacted]

Date: [redacted]

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP615-301.

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

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), the ethical principles of the Declaration of Helsinki, privacy laws, and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address:	_____
(please hand print or type)	_____
	_____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious Adverse Events (AEs) Required by the Protocol Form within 24 hours to Quintiles Transnational Japan K.K., the Shire Global Pharmacovigilance and Risk Management Department and the Shire medical monitor. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the CRO/Shire medical monitor by fax or e-mail using the details below.

Quintiles Medical Advisor fax number: [redacted]

Quintiles Medical Advisor telephone number: [redacted]

Quintiles Medical Advisor email address: [redacted]

For protocol- or safety-related issues during normal business hours, the investigator must contact the Quintiles medical monitor:

Quintiles Medical Advisor name, title: [redacted]

Quintiles Medical Advisor fax number: [redacted]

Quintiles Medical Advisor telephone number: [redacted]

Quintiles Medical Advisor mobile number: [redacted]

For protocol- or safety-related issues outside of normal business hours, the investigator must contact the:

Quintiles Medical Advisor mobile number: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). The product quality includes quality of the drug delivery device combination product. As such device defects should be reported according to the instructions in this section. The reporting of product quality occurrences, when the product does not meet specifications, includes the reporting of device defects. For instructions on reporting AEs related to product complaints, see Section 8.3.

Please use the information below as applicable to report the Product Quality Complaint (PQC):

Origin of Product Quality Complaint	**E-mail Address**
European Union and Rest of World (ROW)	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)
[redacted]

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSE	convulsive status epilepticus
ECG	electrocardiogram
EMA	European Medicines Agency
ESE	early status epilepticus
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
ILAE	International League Against Epilepsy
IM	intramuscular
IRB	institutional review board
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MHOS/SHP615	midazolam hydrochloride oromucosal solution
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PQC	Product Quality Complaint
PUMA	Paediatric-use marketing authorisation
ROW	rest of world

SAE	serious adverse event
SAP	statistical analysis plan
SE	status epilepticus
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VT	ventricular tachycardia

STUDY SYNOPSIS

Protocol number: SHP615-301	**Drug:** Midazolam hydrochloride oromucosal solution (MHOS/SHP615)
Title of the study: 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	
Number of subjects (total and for each treatment arm): Approximately 25 subjects (minimum 3 subjects per age group)	
Investigator(s): Multicenter study (in hospital or healthcare settings)	
Site(s) and Region(s): Approximately 25 hospitals in Japan	
Study period (planned): September 2017 to August 2019	**Clinical phase:** 3

Objectives:

Primary: To assess the efficacy of MHOS/SHP615 administered buccally in pediatric patients with status epilepticus (convulsive) in a healthcare setting.

Secondary: To assess the safety and pharmacokinetics of MHOS/SHP615 administered buccally to pediatric patients with status epilepticus (convulsive) in a healthcare setting.

Rationale: Under the proprietary name BUCCOLAM® MHOS/SHP615 is currently approved for treatment of pediatric patients presenting with status epilepticus (SE) in a hospital or emergency room in several European Union (EU) countries. The intravenous (IV) formulation of midazolam is currently administered buccally off label for the treatment of SE in a healthcare setting in Japan. This study will provide data to support approval and labeling of age-based dosing of MHOS/SHP615 for the treatment of SE in Japanese pediatric patients.

Investigational product, dose, and mode of administration:

Midazolam hydrochloride oromucosal solution (MHOS/SHP615) is a clear, colorless, ready-to-use solution (containing 5 mg midazolam [as hydrochloride] per mL). MHOS/SHP615 has been specifically developed as a single, age-specific, fixed dose (approximately 0.25 to 0.5 mg/kg as midazolam) formulation for buccal administration in children.

Each pre-filled dosing syringe is individually packed in a protective plastic tube.

The four available unit dose packs are:

- 2.5 mg (yellow label) for children aged 3 months (52 weeks corrected gestational age) to <1 year (and weight >5 kg)
- 5 mg (blue label) for children aged 1 year to <5 years
- 7.5 mg (purple label) for children aged 5 years to <10 years
- 10 mg (orange label) for children aged 10 years to <18 years

Methodology: SHP615-301 is a Phase 3, multicenter, interventional, nonrandomized, open-label study of MHOS/SHP615 administered buccally to subjects <18 years who present with SE in the healthcare setting. Children whose corrected gestational age is ≥52 weeks (gestational weeks plus the number of weeks after birth) and <18 years, weight >5 kg ,who arrive at the healthcare setting in full seizure, and have not received immediate treatment, are eligible to participate in this study providing all inclusion/exclusion 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, 10 mg buccally).

The efficacy of MHOS/SHP615 in stopping prolonged 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 participating healthcare setting protocol or guideline. The safety and pharmacokinetics of MHOS/SHP615 will also be assessed.

Subjects will be monitored by vital signs, laboratory tests, and ECGs for safety evaluations. All subjects who withdraw early or who complete treatment in this study will be followed for 1 week after the dose of SHP615 for safety evaluations.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. Male and female subjects whose corrected gestational age is ≥52 weeks (gestational weeks plus the number of weeks after birth) and <18 years, and weight >5 kg, at the time of investigational product administration. If the subject's exact age is not known, the subject should be excluded.
2. Parent, guardian, or legally authorized representative of the child provides informed consent (and assent, when applicable per Shire policy and country regulations) to participate in the study prior to participation in any protocol specific procedures. The subject may be prescreened by the investigator in their clinical practice and parent, guardian, or legally authorized representative may sign informed consent before the subject presents to the healthcare setting for treatment of the seizure.
3. Subjects with generalized tonic-clonic SE with seizures accompanied by loss of consciousness with any of the following characteristics persistent at the time of study drug administration:
    a. Currently presenting with seizure (convulsive) activity and 3 or more convulsions within the preceding hour
    b. Currently presenting with seizure (convulsive) and 2 or more convulsions in succession without recovery of consciousness
    c. Currently presenting with a single seizure (convulsive) persisting ≥5 minutes

Exclusion Criteria:

1. Female subjects who are pregnant, suspected to be pregnant, or nursing.
2. Subjects with major trauma, not necessarily restricted to the head, as the cause of the seizure.
3. Subjects with seizures due to illegal drug or acute alcoholic intoxication.
4. Subjects with known or suspected recurrent seizures due to illegal drug or alcohol withdrawal.
5. Subjects with history of seizures of psychogenic origin.
6. Subjects with known history of hypersensitivities, non-responsiveness or contraindications to benzodiazepines (ie, clinically significant respiratory depression, severe acute hepatic failure, myasthenia gravis, syndrome of sleep apnea, glaucoma with closed angle, use of concomitant drugs determined by the investigator to have a contraindication to the use of benzodiazepines).
7. Subjects with a known history of benzodiazepine abuse.
8. Subjects who, in the judgment of the healthcare provider, have not responded to previous administrations of midazolam systemic therapies, including MIDAFRESA and/or DORMICUM .
9. Subjects who need emergent surgical intervention and general anesthesia/intubation.
10. Subjects with significant hypotension and cardiac dysrhythmia (eg, atrioventricular [AV] block of second or third degree, VT [ventricular tachycardia]).
11. Subjects who have been receiving human immunodeficiency virus (HIV) protease inhibitors or HIV reverse transcriptase inhibitors.

12. Subjects with current hypoglycemia (glucose <60 mg/dL) upon presentation at the hospital or healthcare setting.
13. Subjects with severe cerebral anoxia (except cerebral palsy), in the judgment of the healthcare provider.
14. Subjects have used an investigational product or been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study.
15. Subject has received antiseizure medication prior to arrival in the healthcare setting
16. Subject has prior placement of a vagus nerve stimulator.

Maximum duration of subject involvement in the study:

- ***Planned duration of screening period:*** 1 day
- ***Planned duration of treatment period:*** 1 day (a minimum of 6 hours observation and up to 24 hours)
- ***Planned duration of follow-up:*** 1 week

Endpoints and statistical analysis:

Efficacy

The **primary efficacy endpoint** is the response rate, which is defined as the percentage of subjects with therapeutic success.

