24 June 2021
EMA/442285/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

BUCCOLAM

midazolam

Procedure no: EMEA/H/C/002267/P46/018

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 13/04/2021, the MAH submitted a completed paediatric study for Buccolam in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH declared that study SHP615-302 is part of a clinical development program to support the paediatric status epilepticus indication in Japan per request of the Japanese health authorities. There is no variation or extension to be expected as Buccolam is already approved for use in paediatric subjects in the EU.

2.2. Information on the pharmaceutical formulation used in the study

The investigational product (IP) is a clear, colorless, ready-to-use solution containing 5 mg/mL midazolam (as midazolam hydrochloride salt; each mL contains 5 mg midazolam free base [equivalent to 5.56 mg midazolam hydrochloride]). It was specifically developed as a single, age-specific, fixed-dose (which equates to approximately 0.25 to 0.5 mg/kg) formulation for buccal administration in children, 1 dosage per each of the following age groups:

• 2.5 mg (yellow label) ages more than 6 months to less than 1 year (and weight more than

5 kg)

• 5 mg (blue label) ages 1 year to less than 5 years

• 7.5 mg (purple label) ages 5 years to less than 10 years

• 10 mg (orange label) ages 10 years to less than 18 years

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study SHP615-302: A Phase 3, Multicenter, Open-label Extension Study of Buccally Administered MHOS/SHP615 in Pediatric Patients with Status Epilepticus (Convulsive) in Community Settings.

The study ran from April 2018 to October 2020.

CHMP comments

This is a follow-up study to study SHP615-301, which evaluated Buccolam in Japanese paediatric patients with convulsive status epilepticus in an emergency room setting. Study SHP615-301 was assessed previously in pdWS EMEA/H/C/002267/P46/017.

2.3.2. Clinical study

Study SHP615-302: A Phase 3, Multicenter, Open-label Extension Study of Buccally Administered MHOS/SHP615 in Pediatric Patients with Status Epilepticus (Convulsive) in Community Settings

Description

Study SHP615-302 was a phase 3, open-label study to evaluate efficacy and safety of a single dose of Buccolam (oromucosal midazolam, hereafter referred to as MHOS/SHP615) given by caregivers to Japanese paediatric patients with convulsive status epilepticus in the community setting.

Methods

Objectives

The primary objective of this study was to assess the efficacy of buccally administered midazolam hydrochloride oromucosal solution (MHOS/SHP615) in paediatric subjects with status epilepticus (SE; convulsive) in the community setting.

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

Study design

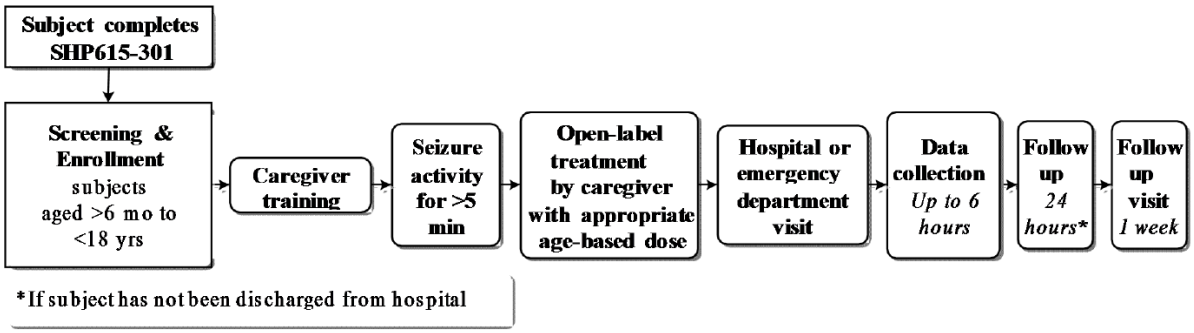
This study was to be conducted in approximately 27 healthcare setting study centers in Japan.

Six subjects were to be enrolled in this study as shown in Figure 1. Screening occurred on the same day as baseline (Visit 1) for the SHP615-301 study (evaluation of Buccolam in Japanese paediatric patients with convulsive status epilepticus in an emergency room setting). After completing the SHP615-301 study, the subject's parent, guardian, or legal representative was dispensed a single oral, prefilled syringe of MHOS/SHP615, along with a diary and training on how to administer the drug and record details associated with the seizure. Upon the onset of the next seizure in the community setting, the caregiver administered the investigational product (IP), as trained, after confirming that the seizure activity was appropriate for MHOS/SHP615 treatment. The caregiver recorded observations on seizure activity, timing of the seizure(s), and dosing-related errors in a study diary. The caregiver and subject visited the study site for examination as soon as possible following MHOS/SHP615 administration, even if the seizure had stopped. If, due to a medical emergency, the subject had received treatment at the closest emergency medical institution, then the caregiver reported the incident and relevant information, including any rescue treatment received, to the investigator/study site within 1 week after the incident.

Subjects remained in the hospital under observation for at least 6 hours and for up to 24 hours after hospital arrival (as needed).

All subjects treated in this study were followed for 1 week after the administration of MHOS/SHP615 for safety evaluations.

Figure 1 Study Design Schematic



Study population / Sample size

Study population

Subject eligibility was reviewed and documented by the investigator or sub investigator before subjects were included in the study.

Each subject had to meet the following criteria to be eligible for the study:

1. Subjects who completed the SHP615-301 study and who tolerated and responded to treatment with MHOS/SHP615 in the hospital and/or emergency room and were considered stable for discharge from the hospital.
2. Subjects who were more than 6 months and less than 18 years of age at the time of MHOS/SHP615 administration. If the subject's exact age was not known, the subject was excluded.
3. Parent, guardian, or legally authorized representative of the child provided informed consent and assent (when applicable) to participate in the study after initial stabilization of the subject with SE in hospital or emergency room during the SHP615-301 study. The subject also provided informed consent prior to participation, where applicable.
4. Parent, guardian, or legally authorized representative had received appropriate training/education and was deemed qualified by the investigator and was willing to:
    a. properly administer MHOS/SHP615;
    b. record seizure information and dosing of MHOS/SHP615 in a subject diary (including time of seizure onset, type of seizure, time necessary to administer MHOS/SHP615, time between MHOS/SHP615 administration to seizure cessation, etc);
    c. follow the necessary instructions to secure the safety of the subject.
5. Subjects who experienced 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:
    d. presented, at the time, with seizure (convulsive) activity and 3 or more convulsions within the preceding hour;
    e. presented, at the time, with seizure (convulsive) and 2 or more convulsions in succession without recovery of consciousness;
    f. presented, at the time, with a single seizure (convulsive) persisting ≥5 minutes

Subjects who met any of the following criteria were excluded from the study:

1. Female subjects who were 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 known or suspected recurrent seizures due to illegal drug or alcohol withdrawal.
4. Subjects with seizures due to illegal drug or acute alcoholic intoxication.
5. Subjects with seizures of psychogenic origin.
6. Subjects with seizures due to severe cases of encephalitis or meningitis, as determined by the investigator.
7. Subjects with a known history of hypersensitivities, nonresponsiveness or contraindications to benzodiazepines (ie, clinically significant respiratory depression, severe acute hepatic failure, myasthenia gravis, syndrome of sleep apnoea, glaucoma with closed angle, or use of concomitant drugs determined by the investigator to have a contraindication to the use of benzodiazepines.)
8. Subjects with a known history of benzodiazepine abuse.
9. Subjects who had not responded to previous administrations of midazolam systemic therapies, including Midafresa and/or Dormicum.
10. Subjects who needed emergent surgical intervention and general anaesthesia/intubation.
11. Subjects who had been receiving human immunodeficiency virus (HIV) protease
12. inhibitors or HIV reverse transcriptase inhibitors.
13. Subjects with severe cerebral anoxia (except cerebral palsy), in the judgment of the healthcare provider.
14. Had used an IP or been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this TDC Americas-sponsored study.
15. Subject had prior placement of a vagus nerve stimulator.