- Therapeutic success will be defined as:
  - the cessation of visible seizure activity within 10 minutes, with
  - a sustained absence of visible seizure activity for 30 minutes following a single dose of MHOS/SHP615.

The **secondary efficacy endpoints** will include:

- Percentage of subjects whose seizure event(s) stopped within 10 minutes of a single dose of MHOS/SHP615 and who have sustained absence of seizure activity for the following time periods after the single dose of MHOS/SHP615:
  - 1 h
  - 4 h
  - 6 h
- Time to resolution of seizures (convulsions)
- Time to recovery of consciousness
- Percentage of subjects who fail to respond to treatment.
  - Treatment failure/Nonresponder 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.

Safety

The **primary safety endpoints** will be respiratory depression, which will include the following measures within the 4 hours after MHOS/SHP615 administration

- Persistent decrease in oxygen saturation to <92% measured at 10 minutes, 30 minutes, and 4, 6, and 24 hours postdose (ie, <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)

The **secondary safety endpoints** include the following:

- Aspiration pneumonia
- Sedation or agitation as measured by the Riker Sedation-Agitation Scale

- Incidences/monitoring of treatment-emergent adverse events (TEAEs), vital sign measurements, laboratory tests, oxygen saturation, and ECG
- Occurrence of buccal irritation

Pharmacokinetics (population PK)

- Plasma concentrations of midazolam, its active metabolite (1-hydroxymidazolam), and any potential additional metabolite(s) will be evaluated. Exploratory evaluation of potential additional metabolite(s) may also be performed. PK samples will be collected at 1, 3, and 6 hours (or time of discharge, if earlier than 6 hours) after administration of MHOS/SHP615.

Statistical methods

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.

Efficacy analysis

Efficacy data of the full analysis set (FAS) will be summarized using descriptive statistics. The FAS will include the population of subjects with SE who received a single dose of MHOS/SHP615 and have at least 1 assessment of therapeutic success performed after the administration of MHOS/SHP615.

The primary efficacy analysis will be conducted on the FAS, by constructing the 2-sided, 95% confidence interval (CI) for the percentage of subjects reaching therapeutic success defined as:

- the cessation of visible seizure activity within 10 minutes, with
- a sustained absence of visible seizure activity for 30 minutes following a single dose of MHOS/SHP615.

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.

Safety analysis

Safety data will be summarized using descriptive statistics on the Safety Set. The Safety Set will include subjects who receive a single dose of MHOS/SHP615. TEAEs will be summarized and will include treatment, seriousness, and severity. Other TEAE data that will be reported in the listings include treatment, relationship to MHOS/SHP615, and the time of event onset.

Other safety data (including vital signs, laboratory tests, ECG findings, aspiration pneumonia, Riker Sedation-Agitation Scale, and oxygen saturation) will be summarized.

Population PK analysis

Plasma concentrations of midazolam, its active metabolite (1-hydroxymidazolam), and any potential additional metabolites will be evaluated using the Pharmacokinetic Set. The Pharmacokinetic Set will include subjects who receive a single dose of MHOS/SHP615 and for whom at least 1 post-dose PK blood sample was collected. Pharmacokinetic parameters will be calculated using population PK modeling.

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	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[k]	X			X	X	X	
Supportive care		X							X	
Physical examination[l]		X								X
Concomitant medications	X	X		X[a]					X	X
Adverse event monitoring	X	X		X[a]					X	X

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

Table 1 Schedule of Assessments

	Treatment Period - Time from SHP615 Administration									Follow-up
Assessment	**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)**

[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 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.

1 BACKGROUND INFORMATION

1.1 Status Epilepticus

A seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal, excessive, and synchronous neuronal activity in the brain. Several seizure types can be described, but they all fall into 1 of 2 classifications: primary generalized seizures (eg, grand mal, petit mal, or absence seizures) and partial (focal) onset seizures (ie, localized). Regardless of seizure type, most seizures (>90%) last less than a few minutes (<2 minutes) (Theodore et al., 1983). If seizures are prolonged or occur in a series, there is an increased risk of status epilepticus (SE), which literally means a continuous state of seizure (Epilepsy Foundation, 2015).

SE, a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures, is a life-threatening neurologic emergency with significant morbidity and mortality. Mortality rates are 15% to 20% in adults and 3% to 15% in children. Acute complications result from hyperthermia, pulmonary edema, cardiac arrhythmias, and cardiovascular collapse. Long-term complications include epilepsy (20% to 40%), encephalopathy (6% to 15%), and focal neurologic deficits (9% to 11%). Prompt cessation and rapid control of SE is critical to prevent this neurological and systemic pathology (Fountain, 2000).

Convulsive SE (CSE), the most common childhood neurological emergency in developed countries, can lead to neurocognitive sequelae and death. History with epilepsy is the strongest single risk factor for generalized CSE: 15% to 27% of patients with epilepsy will experience at least 1 episode of SE; 25% to 40% of SE occurs in patients with epilepsy.

The term SE includes not only epilepsy, but also status of serial convulsive seizures associated with febrile convulsion, encephalitis, and encephalopathy. The International League Against Epilepsy (ILAE) defines SE as a seizure lasting longer than a defined period of time or more than 1 seizure occurring within a shorter timeframe without return to normalcy between seizures (ILAE, 1989). More recently, the minimum seizure duration had been defined as 30 minutes (Riviello et al., 2006); however, because epileptic discharge longer than 30 minutes has been reported to damage the brain, the diagnosis of SE was subsequently updated to a seizure lasting longer than either 10 minutes (Treiman et al., 1998) or 5 minutes (Alldredge et al., 2001), at which time treatment should be promptly initiated. The urgency to treat this condition, supported by evidence that seizures rarely last more than a few minutes, led to implementation of an operational definition of early status epilepticus (ESE), or seizures lasting more than 5 minutes (Dham et al., 2014; Brophy et al., 2012; Lowenstein et al., 1999; Lowenstein, 1999). This definition of SE (ie, seizures lasting more than 5 minutes) will be used throughout this study.

Incidence, cause, and prognosis of pediatric SE vary geographically, as well as by different socioeconomic conditions, environments, and genetic susceptibility. The incidence of SE is bimodally distributed, occurring most frequently during the first year of life and after age 60 years. Amongst children (<15 years of age), infants <12 months have the highest incidence and frequency of the disease.

In Japan, annual incidence of SE in children younger than 17 years is 42 cases per 100,000 persons. In addition to young age, other risk factors include genetic predisposition and acquired brain insults (Fountain, 2000; Working Group on Status Epilepticus, 1993; Shinnar et al., 1996; Berg et al., 1999).

Left untreated (or undertreated) SE, depending on the type and duration of seizures, can cause permanent neurological injury (including neuronal death, neuronal injury, and alteration of neuronal networks) or death (Trinka et al., 2015). Therefore, a rapid treatment must be initiated.

1.2 Current Treatment Options

For an anti-epileptic drug to be effective in SE, it is usually administered intravenously (IV) by health professionals to provide quick access to the brain without the risk of serious systemic and neurological adverse effects (Sirven and Waterhouse, 2003). Multiple drugs are available; the first line treatment is benzodiazepines (eg, diazepam), and midazolam (midazolam is not authorized for SE in the United States [US]).

The first-choice medication in Japan for treating SE in pediatric patients without venous access is diazepam suppositories administered rectally. Rectal diazepam is the medication most commonly used throughout the European Union (EU) in the community setting, and is authorized for this indication. Diazepam is effective in 60% to 80% of patients but with a risk of early seizure recurrence of up to 30% and respiratory depression (McIntyre et al., 2005). The increase of drug concentration in the blood is slow by this route; constipation and bowel movements can interfere with absorption of drug (Wilson et al., 2004). Rectal administration can be difficult during tonic-clonic seizures. For wheelchair users, it can be challenging to remove clothing and to insert the suppository in a convulsing child. Therefore, the rectal route of administration is not always practical, socially acceptable, or convenient.