CHMP comments

The in- and exclusion criteria are largely in line with the criteria of previous study SHP615-301.

Sample size

The target sample size (at least 6 subjects) was estimated based on feasibility analysis rather than based on statistical rationale.

Maximum sample size: approximately 25 subjects. Evaluable sample size in this extension study depended on the actual efficacy and safety of MHOS/SHP615 in the SHP615-301 study.

Estimated minimum sample size: 25 × 0.585 (expected response rate in hospital) × 0.4 (60% expected drop-out rate from screening) = approximately 6 subjects. Based on the reported global clinical studies study data outside of Japan, expected response rate in hospital settings was conservatively estimated to be 58.5%. This was close to the lowest response rate reported in worldwide clinical studies.

Treatments

The IP, MHOS/SHP615, was administered buccally by caregivers as a single, fixed-dose product, banded by age to subjects with SE (convulsive) in community settings.

There were 4 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: at least 6 months to less than 1 year (and weight >5 kg)

• 5 mg: 1 year to less than 5 years

• 7.5 mg: 5 years to less than 10 years

• 10 mg: 10 years to less than 18 years

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 hospital settings. For buccal administration, midazolam was administered into the space between the lower gum and the inside of the cheek.

Before dosing:

- The airway was secured, and respiratory and cardiac function were assessed.
- The caregiver recorded observations on the seizure activity and timing of the seizure(s) in a study diary.
- The caregiver organized emergency transport, and the subject was brought to the study site immediately (hospital or healthcare center), even if the seizure had stopped.

Single-dose administration:

- The caregiver was instructed to administer a single dose of MHOS/SHP615 after confirming that the seizure activity was appropriate for MHOS/SHP615 treatment (e.g, the seizures lasted at least 5 minutes, or a second seizure occurred before recovery of consciousness from the first seizure, or 3 seizures occurred within 1 hour).
- Only 1 oral syringe with the specified dose was given. The full amount of the MHOS/SHP615 prefilled oral dosing syringe was administered slowly into the buccal mucosa. In some cases, it might have been necessary to divide the dose so that half of the solution was administered into each side of mouth.

After dosing:

- The caregiver recorded observations on the seizure activity and timing of the seizure(s) in a study diary.
- If the seizure had not stopped within 10 minutes of administration, and/or if a SAE emerged, then emergency medical assistance was sought. Note: A second or repeat dose of MHOS/SHP615 was not given even if the seizure recurred after an initial response.
- In the event of a medical emergency, and if it was not possible to bring the subject to the study site, the caregiver was instructed to bring the subject to the closest emergency medical institution so that the subject could receive treatment as quickly as possible. If this occurred, then the caregiver reported the incident and relevant information, including any rescue treatment received, to the investigator/study site within 1 week after the incident.

- The caregiver/parent and subject visited the study site for examination after MHOS/SHP615 administration, even if the seizure had stopped. All subjects were followed up at study sites even if the seizure had resolved.
- The caregiver was instructed to save the used MHOS/SHP615 oral dosing syringe and bring it to the study site. Any dosing-related errors, such as leaking liquid, were recorded in the study diary.

CHMP comments

The treatment is the same as the registered product Buccolam in the EU (EMEA/H/C/002267).

Outcomes/endpoints

The **primary efficacy endpoint** was response rate, which was defined as the percentage of subjects with therapeutic success. Therapeutic success was declared for subjects who met both of the following conditions:

1. Cessation of visible seizure activity within 10 minutes, ie, the time from MHOS/SHP615 administration to the end of the initial seizure was less than or equal to 10 minutes. The initial seizure referred to the seizure that triggered the use of the IP and that was captured on the "confirmation of status epilepticus" eCRF.
2. A sustained absence of visible seizure activity for 30 minutes following a single dose of MHOS/SHP615 without the need for additional rescue medication, ie, subject had no recurrence of seizure within 30 minutes of MHOS/SHP615 administration as documented on the "subject seizure status (recurrence)" eCRF, and no rescue medication had been administered within 30 minutes of IP administration (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** included:

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

The endpoints related to **safety** were:

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

- Incidences/monitoring of TEAEs, vital sign measurements, laboratory tests, oxygen saturation, and ECGs
- Occurrence of buccal irritation

CHMP comments

Treatment success was defined as cessation of visible seizure activity < 10 minutes with sustained absence for 30 minutes. This is the same definition of treatment success used in the previous study SHP615-301, which evaluated oromucosal midazolam in an emergency room setting. Sustained absence for 30 minutes is shorter than the 1 hour sustained absence which was used in the studies discussed in the initial marketing authorisation for Buccolam. However, sustained absence over a longer duration is covered by the secondary endpoints.

Statistical Methods

Primary endpoint

The response rate, i.e. therapeutic success will be expressed in percentages. For a definition of therapeutic success see previous section.

Secondary endpoints

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

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

A listing presented the response status for subjects in the FAS.

Time to Resolution of Seizures (Convulsions)

Time to resolution of seizures (convulsions) in minutes was calculated as time from IP administration to the end of the initial seizure or administration of rescue anticonvulsant medication, whichever occurred first. The initial seizure referred to the seizure that triggered the use of the IP and that was captured on the "confirmation of status epilepticus" eCRF.

Note that, as per the definition of the FAS, there was no censoring in this time to event analysis as all subjects had a date and time captured for the initial seizure cessation.

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

Time to Recovery of Consciousness

Time to recovery of consciousness in minutes was calculated only for subjects who lost consciousness pre-dose as the time from IP administration to recovery of consciousness postdose or administration of rescue anticonvulsant medication, whichever occurred first. If the time of recovery of consciousness was missing and there was no administration of rescue anticonvulsant medication during the 24-hour treatment period, the time to recovery of consciousness was censored at the latest time of any assessment captured in the eCRF up to hospital discharge during the 24-hour treatment period, ie, vital

signs, oxygen saturation, buccal cavity assessment, Riker Sedation-Agitation Scale (Riker SAS), laboratory, ECG or time the subject was discharged from the hospital.

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

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

Anticonvulsant medications for ongoing SE (rescue treatment) were captured on the "prior and concomitant medications" eCRF. Subjects who required additional anticonvulsant medication for ongoing SE 10 minutes after IP administration and before the end of the initial seizure were listed.

Percentage of Subjects Who Failed to Respond to Treatment

A responder was defined as a subject with cessation of visible seizure activity within 10 minutes after administration of MHOS/SHP615. A treatment failure/no responder was defined as a subject with continuing seizure for more than 10 minutes after a single dose of MHOS/SHP615 or the need for any additional anticonvulsant rescue medication to treat the initial seizure any time after the single dose of MHOS/SHP615 according to the participating healthcare setting protocol or guideline. Any of the following events qualified as a treatment failure:

- The time from IP administration to the end of the initial seizure was more than 10 minutes. The initial seizure referred to the seizure that triggered the use of the IP and that was captured on the "confirmation of status epilepticus" eCRF.
- Rescue anticonvulsant medication was administered to treat the initial seizure any time after MHOS/SHP615 administration.

Subjects who failed to respond to treatment were listed.

Sensitivity analyses

Not applicable

CHMP comments

Results will be provided in a descriptive format; no statistical analyses were planned.

Results

Recruitment/ Number analysed

Subjects included in this study retained the subject numbers they were assigned in Study SHP615-301 upon enrolment in Study SHP615-302.