For resistant cases, phenytoin (or fosphenytoin), phenobarbital, and thiopentone are injectable, fast-acting drugs that have strong anti-convulsant effects and a positive safety profile. Securing vascular access in children, however, is generally more difficult and prolongs stopping the convulsion by IV injection upon arrival at the healthcare setting. In the community setting, a therapeutic agent that can be administered by a nonmedical expert, such as a parent or caregiver, would be more appropriate for emergency treatment.

For pediatric patients in Japan, midazolam has been used off-label as a first or second choice medication for seizures intractable to diazepam treatment. Since the approval of MIDAFRESA Injection 0.1% in 2014, midazolam IV injection is now positioned as first-choice medication in Japan for pediatric patients with SE; however, the IV formulation is too dilute to use for oromucosal delivery. DORMICUM (an injectable IV formulation of midazolam) is frequently administered oromucosally or intranasally, which is considered to be an off-label use of this drug.

Accordingly, it has been recognized that there is an unmet need for an effective, fast-acting treatment that can easily be administered by a more convenient route and by individuals other than medical experts and that is suitable for use in both the healthcare setting and community (Scott et al., 1999).

1.3 Unmet Medical Need for Buccal Midazolam

To fulfill such unmet needs as outlined above, it has been common practice to administer midazolam buccally (oromucosal administration of other midazolam formulations) off-label for the treatment of SE. Buccal administration does not cause pain or distress to the patient or require that the patient be in the prone position.

Currently, the national average time in Japan for patients with SE to be transported to the healthcare setting is 39.6 minutes. In many cases as much as 50 minutes has been reported until medical treatment has been received at the healthcare setting. Buccal midazolam treatment in children with seizures could be started at home by trained clinical personnel, family members, or caregivers before securing vascular access, as well as after arriving at a medical institution, thus potentially reducing life-threatening risks of brain disorders (eg, encephalopathy) and other sequelae due to prolonged seizures and resulting from delays in getting the child to a healthcare setting.

1.4 Product Background and Clinical Information

The investigational product midazolam hydrochloride oromucosal solution (hereafter referred to as MHOS/SHP615) contains 5 mg/mL of the active substance midazolam and has been specifically developed for the buccal administration of midazolam in children with SE.

Currently, there is extensive clinical experience with midazolam as it is authorized for use in children (including neonates <32 weeks' gestational age in intensive care units) and adults as a sedative and in anesthesia and may be given by the IV, intramuscular (IM), or rectal route of administration. As midazolam undergoes significant first pass metabolism in both the small intestine and the liver, a systemic drug delivery system was selected for MHOS/SHP615. In suspension, midazolam is water soluble and, therefore, readily absorbed via the buccal mucosa. At physiological pH the drug becomes lipid soluble, which enables it to cross the blood-brain barrier. In addition, its PK parameters such as the short elimination half-life (1.5-2.5 hours) and rapid plasma clearance (300-500 mL/min) are optimal for a rescue medication (Hypnovel SmPC, 2008). The buccal mucosa, with its expanse of smooth muscle and relative immobility, makes it a desirable region for retentive systems used for oral transmucosal drug delivery.

MHOS/SHP615 has a formulation essentially identical to its authorized originator product, a systemically administered midazolam hydrochloride (HYPNOVEL® Injection 10 mg/2 mL [EU], VERSED® Oral Syrup 2 mg/mL now marketed generically [US], and DORMICUM Injection 10 mg [Japan]) used for sedation or anesthetic premedication. When approved in Japan, MHOS/SHP615, will provide major advantages over unauthorized/off-label buccal midazolam preparations and other formulations of authorized rescue medication (such as IV, IM, or rectal routes of administration) currently used for SE.

In the EU, MHOS is commercially known as BUCCOLAM®, a non-IV treatment to stop seizures (including convulsive seizures). An oromucosal solution, BUCCOLAM contains 5 mg/mL of the active substance midazolam and was approved in the EU on 05 Sep 2011 for the treatment of

prolonged, acute, convulsive seizures in infants, toddlers, children, and adolescents (from 3 months to ≤18 years).

Parents and/or caregivers are allowed to administer BUCCOLAM only to patients older than 6 months who have been diagnosed with epilepsy. For infants between 3 and 6 months of age, treatment should be in a healthcare setting, where close medical supervision and resuscitation equipment are available.

Efficacy

The age range proposed for the SHP615-301 study is ≥52 weeks corrected gestational age (gestational weeks plus the number of weeks after birth) and <18 years. The efficacy and safety of buccal midazolam have been established in 4 pivotal, rectal-diazepam-controlled clinical studies. These studies all used the HYPNOVEL 10 mg/2 mL formulation delivered buccally. All 4 studies demonstrated that buccal midazolam was either more effective than or as effective as rectal diazepam for the treatment of acute seizures in children (licensed indication and dosage of diazepam). However, the meta-analysis of the 3 (standard randomized) pivotal studies (Mpimbaza et al., 2008; McIntyre et al., 2005; Scott et al., 1999; Baysun et al., 2005) (comprising a total of 628 seizure events [525 patients]) demonstrated that buccal midazolam is significantly more effective than rectal diazepam in stopping seizures within 10 minutes (Mantel-Haenszel Weighted Risk Ratio [buccal midazolam/rectal diazepam] of 1.24 [95% confidence interval {CI}: 1.11 - 1.39] P = 0.0002).

In a study vs IV diazepam (Talukdar and Chakrabarty, 2009), the buccal midazolam dose was slightly lower than that used in the pivotal rectal diazepam studies (0.2 mg/kg vs ~0.25-0.5 mg/kg in the pivotal studies). Nevertheless, this study supported the results of the pivotal studies and meta-analysis. It demonstrated that buccal midazolam is an effective treatment for acute seizures with no statistically significant difference compared with IV diazepam for overall control of convulsive episodes within 5 minutes (85% vs 93.3% in buccal midazolam vs IV diazepam groups, respectively; p = 0.142).

Safety

The clinical safety profile of midazolam (and other benzodiazepines) from the authorized uses is well established (and summarized in the EU and US labeling [Hypnovel SmPC, 2008; Midazolam HCl Injection US Prescribing Information, 2009; Midazolam HCl Syrup US Prescribing Information, 2009]). The main adverse effects (reported to occur rarely for HYPNOVEL) and precautions applicable to the buccal route of administration in children include cardiorespiratory adverse events (AEs) (respiratory depression, apnea, respiratory arrest, and/or cardiac arrest), anterograde amnesia, and paradoxical reactions. Precautions are required for patients with impaired respiratory function or cardiovascular instability. Pediatric patients <6 months of age are particularly vulnerable to airway obstruction and hypoventilation.

Pharmacokinetics

Published PK studies in healthy adult volunteers have shown that buccal midazolam is quickly absorbed (producing peak concentrations at 30 minutes with a mean buccal midazolam bioavailability of 74.5% [Schwagmeier et al., 1998]) and has a rapid effect (≤5-10 minutes) on the central nervous system (CNS), shown on electroencephalography (Scott et al., 1998). The rapid absorption of midazolam by the buccal route has also been demonstrated in a published

study in children with severe malaria and convulsions (peak concentration at 10 [5–40] minutes with bioavailability estimated at 87%) (Muchohi et al., 2008).

For this open label SHP615-301 study, the MHOS/SHP615 formulation (the same as the HYPNOVEL 10 mg/2 mL formulation) and the proposed fixed doses will be the same as the 4 pivotal, rectal-diazepam-controlled clinical studies. Thus, the PK/pharmacokinetics should not be different for MHOS compared to that in the pivotal efficacy/safety studies.

Always refer to the latest version of the SHP615 Midazolam HCl investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of MHOS/SHP615.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Open-Label Study (SHP615-301)

For treatment of acute seizures in children, rectal diazepam is the medication most commonly used when IV access is not possible either in the medical or community settings. The rectal route of administration, however, is not always practical, socially acceptable, or convenient.