Twelve subjects were screened for inclusion. Of these, 9 subjects were screen failures and were withdrawn. Overall, 3 subjects provided informed consent and completed Study SHP615-301. No subjects terminated early from the study (see table 1).

Table 1 Patient Disposition (Screened Set)

	MHOS/SHP615
Screened Set	12
Screen Failure	9
Withdrawal before Study Drug Administration for	0
Safety Set	3 (100)
Full Analysis Set	3 (100)
Per Protocol Set	3 (100)
Completed Study	3 (100)
Did not Complete Study	0
Primary Reason for Withdrawal	
Adverse Event	0
Withdrawal by Subject	0
Withdrawal by Parent/Guardian	0
Study Terminated by Sponsor	0
Lost to Follow-up	0
Protocol Deviation	0
Other	0

- Percentages are calculated based on the number of subjects in the Safety Set

CHMP comments

Out of the 12 subjects screened, 3 subjects were enrolled into the study and also completed the study.

Baseline data

Demographics

Two subjects in the safety set were in the 5 to <10 years age group and 1 subject was in the 1 to <5 years age group.

History of epilepsy

One subject had epilepsy with a genetic aetiology and a duration of 5.3 years.

One subject had severe myoclonic epilepsy of infancy and a duration of 5.3 years.

One subject had epilepsy with a genetic aetiology and a duration of 2.7 years.

Study SHP615-301 qualifying seizure

One subject presented with seizure activity and 3 or more convulsions within the preceding hour. 1 subject presented with a single seizure lasting at least 5 minutes. 1 subject presented with convulsive seizure activity and 3 or more convulsions within the preceding hour.

None of the 3 subjects was already hospitalized when the seizure occurred.

Prior and concomitant medications

One subject had received prior treatment with chloral hydrate as a sedative (stop date May 2018) and valproate sodium as anticonvulsant prophylaxis (stop date June 2018), and was receiving ongoing treatment with levetiracetam, lacosamide, clobazam, pyridoxal phosphate, and stiripentol as anticonvulsant prophylaxis and mucopolysaccharide polysulfuric acid ester for dry prevention.

One subject had received prior treatment with diazepam on April 2018 and on May 2018 as anticonvulsant prophylaxis and had received intravenous fluid replacement in May 2018. The subject was receiving ongoing treatment with stiripentol, topiramate, clobazam, valproate sodium and potassium bromide as anticonvulsant prophylaxis, levocarnitine for carnitine deficiency, ferric pyrophosphate for iron replenishment, and hydrocortisone butyrate for dermatitis. The subject had received levocarnitine on August 2013.

One subject had received lactomin and potassium chloride as ongoing treatment for constipation, ramelteon and triclofos sodium as ongoing treatment for insomnia, zonisamide, potassium bromide, clobazam and diazepam as ongoing anticonvulsive treatment, and tipepidine hibenzate and carbocisteine for treatment of the common cold (stop date: December 2019).

Efficacy results

Primary endpoint

Therapeutic success was defined as cessation of visible seizure activity within 10 minutes and sustained absence of visible seizure activity for 30 minutes following a single dose of MHOS/SHP615 without the need for additional rescue medication. All 3 subjects achieved therapeutic success at 30 minutes after dosing.

CHMP comments

All subjects achieved treatment success following a single dose of oromucosal midazolam.

Secondary endpoints

Subjects whose seizure event(s) stopped within 10 minutes of single dose of MHOS/SHP615 and who had sustained absence of seizure activity for at least 1 hour/4 hours/6 hours

All three subjects achieved therapeutic success at 1 hour after dosing.

For 1 subject, seizures recurred before the 4-hour postdose timepoint. The seizure during the treatment period (up to 6 hours postdose) was focal to bilateral tonic-clonic.

For 1 subject, there was no recurrence of seizure activity, 0 to 6 hours postdose, 24 hours postdose or during follow-up.