The need to remove clothing and the difficulty with rectal administration during seizures, particularly for wheelchairs users, is socially embarrassing or unacceptable by some individuals, parents, or caregivers.

MHOS/SHP615 has been specifically developed as a single, age-specific, fixed dose (approximately 0.25 to 0.5 mg/kg as midazolam) presentation for children. The 4 different, age-specific, fixed-dose presentations were selected as a convenient oromucosal administration of midazolam injectable solution to enable rapid treatment in the emergency and community settings where individual dosing by body weight is not feasible (except for infants aged from 3 months to <6 months: this age population should be treated in a healthcare setting only). This dosing regimen was evaluated extensively by the European Medicines Agency (EMA) Paediatric Committee as part of the PIP application and by the EMA Committee for Medicinal Products for Human Use (CHMP) as part of the review and approval of the Paediatric-use marketing authorisation (PUMA).

The rationale for this interventional open-label study is to determine the efficacy, safety, and pharmacokinetics of MHOS/SHP615 in pediatric patients with CSE.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of this study is to assess the efficacy of MHOS/SHP615 administered buccally in pediatric patients with status epilepticus (convulsive) in a healthcare setting.

2.2.2 Secondary Objectives

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

3 STUDY DESIGN

3.1 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 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 TEAEs, vital signs, laboratory tests, oxygen saturation, physical examination, and ECGs for safety evaluations. All subjects treated in this study will be followed for 1 week after dosing for safety evaluations.

3.2 Duration and Study Completion Definition

The duration of the treatment visit will be at least 6 hours and up to 24 hours, with a follow-up visit 1 week after the administration of MHOS/SHP615. It is anticipated that subjects will arrive at the healthcare setting while experiencing a seizure. Subjects will be screened and assessed at baseline immediately before administration of investigational product even if the informed consent and some prescreening assessments were completed at a previous clinical visit.

Evaluation of seizure symptoms will be conducted up through 6 hours after the administration of the investigational product. After 6 hours, the subject may be discharged from the healthcare setting study site.

The subject's maximum duration of participation is expected to be approximately 1 week. The study will be completed in approximately 2 years.

The Study Completion Date is defined as the date the final subject, across all sites, completes the protocol-defined assessments, or discontinues the study. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

This study will be conducted in approximately 25 healthcare setting study sites in Japan.

4 STUDY POPULATION

Each subject (parent, guardian, or legally authorized representative) must participate in the informed consent process and provide written informed consent/assent (when applicable, per Shire policy and country regulations) before any procedures specified in the protocol are performed. The subject may be prescreened by the investigator in their clinical practice and the parent, guardian, or legally authorized representative may sign informed consent before the subject presents to the healthcare setting for treatment of the seizure.

The total enrollment for the SHP615-301 study is expected to be approximately 25 subjects (minimum 3 subjects per age group) with active generalized tonic-clonic SE with seizures. Diagnosis of SE will be confirmed through documented medical history and evaluation of seizure symptoms conducted either during the screening/baseline assessment period or during treatment.

4.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by the investigator or subinvestigator before subjects are included in the study.

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. Male and female subjects whose corrected gestational age is ≥52 weeks (gestational weeks plus the number of weeks after birth) and <18 years (and weight >5 kg), at the time of investigational product administration. If the subject's exact age is not known, the subject should be excluded.
2. Parent, guardian, or legally authorized representative of the child provides informed consent (and assent, when applicable per Shire policy and country regulations) to participate in the study prior to participation in any protocol specific procedures. The subject may be prescreened by the investigator in their clinical practice and the parent, guardian, or legally

authorized representative may sign informed consent before the subject presents to the healthcare setting for treatment of the seizure.

3. Subjects with generalized tonic-clonic SE with seizures accompanied by loss of consciousness with any of the following characteristics persistent at the time of study drug administration:

    a. Currently presenting with seizure (convulsive) activity and 3 or more convulsions within the preceding hour
    b. Currently presenting with seizure (convulsive) and 2 or more convulsions in succession without recovery of consciousness
    c. Currently presenting with a single seizure (convulsive) lasting ≥5 minutes

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Female subjects who are pregnant, suspected to be pregnant, or nursing.
2. Subjects with major trauma, not necessarily restricted to the head, as the cause of the seizure.
3. Subjects with seizures due to illegal drug or acute alcoholic intoxication.
4. Subjects with known or suspected recurrent seizures due to illegal drug or alcohol withdrawal.
5. Subjects with history of seizures of psychogenic origin.
6. Subjects with known history of hypersensitivities, non-responsiveness or contraindications to benzodiazepines (ie, clinically significant respiratory depression, severe acute hepatic failure, myasthenia gravis, syndrome of sleep apnea, glaucoma with closed angle, use of concomitant drugs determined by the investigator to have a contraindication to the use of benzodiazepines.)
7. Subjects with a known history of benzodiazepine abuse.
8. Subjects who, in the judgment of the healthcare provider, have not responded to previous administrations of midazolam systemic therapies, including MIDAFRESA and/or DORMICUM.
9. Subjects who need emergent surgical intervention and general anesthesia/intubation.
10. Subjects with significant hypotension and cardiac dysrhythmia (eg, atrioventricular [AV] block of second or third degree, VT [ventricular tachycardia]).
11. Subjects who have been receiving HIV protease inhibitors or HIV reverse transcriptase inhibitors.
12. Subjects with current hypoglycemia (glucose <60 mg/dL) upon presentation at the hospital or healthcare setting.
13. Subjects with severe cerebral anoxia (except cerebral palsy), in the judgment of the healthcare provider.

14. Subjects have used an investigational product or been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study.
15. Subject has received antiseizure medication prior to arrival in the healthcare setting.
16. Subject has prior placement of a vagus nerve stimulator.

4.3 Restrictions

4.3.1 Medical Intervention

There will be no special restrictions on medical interventions deemed necessary by the investigator for the health and wellbeing of the subject during the study.

4.4 Reproductive Potential

4.4.1 Female Contraception

Female children and adolescent subjects should be either:

- Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of childbearing potential with a negative urine pregnancy test at screening/baseline. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use medically acceptable methods of contraception.

Medically acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms with spermicidal agent)
- Oral hormonal contraceptives, stabilized for at least 30 days prior to the treatment visit, plus condoms.

4.4.2 Male Contraception

Males should use condoms if they are sexually active for 7 days after administration of study drug and must not donate or use sperm for the purposes of making a woman pregnant until 7 days after the administration of study drug.

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss with the medical monitor prior to withdrawal of a subject from the study, if possible.

If a subject is withdrawn for whatever reason within a week following administration of study drug, the evaluations listed for the 1-week follow-up visit are to be performed as completely as

possible. The reason for termination and date of stopping the study must be recorded in the CRF and source documents.

Subjects who discontinue will not be replaced.

4.5.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- AE
- Protocol deviation
- Withdrawal by subject, parent, guardian, or legally authorized representative
- Lost to follow-up
- The sponsor or investigator terminates the study

Withdrawal/discontinuation due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page. When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined in Section 8.2.

Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the reviewing institutional review board (IRB), or investigational product safety problems, or at the discretion of the sponsor. In addition, the sponsor retains the right to discontinue development of SHP615 at any time.

If a study is prematurely terminated or discontinued, the sponsor will promptly notify the investigator. After notification, the investigator must contact all subjects and subject's parents, guardians, or legally authorized representatives and the healthcare setting pharmacy (if applicable) within 28 days. As directed by the sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

4.5.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent, guardian, or legally authorized representative of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the parents, guardians, or legally authorized representatives at subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations.

4.5.3 Stopping Rules

An urgent safety review will be conducted within 7 days by the sponsor if 1 or more of the following criteria are met:

- Death that is considered related to the study drug.
- 2 SAEs of similar type (defined as the same or similar Medical Dictionary for Regulatory Activities [MedDRA] higher level group code), and considered related to the study drug.

The urgent review will be performed by a sponsor safety review group, which will include the study Global Safety Lead physician and the Global Drug Safety therapeutic area Head. Following the sponsor's review of safety data, 1 of the following actions will be taken with respect to study status:

- Continue study with protocol unchanged;
- Continue study with modifications to the protocol; or
- Terminate study.

Subject safety will be monitored on a continuous basis during this study until the last subject completes his or her last scheduled study time point/assessment.

4.5.3.1 Study Level Stopping Rules

Safety data, including SAEs and adverse events of special interest (AESIs), will be monitored regularly throughout the duration of the study and submitted to Regulatory Authority(ies), as appropriate. If any potential safety signal is identified during safety monitoring in this study by the sponsor and/or following a safety data review, a comprehensive analysis of the issue will be undertaken by the sponsor. As a result of this assessment, the sponsor may take actions as deemed appropriate (which may include changing or suspending dosing in the study).

4.5.3.2 Follow-up for Subjects Meeting Stopping Criteria

Subjects that develop either an SAE or other toxicity considered clinically relevant (AE, laboratory, physical examination, vital sign, or ECG finding) will be carefully monitored until resolution, which may include the following:

- Additional clinical laboratory tests and/or other clinical investigations.
- Additional visits or extended duration of follow-up.
- Obtaining a specialist consultation.

5 PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received within 30 days prior to the treatment visit and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate CRF page.

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received within 30 days of the date of investigational product administration. Prior treatment information must be recorded on the appropriate CRF page.

Medications taken before investigational product administration will be documented as prior medications.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the time of the investigational product administration and the end of the follow-up period, inclusive. All concomitant medication(s) and treatment(s) during the study must be recorded on the appropriate CRF page, with indication, daily dose, start and stop dates of administration. All subjects (or parent, guardian, or legally authorized representative) will be questioned about concomitant medication during their follow-up visit.

The investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

MHOS/SHP615 is a clear, colorless, ready-to-use solution (containing 5 mg midazolam [as hydrochloride] per mL). MHOS/SHP615 has been specifically developed as a single, age-specific, fixed dose (approximately 0.25 to 0.5 mg/kg as midazolam) formulation for buccal administration in children, 1 dosage per each of the following age groups:

- 2.5 mg (yellow label) ages 3 months (52 weeks corrected gestational age) to <1 year (and weight >5 kg)
- 5 mg (blue label) ages 1 year to <5 years
- 7.5 mg (purple label) ages 5 years to <10 years
- 10 mg (orange label) ages 10 years to <18 years

The investigational product MHOS/SHP615 will be provided in prefilled single-use, ready-to-use, amber, age-specific, and color-coded oral dosing syringes, and is to be administered by the buccal (oromucosal) route. The full amount of solution will be delivered slowly into the space between the inside of the cheek and the lower gum.

Buccal (oromucosal) administration was considered to be an appropriate route to be progressed to address the unmet need for a convenient, fast–acting product suitable for use in both the

community and healthcare setting. Additional information is provided in the current version of the SHP615 Midazolam HCl investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product(s)

6.2.1 Allocation of Subjects to Treatment

This is an open-label, nonrandomized study; therefore, assignment to MHOS/SHP615 will be unblinded to the investigators, subjects, and the sponsor study team. Study treatment will only be administered by the healthcare setting study investigator or subinvestigator to subjects who have a signed and dated IRB-approved ICF and who have met all eligibility criteria.

All subjects enrolled in the study will receive treatment with the investigational product based on their age (Section 6.2.2.1).

Subject numbers are assigned to all subjects as they present for enrollment. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. This identifying number will be retained throughout the study.

Once a unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If an identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

6.2.2 Dose Regimen and Dose Administration

MHOS/SHP615 will be administered buccally by the investigator or subinvestigator as a single, fixed dose product, banded by age to subjects with CSE in the healthcare setting. For buccal administration, MHOS/SHP615 is administered into the space between the lower gum and the inside of the cheek.

6.2.2.1 Dosing Regimen

Details of subject dosing and follow-up are outlined in Section 3.1 and included in the Schedule of Assessments (Table 1).

There are 4 single, fixed, banded by age, dose regimens of the MHOS/SHP615 formulation for the treatment of SE; 1 dosage per buccal administration for each of the following age groups:

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

6.2.2.2 Dose Administration

Only 1 syringe with the specified dose must be given. The full amount of the MHOS pre-filled dosing syringe is injected slowly into the buccal mucosa. In some cases, it might be necessary to divide the dose so that half of the solution is injected into each side of mouth.

All investigational product is dispensed by the investigator or subinvestigator.

Prior to administration of drug therapy, the airway should be secured and respiratory and cardiac function assessed (NICE Guidance National Institute for Health and Care Excellence, 2011).

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

A computer-generated label is applied to the investigational product. All investigational product is labeled with a minimum of the protocol number, pack number (if applicable), dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements “For clinical trial use only” and the name and country of the sponsor and Quintiles name and address.
Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.

Additional labels may not be added without the sponsor’s prior full agreement.

6.3.2 Packaging

The investigational product MHOS/SHP615 will be provided in individual, labeled, single-dose, prefilled plastic, oral dosing syringes available in 4 different, age-specific, color-coded doses (2.5, 5, 7.5, and 10 mg dose packs) in a protective plastic tube which are packaged and dispensed in cartons with tamper-evident seals. The cartons should not be opened until the investigational product is to be administered.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Keep the oral dosing syringe containing the investigational product in the protective plastic tube. Keep at or below 25°C (77°F). Do not refrigerate or freeze.

Investigational products are distributed by the pharmacy or nominated member of the study team. The subinvestigator/designated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording.
The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

Investigational product for the sponsor's studies must be stored according to all applicable local, state, and/or national laws.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a subinvestigator who is adequately trained in the

protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented on the CRFs and/or other investigational product record.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

At the end of the study, or as instructed by the sponsor, all unused stock and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

6.5 Subject Compliance

All doses of open-label MHOS/SHP615 administered at the investigational site will be by the investigator or subinvestigator.

Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist or investigator-identified designee will record details on the drug accountability form.

6.6 Destruction of Investigational Product

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor, and all destruction must be adequately documented.

7 STUDY PROCEDURES

7.1 Study Schedule

The detailed study procedures/assessments to be performed throughout the study are outlined in the Schedule of Assessments (Table 1).

7.1.1 Screening/Baseline Assessments

Screening/Baseline assessments for subject eligibility into this study occur on the same day as the Treatment Period when subjects <18 years present with SE in the healthcare setting after informed consent has been obtained. Alternatively, the subject may be prescreened by the investigator for subjects at risk of SE in their clinical practice and parent, guardian, or legally authorized representative may sign informed consent before the subject presents to the healthcare setting for treatment of the seizure. However, confirmation of SE, evaluation of seizure symptoms, blood and urine samples, and AE monitoring must be completed in the healthcare setting.

Written informed consent must be obtained prior to performing any protocol-specific procedures. The complete list of assessments that will be performed in the study is listed below:

- Informed consent/assent (when applicable, per Shire policy and country regulations)
- Inclusion/exclusion criteria (Sections 4.1 and 4.2)
- Demographics
- Medical/procedural history
- Confirmation of SE
- Evaluation of seizure symptoms (based on clinical judgment and healthcare setting procedures)
- Riker Sedation Agitation Scale
- Obtain blood and urine samples for the following laboratory tests:
    - Safety laboratory tests for serum biochemistry and urinalysis
    - Blood glucose can be measured by local lab or testing kit
    - Urine pregnancy test (females of childbearing potential only)
- Vital signs
- Review concomitant medications/treatments
- Monitor AEs
- Measure oxygen saturation on room air, if feasible

Table 2 lists recommend prescreening procedures and assessments that can be performed for subjects at risk of SE prior to presenting for treatment.