For 1 subject, seizures recurred before the 4-hour postdose timepoint. The seizure during the treatment period (up to 6 hours postdose) was focal onset-impaired awareness.

Time to resolution of seizures (convulsions)

For 1 subject, the seizure stopped within 1 minute of study drug administration.

For 1 subject, the seizure stopped within 2 minutes of study drug administration.

For 1 subject, the seizure stopped within 5 minutes of study drug administration.

Time to recovery of consciousness

One subject recovered consciousness 4 minutes after study drug administration.

One subject recovered consciousness 143 minutes after study drug administration.

One subject recovered consciousness 5 minutes after study drug administration.

Subjects who required additional anticonvulsant medication for ongoing SE 10 minutes after a single dose of MHOS/SHP615.

No subject required additional anticonvulsant medication at any time after study drug administration.

Subjects who failed to respond to treatment

No subject failed to respond to treatment

CHMP comments

The secondary endpoints support the findings of the primary endpoint, i.e. fast cessation of seizures following study drug administration and subjects remain seizure free at least one hour.

Safety results

Two subjects each received a single 7.5 mg dose of MHOS/SHP615, consistent with the age group of these subjects.

One subject received a single 5 mg dose of MHOS/SHP615, consistent with the age group of this subject.

Primary safety endpoint

The primary safety endpoint was respiratory depression, characterized by a decrease in oxygen saturation and an increase in respiratory effort. No subject reported respiratory depression.

Adverse events

Overall, 4 treatment-emergent adverse events (TEAEs) were reported for 2 subjects.

For 1 subject, no TEAEs were reported.

See table 2 for an overview of adverse events.

Table 2 Summary of Adverse Events

Subject ID	Adverse Event Text	Severity	Not related	Related	Therapeutic success/ failure on same date
Subject A	Febrile convulsion	Moderate	X		Not Applicable
	Nausea	Mild		X	Not Applicable
	Vomiting	Mild		X	Not Applicable
	Upper respiratory tract infection	Mild	X		Not Applicable
Subject B	Sleepiness	Mild		X	Not Applicable

Source: Study SHP615-302 CSR

Descriptions of adverse events

For 1 subject, a single event of mild somnolence was reported which started on the day of study drug administration, had a duration of 2 days and was considered by the investigator to be related to study drug. No other TEAEs were reported for this subject.

For 1 subject, 3 TEAEs were reported:

- Nausea, which started and stopped on the same day. This event started on the same day as study drug administration, was mild in severity and was considered by the investigator to be related to study drug treatment.
- Vomiting, which started and stopped on the same day. This event started on the same day as study drug administration, was mild in severity and was considered by the investigator to be related to study drug treatment.
- Upper respiratory tract infection, which started and stopped within 7 days. This event started 7 days after study drug administration, was mild in severity and was considered by the investigator to be not related to study drug treatment.

Serious adverse events

No treatment-emergent SAEs occurred during this study. One SAE was reported during the period prior to study drug administration.

For 1 subject, febrile convulsion was reported, which started 22 days before study drug administration and stopped within 2 days. This event was not a TEAE but was reported as an SAE due to initial or prolonged hospitalization. The event was moderate severity and was considered by the investigator to be not related to study drug treatment.

Other safety related endpoints

Riker sedation-Agitation Scale

The Riker SAS was to be performed 30 minutes postdose if possible, and at 1 hour, 4 hours, 6 hours, and 24 hours postdose. The Riker SAS ranges from 1 to 7. A score of 1 indicates "unarousable", a score of 4 indicates "calm and cooperative", and a score of 7 indicates "dangerous agitation".