Table 2 Recommended Prescreening Procedures and Assessments

Obtain informed consent[a]	
Collect demographic information	
Review medical history	
Take blood and urine sample for laboratory analysis[b]	
Review inclusion/exclusion criteria:	
Inclusion Criteria	Exclusion Criteria
1. Age	1. Pregnancy
2. Informed consent	4. Known seizures due to drugs/alcohol
	6. Contraindications to benzodiazepines
	7. History of benzodiazepine abuse
	8. Prior non-response to midazolam
	11. Prior treatment for HIV
	13. Severe cerebral anoxia (except cerebral palsy)
	14. Prior study involvement impacting this study
	16. Prior placement of a vagus nerve stimulator

Note: Procedures and assessments should be reviewed and reconfirmed when the subject arrives at the hospital or healthcare center for SE treatment.

[a] To be repeated every 3 months if no seizure resulting in study drug administration.
[b] To be repeated every 6 months if no seizure resulting in study drug administration.

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been administered investigational product(s). Subjects cannot be rescreened once they have been designated as a screen failure.

7.1.2 Treatment Period Procedures (0 min from MHOS/SHP615 administration)

Healthcare setting study investigator or subinvestigator will administer investigational product MHOS/SHP615 (age-based dose of 2.5, 5, 7.5, or 10 mg) buccally.

The following procedures will be performed:

- Evaluate seizure symptoms
- Riker Sedation Agitation Scale
- Provide supportive care per healthcare setting guidelines
- Review concomitant medications/treatments
- Monitor AEs
- Measure oxygen saturation

7.1.3 Treatment Period (0 minutes to 6 hours postdose)

- Perform physical examination when possible during the 6 hour time period.

7.1.4 Treatment Period (10 minutes to 24 hours postdose)

The following procedures will be performed throughout the Treatment Period at time points specified in the Schedule of Assessments (Table 1):

- Evaluate seizure symptoms and Riker Sedation Agitation Scale at 10 and 30 (±5) minutes, and 1 (±10 min), 4 (±30 min), 6 (±30 min), and 24 (±30 min) hours postdose
- 4 hours and 24 hours (±30 min) postdose (if subject has not been discharged from the healthcare setting): Obtain blood and urine samples for safety laboratory tests for serum biochemistry and urinalysis
- 1 (±10 min), 3 (±30 min), and 6 hours (±30 min) postdose:
  - Collect blood samples for PK analysis.
- 10 and 30 (±5) minutes, and 4, 6, and 24 hours (±30 min) postdose (if subject has not been discharged from the healthcare setting):
  - Measure vital signs: single supine blood pressure (BP), pulse rate, respiratory rate, temperature (°C or °F).
  - Measure oxygen saturation.
  - Perform standard 12-lead ECG.
- Administer supportive care throughout this time period.
- Review concomitant medications/treatments.
- Monitor AEs (minimum 6-hour observation period after dosage for safety monitoring and blood sampling).
- Assess buccal cavity where MHOS/SHP615 was administered between cheek and gum line for redness, inflammation, and ulceration at 1 (±10 min), 4 (±30 min), and 6 (±30 min) hours postdose.

Note: Evaluate by telephone if subject is discharged between 6 hours (±30 min) and 24 hours (±1 hour) after SHP615 administration.

- Telephone contact: The subject's parent or caregiver should be contacted by telephone by the investigator or subinvestigator at the site to assess the status of the subject at approximately 24 hours after SHP615 administration, specifically to collect AE and SAE information. If the subject, parent, or caregiver reports significant AEs, the subject should be requested to return to the site for a more thorough evaluation as soon as possible. The telephone contact for all subjects should be clearly documented in the source documents.

7.1.5 Follow-up Visit

The follow-up period for this protocol is 1 week after the Treatment Period.

At the end of this period there will be a follow up visit to evaluate seizure symptoms, review concomitant medications, conduct a physical examination, and query for serious adverse events (SAEs), AEs. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Section 8).

7.1.6 Additional Care of Subjects after the Study

No aftercare is planned for this study. It is the responsibility of the investigator to counsel subjects on their treatment alternatives when they exit the study.

7.2 Study Evaluations and Procedures

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.2.1 Informed Consent

The informed consent form (ICF) must be executed prior to performing any study-related activities and the ICF must be approved by the reviewing IRB. The subject or the subject's parents, guardians, or legally authorized representatives may withdraw consent at any time. The subject may be prescreened by the investigator in their clinical practice and the parent, guardian, or legally authorized representative may sign informed consent before the subject presents to the healthcare setting for treatment of the seizure. If more than 3 months have elapsed between initial informed consent and seizure, the parent, guardian, or legally authorized representative should re-sign at the time of admission prior to treatment. Participation in the study may be terminated at any time without the consent of subjects or subject's parents, guardians, or legally authorized representatives as determined by the investigator.

7.2.2 Demographic and Other Baseline Characteristics

Demographics: date of birth, sex, race and ethnicity (where locally permitted) and medical history will be obtained at Screening from parents or caregivers and will be recorded on the source document and CRF.

Medical history (including SE) will capture the subject's current medical status (current SE or CSE disease process), past medical status (past disease processes), history of surgery, allergies, and concomitant medications/treatments.

7.2.3 Efficacy

Evaluation of seizure activity will be conducted throughout the study to assess the therapeutic success.

- Therapeutic success will be defined as:
  - the cessation of visible seizure activity within 10 minutes, with
  - a sustained absence of visible seizure activity for 30 minutes following a single dose of MHOS/SHP615.

7.2.4 Safety

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

7.2.4.1 Medical and Medication History

The investigator will perform a complete medical history at Screening, including a medication history, and record all information gathered. The investigator must record all clinically or medically relevant information regardless of how much time has elapsed since the date of diagnosis.

With the consent of parents, guardians, or legally authorized representatives of participating subjects, medical records from other treatment providers should be requested.

Refer to Section 5.1 for full details on collection of prior treatment. Prior treatment information, including any prior treatments for SE (eg, dietary, medication, or other), must be recorded on the appropriate CRF page.

7.2.4.2 Physical Examination

A complete physical examination will be performed at some time point between dosing (0 minute) and 6 hours post-dose, and at the follow-up. Height (without shoes) and weight will be measured during the first exam.

Complete physical examinations must be performed by the investigator or subinvestigator in accordance with standards at the site and per local guidelines. Complete physical examinations consist of assessments of:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat; buccal cavity where MHOS/SHP615 was administered between cheek and gum line will be examined for redness, inflammation, and ulceration and noted on physical examination CRF
- Spine/neck/thyroid
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal

- Neurological

Abnormalities identified at Screening will be documented in the subject's source documents and on the medical history CRF. Changes after the Screening visit will be captured as AEs on the AE CRF page, as deemed by the investigator.

7.2.4.3 Adverse Event Collection

At each study time point, subjects (or parent, guardian, or legally authorized representative) will be questioned in a general way to ascertain if AEs have occurred since the previous time point. Adverse events are collected from the time informed consent is signed when the subject with SE arrives at the hospital or healthcare setting, or if the informed consent has been previously signed, from the time the subject begins evaluation and treatment in the hospital or healthcare setting for SE, to completion of the follow-up visit. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.4.4 Vital Signs

Vital signs will be conducted after the subject has been supine for at least 5 minutes immediately prior to the assessment include blood pressure (systolic and diastolic), pulse rate, respiration rate (after 5 minutes of rest), and body temperature to be performed at the time points specified in the Schedule of Assessments (Table 1). Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg. It is preferred that the same arm (preferably the dominant arm) will be used throughout the study. The same size BP cuff that has been properly sized and calibrated will be used to measure BP each time.

The use of automated devices for measuring BP and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, all vital signs should be obtained prior to the nominal time of the blood collection.

It is preferred that body temperature be collected using tympanic, oral, or axillary methods and that the same method be used consistently throughout the study.