- The Riker SAS score for 1 subject was 5-agitated 1-hour postdose and 4-calm and cooperative 4 hours and 6 hours postdose.
- The Riker SAS score for 1 subject was 2-very sedated 30 minutes and 1-hour postdose, 3-sedated 4 hours and 6 hours postdose, and 4-calm and cooperative 24 hours postdose.
- The Riker score for 1 subject was 4-calm and cooperative, 1-hour, 4-hours, 6-hours and 24-hours postdose.

Post marketing safety experience

Limited post-marketing safety experience was discussed by the MAH in the clinical overview regarding risk of off-label use. As this is considered outside of the scope of a pdWS this is not discussed further.

CHMP comments

Adverse events reported to be related to study drug administration were nausea, vomiting and sleepiness. All events were considered mild and either resolved on the same day or 2 days thereafter. These adverse reactions are well known to be associated with midazolam and are also included in section 4.8 of the Buccolam SmPC.

There was one serious adverse event of febrile convulsions. However, this event occurred prior to study drug dosing, hence it is agreed with the Investigators that this is unrelated to the study drug.

With regard to the Riker sedation-agitation scale, all subjects reported a score of 4 (calm and cooperative) at 24 hours after study drug dosing. One subject initially had scores indicating a high level of sedation up to 6 hours post dose. This is not surprising as the subject took the longest to recover consciousness after the dose of study drug (143 minutes, see p. 14). Nevertheless, the subject reached the same level of alertness (4- calm and cooperative) at 24 hours, same as the other subjects.

2.3.3. Discussion on clinical aspects

Study SHP615-302 was an open label study designed to evaluate use of a single dose of oromucosal midazolam (Buccolam) for seizure cessation in an outpatient setting in Japan. The study was in essence a follow up study to SHP615-301, which evaluated oromucosal midazolam in an emergency room setting. Both studies are intended to support approval of Buccolam in Japan.

The study population consisted of 3 subjects who completed the previous study SHP615-301. No formal statistical testing was performed, the results of the endpoints were provided in a descriptive manner.

The definition of the primary endpoint therapeutic success is the same as the endpoint used in the previous Japanese study. Seizure cessation had to be sustained for at least 30 minutes and this is shorter than the 1hour mark used in the previous studies that supported the approval of Buccolam in de EU (see Buccolam EPAR, EMEA/H/C/002267). However, seizure cessation up to 6 hours is covered by a secondary endpoint.

All three subjects received a single dose of Buccolam in accordance with the posology for their age group and all completed the study. Therapeutic success, i.e. seizure cessation within 10 minutes and absence of further seizures up to 30 minutes was reached for all three subjects. All subjects remained seizure free for at least an hour, which is in line with the studies described in the Buccolam EPAR.

Due to the open label design of the study, no formal conclusions on efficacy can be made. However, the results of the study are considered in line with the previous findings described in the Buccolam EPAR.

With regard to safety, two subjects reported adverse events of sleepiness, nausea and vomiting. These are well-known adverse reactions of Buccolam and are described in section 4.8 of the SmPC. There appears to be no new safety signals identified with use of oromucosal midazolam in a Japanese outpatient setting. However due to the small sample size (n=3) no definitive conclusions can be drawn.

Taken together, study SHP615-302 which evaluated oromucosal midazolam for seizure cessation in a Japanese outpatient setting appears in line with the findings reported previously with Buccolam. However, due to the open label design and small sample size, no definitive conclusions can be drawn with regard to efficacy and safety.

3. Rapporteur's overall conclusion and recommendation

Study SHP615-302 was an open label extension study which evaluated a single dose of oromucosal midazolam in a Japanese outpatient setting. The study enrolled 3 subjects whom all achieved seizure resolution within 10 minutes after midazolam administration and remained seizure free for at least 30 minutes. Adverse events reported were in line with what has been described previously in the Buccolam SmPC. Due to the open label design and small sample size, no conclusions can be drawn with regards to efficacy and safety, though the study results are in line with previous observations with Buccolam. As such no further regulatory action is considered necessary.

☒ **Fulfilled:**

No regulatory action required.