Any clinically significant deviations from the initial vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.4.5 Clinical Laboratory Evaluations

Clinical laboratory assessments will be performed at Screening, at 4 hours postdose, and at 24 hours postdose if the subject is still at the healthcare setting. The following clinical laboratory assessments will be performed:

Chemistry	Urinalysis	Other
BUN and Creatinine[a]	pH	Urine pregnancy test[d]
Glucose (fasting if possible)	Glucose (qual)	
Calcium (total)	Protein (qual)	
Sodium	Blood (qual)	
Potassium	Ketones	
Chloride	Nitrites	
AST, ALT	Leukocyte esterase	
Total bilirubin	Specific gravity	
Direct bilirubin[b]	Microscopy[c]	
Indirect bilirubin[b]		
Alkaline phosphatase		
Albumin		
Total protein		
Bicarbonate		

ALT = alanine aminotransferase ; AST = aspartate aminotransferase.

[a] Creatinine Clearance determination by central lab using Schwartz method.

[b] Only if total bilirubin is elevated.

[c] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

[d] Complete at screening for women of childbearing potential; may be repeated at the follow-up visit or withdrawal from study if pregnancy is suspected.

Aliquots from the PK samples may be retained as back-up for additional parameter testing if necessary. Subjects will be in a seated or supine position during blood collection. The total blood draw for each subject will be approximately 14.25 mL.

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by Quintile's central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Blood samples for laboratory assessments will be collected at the site by a trained phlebotomist designated and/or approved by the study investigator. Details for the collection, processing, storage and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual.

Blood, serum, and urine samples will be stored and secured in a manner that assures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

7.2.4.6 Pregnancy Test

A urine pregnancy test is performed on all females of childbearing potential at Screening and at the follow up visit, if pregnancy is suspected, or upon withdrawal of the subject from the study.

7.2.4.7 Electrocardiogram

A standard twelve (12)-lead electrocardiogram (ECG, single recording) will be performed at time points specified in the Schedule of Assessments (Table 1).

When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, BP, and pulse rate.

The investigator or subinvestigator at the investigator site will make comparisons to baseline measurements taken at screening, if available. A copy of the ECG should be available as source documents for review.

7.2.4.8 Oxygen saturation

Oxygen saturation will be measured at time points specified in the Schedule of Assessments (Table 1). 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 and the investigator will record the oxygen saturation of the patient while on oxygen therapy as well as the oxygen delivery system and amount of oxygen administered (eg, 2 L/min via nasal cannula).

7.2.5 Others

7.2.5.1 Pharmacokinetic Assessments

Blood samples (~1.25 mL) to provide a minimum of 0.5 mL plasma for the assessment of plasma midazolam and 1-hydroxymidazolam concentrations will be collected (from all subjects who received investigational product) and analyzed at the specified time points for the duration of the study at the time points specified in the Schedule of Assessments (Table 1). The exact time of the sample collection should be noted on the source document and data collection tool (eg, CRF).

Samples will be analyzed for midazolam and 1-hydroxymidazolam using a validated assay. The methodologies will be appropriately validated in compliance with the CRO's standard operating procedures.

The address for shipment of serum samples and contact information for the laboratory analysis of midazolam and 1-hydroxymidazolam will be provided to the investigator site prior to initiation of the trial.

7.2.6 Volume of Blood to Be Drawn from Each Subject

Table 3 Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples[a]		1.25	3	3.75
Safety	Biochemistry	3.5	3	10.5
Total mL				14.25

[a] If a catheter is used, the first mL is to be discarded; then take 1.25 mL into appropriate tube for PK sample. A total of 1.25 mL of blood drawn has been used in determination of sample volume.

During this study, it is expected that up to approximately 14.25 mL of blood will be drawn from each subject.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 14.25 mL. Additional considerations may be made for small children and infants with sponsor review. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed when the subject with SE arrives at the hospital or healthcare setting or if the informed consent has been previously signed, from the time the subject begins evaluation and treatment in the hospital or healthcare setting for SE, until the defined follow-up period stated in Section 7.1.5. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in

the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his/her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related.” Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.” The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.5.

Any report of pregnancy for any female study participant must be reported within 24 hours to Quintiles Transnational Japan K.K. and the Shire Global Pharmacovigilance and Risk Management Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)

- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of the product.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the SHP615 Midazolam HCl investigator's brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Quintiles Transnational Japan K.K., the Shire Global Pharmacovigilance and Risk Management Department, and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to Quintiles Transnational Japan K.K. and the Shire Global Pharmacovigilance and Risk Management Department. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

An **SAE** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a

hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).

- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in a hospital or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

Hospitalization

For this protocol, hospitalization is defined as any admission to a medical or equivalent healthcare facility or any prolongation of an existing admission lasting **more than 24 hours.** Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). A healthcare setting visit does not necessarily constitute a hospitalization; however, the event leading to the healthcare setting visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;

- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the informed consent is signed when the subject with SE arrives at the hospital or healthcare setting, or if the informed consent has been previously signed, from the time the subject begins evaluation and treatment in the hospital or healthcare setting for SE, until the defined follow-up period stated in Section 7.1.5 and must be reported to Quintiles Transnational Japan K.K., the Shire Global Pharmacovigilance and Risk Management Department, and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to Quintiles Transnational Japan K.K. and the Shire Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the ICF, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The

investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, and Site Reporting

The sponsor and Quintiles Transnational Japan K.K. are responsible for notifying the relevant regulatory authorities/and institutional IRBs of related, unexpected SAEs.

In addition, the sponsor or Quintiles Transnational Japan K.K., is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP615 program.

The investigator is responsible for notifying the local IRB or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Product Quality Complaints

The product quality includes quality of the drug delivery device combination product. As such device defects should be reported according to the instructions in this section. The reporting of product quality occurrences, when the product does not meet specifications, includes the reporting of device defects. Quality complaints may be reportable to PMDA as a device malfunction report, regardless of whether or not the event relates to an AE.

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints.

Please use the information below as applicable to report the Product Quality Complaint (PQC):

Origin of Product Quality Complaint	**E-mail Address**
European Union and Rest of World (ROW)	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)
[redacted]

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

All data collected are to be recorded on the appropriate case report form (CRF).

The authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by the investigator or qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel.

Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is enrolled, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the sponsor's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

All available data will be included in the analysis. No imputation of missing data will be performed.

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.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock. All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC, USA 27513).

9.4.1 Appropriateness of Measurements

This is a Phase 3, open-label study that is designed to evaluate the efficacy and safety of MHOS/SHP615 in therapy for subjects with SE or CSE. Measures employed in this protocol are standard measures routinely used for the evaluation of the efficacy, safety, and tolerability of an investigational product.

9.4.2 General Considerations

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. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Where applicable, estimates from statistical model of least squares means, standard errors, and 95% CIs for least squares means will be provided.

Time-to-event data will be summarized using Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations. Plots of the Kaplan-Meier curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

9.5 Planned Interim Analysis

There is no planned interim analysis for this study.

9.6 Sample Size Calculation and Power Considerations

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.

9.7 Study Population

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

The **Safety Set** will consist of all subjects who have received a single dose of MHOS/SHP615.

The **Full Analysis Set** (FAS) will consist of all subjects who have received a single dose of MHOS/SHP615 and who have at least 1 assessment for therapeutic success (cessation of seizure within 10 minutes with sustained absence of seizure for 30 minutes) performed after the administration of MHOS/SHP615.

The **Pharmacokinetic 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.

9.8 Efficacy Analyses

The primary efficacy analysis will be conducted on the FAS.

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is response rate, which is defined as the percentage of subjects with therapeutic success.

- Therapeutic success will be defined as:
  - the cessation of visible seizure activity within 10 minutes, with
  - a sustained absence of visible seizure activity for 30 minutes following a single dose of MHOS/SHP615.

The primary efficacy analysis will be conducted on FAS by constructing the 2-sided, 95% 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.

9.8.2 Secondary Efficacy Endpoints

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 the 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 the 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/Nonresponder 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.

9.8.3 Subgroup Analyses of Efficacy Endpoints

Selected efficacy endpoints will be evaluated using descriptive statistics by the following subgroups, to the extent the data allow:

- Age group:
  - 3 months (52 weeks corrected gestational age) to <1year (and weight >5 kg)
  - 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)

9.8.4 Exploratory Efficacy Endpoints

A description of the analyses will be included in the SAP.

9.9 Safety Analyses

Safety data will be summarized using descriptive statistics for the Safety Set.

9.9.1 Primary Safety Endpoints

The primary safety endpoints will be respiratory depression, which will include the following measures within the 4 hours after MHOS/SHP615 administration:

- Persistent decrease in oxygen saturation to <92% measured at 10 minutes, 30 minutes, and 4, 6, and 24 hours postdose (ie, <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)

9.9.2 Secondary Safety Endpoints

The secondary safety endpoints include the following:

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

Adverse events and medical history will be coded using MedDRA. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, and by age. Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Vital signs (systolic and diastolic blood pressure, pulse, and weight) including potentially clinically important vital signs will be summarized using the appropriate descriptive statistics.

The ECG results, including potentially clinically important results, will be summarized.

9.9.3 Clinical Laboratory Tests

Clinical laboratory tests will be summarized using the Safety Set.

Actual values and change from baseline clinical laboratory tests will be summarized. If more than 1 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, non-clinically significant result less than the lower limit of normal, 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 1 laboratory result is reported per study time point per parameter, the result yielding the most severe classification will be selected for analysis.

Categorical laboratory test results (urinalysis excluding pH) will be summarized by study time point. If more than 1 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 point to identify any trends.

9.9.4 Vital Signs

Vital signs will be summarized using the Safety Set.

Actual values and changes from baseline in vital signs will be summarized. All vital sign data will be presented in subject listings.

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.

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.

9.9.5 Electrocardiography

Electrocardiography results will be summarized using the Safety Set.

The number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results, or ECG not performed, will be summarized. 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.

9.10 Pharmacokinetic Analyses

Plasma concentrations of midazolam, its active metabolite (1-hydroxymidazolam), and any potential additional metabolite(s) will be evaluated using the Pharmacokinetic population.

The Pharmacokinetic population will include subjects who receive a single dose of MHOS/SHP615 and for whom at least 1 post-dose PK blood sample was collected. PK samples will be collected at 1, 3, and 6 hours after administration of MHOS/SHP615.

PK parameters (eg, C_{max}, T_{max}, AUC and $t_{1/2}$) will be calculated using population PK modeling.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, the ethical principles in the Declaration of Helsinki, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996) and any updates, EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Institutional Review Boards

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), and any updates, EU Directive 2001/20/EC, the ethical principles in the Declaration of Helsinki, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (July 1996).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

Once the CRA/study monitor has verified the contents of the completed CRF pages against the source data, the duplicate pages are retrieved and forwarded to the study sponsor (or designee) for data entry. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB or regulatory inspectors) may check the CRF entries against the source documents. The ICF includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, PMDA) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the Japan Pharmaceuticals and Medical Devices Agency (PMDA), US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.2.4 Compliance to all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation

When using controlled substances the investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects (parent, guardian, or legally authorized representative) prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's parent, guardian, or legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject (parent, guardian, or legally authorized representative) has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's parent, guardian, or legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the blank informed consent form that was reviewed by the IRB and received their favorable opinion/approval.
A copy of the IRB's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB for review, and all must be approved prior to site initiation.

The applicant for an IRB opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor has received written IRB approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects (parent, guardian, or legally authorized representative) have consented to take part in the study, the sponsor and/or its representatives review their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market MHOS/SHP615; national or local regulatory authorities; and the IRB that gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the

publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11 REFERENCES

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12 APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	20 Mar 2017	Japan
Amendment 1	08 Jul 2017	Japan
Amendment 2	28 Aug 2017	Japan

APPENDIX 2 SCALES AND ASSESSMENTS

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment	Version Number	Date Issued
Riker Sedation-Agitation Scale		2016

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.

Riker Sedation-Agitation Scale (SAS)

Score	Term	Descriptor
7	Dangerous Agitation	Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very Agitated	Requiring restraint and frequent verbal reminding of limits, biting ETT
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and Cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very Sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Guidelines for SAS Assessment

1. Agitated patients are scored by their most severe degree of agitation as described
2. If patient is awake or awakens easily to voice ("awaken" means responds with voice or head shaking to a question or follows commands), that's a SAS 4 (same as calm and appropriate – might even be napping).
3. If more stimuli such as shaking is required but patient eventually does awaken, that's SAS 3.
4. If patient arouses to stronger physical stimuli (may be noxious) but never awakens to the point of responding yes/no or following commands, that's a SAS 2.
5. Little or no response to noxious physical stimuli represents a SAS 1.

This helps separate sedated patients into those you can eventually wake up (SAS 3), those you can't awaken but can arouse (SAS 2), and those you can't arouse (SAS 1).

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APPENDIX 3 BIOANALYSIS: SAMPLE HANDLING

1.1 Blood Sample Collection

Blood samples will be collected at the times specified in Table 1 to measure plasma concentrations of midazolam, 1-hydroxymidazolam, and any potential additional metabolite(s).

Blood samples (~1.25 mL) for pharmacokinetic analysis will be drawn by in-dwelling catheters or direct venipuncture into K2EDTA tubes, capped, and chilled immediately on crushed ice. The actual time that the sample was obtained will be recorded in the subject's source document and on the appropriate CRF page. After applying a tourniquet, venous blood will be drawn with a disposable needle. If a catheter is used, the first milliliter of blood on each sampling occasion will be discarded. Saline can be used to keep catheters patent.

1.2 Blood/Plasma Sample Handling

Samples should be kept on crushed ice until plasma is separated as soon as possible after collection (within <15 minutes) by refrigerated centrifugation (4°C, 1500 g, 15 minutes). The separated plasma will be transferred into appropriately labeled polypropylene tubes via a plastic pipette. Plasma to be split in two aliquots: first tube minimum 0.25 mL (primary sample), second tube remaining plasma volume (back-up sample). Aliquots should be shipped separately to the bioanalytical laboratory. All samples will be stored at approximately -80°C or colder and the freezer temperature will be controlled, monitored, and recorded during the storage period until they are transferred in the frozen state to a designated bioanalytical contract laboratory. Samples will remain frozen at -80°C or colder until analysis. Note: For sites that do not have access to -80°C storage, samples may be stored at -20°C for a limited time (maximum 90 days) before shipping to the bioanalytical CRO.

Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the clinical pharmacology unit. The labels will contain the following information:

- Study number
- Treatment
- Subject identifier
- Matrix identifier (plasma)
- Nominal time

1.3 Shipment of Plasma Samples

Plasma samples should be double bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment. All applicable shipping regulations must be followed. Shipments should be scheduled so that no samples arrive on the weekend and should be shipped Monday to Wednesday only.
Samples should be transported to ensure that they arrive at the bioanalytical laboratory between

the hours of 0900 and 1600. The recipient and primary Shire contact must be notified by phone, fax, and e-mail when the samples are shipped and must be provided with the shipment tracking number.

Plasma samples, along with the corresponding documentation, will be shipped to:

Name of bioanalytical laboratory: York Bioanalytical Solutions (YBS)

Primary contact: [redacted]

Telephone DDI: [redacted]

E-mail: [redacted]

Plasma samples will be stored nominally at -80°C prior to and after analysis at York Bioanalytical Solutions Limited until their disposal is authorized by Shire.

1.4 Assay Methodology

Drug analysis will be performed at YBS under the guidance of the Department of Nonclinical Development, Shire Pharmaceuticals. Plasma sample analysis will be performed according to the bioanalytical study plans prepared for the study.

Plasma samples (K2EDTA) will be analyzed at York Bioanalytical Solutions Limited for midazolam, 1-hydroxymidazolam, and any potential additional metabolite(s) using the most current validated bioanalytical method.

In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate.

Raw data will be stored in the archives at York Bioanalytical Solutions Limited.