25 June 2020
EMA/CHMP/383769/2020
Human Medicines Division

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/P46/017

Note

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

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1. Introduction

On the 27th of January 2020, 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 stated that study SHP615-301 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), was 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]). The IP was specifically developed as a single, age-specific, fixed-dose (approximately 0.25-0.5 mg/kg) formulation for buccal administration in children; 1 dosage per each of the following age groups:

- 2.5 mg (yellow label) ages 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

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

SHP615-301: 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.

2.3.2. Clinical study

SHP615-301: 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

Description

Study SHP615-301 was a phase 3, open-label study to evaluate the efficacy, safety and pharmacokinetics of a single dose of Buccolam in Japanese paediatric patients with convulsive status epilepticus in the hospital or emergency room.

Methods

Objective(s)

The primary objective of this study was to assess the efficacy of oromucosal midazolam (referred to in the report as MHOS/SHP615) administered buccally in pediatric patients with convulsive status epilepticus (CSE) in a healthcare setting.

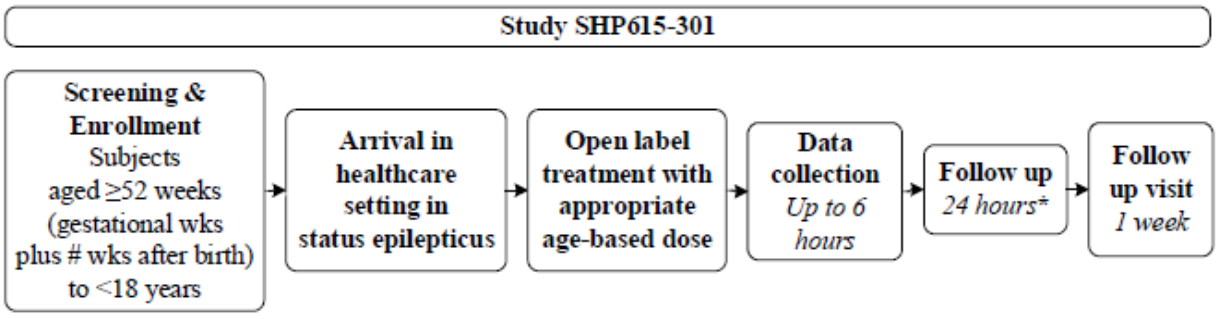
The secondary objectives of this study were to assess the safety and PK of MHOS/SHP615 administered buccally to pediatric patients with CSE in a healthcare setting.

Study design

This study was to be conducted in approximately 25 healthcare setting study centers in Japan.

Twenty-five subjects were to be enrolled in this study as shown in Figure 1. The study consisted of a 24-hour, open-label treatment period followed by a 1-week safety follow-up period. Subjects were to be screened and assessed at baseline immediately before administration of IP even if the informed consent and some prescreening assessments had been completed at a previous clinical visit.

Figure 1 Study Design



*If subject has not been discharged from hospital

MHOS/SHP615=midazolam hydrochloride oromucosal solution; wks=weeks.

Study population /Sample size

Study population

Children whose corrected gestational age was ≥52 weeks (gestational weeks plus the number of weeks after birth) and <18 years (and weight >5 kg) who arrived at the healthcare setting in full seizure, had not received immediate treatment, and had parent, guardian, or legally authorized representative informed consent/assent (when applicable, per Shire policy and country regulations), were eligible to participate, provided all eligibility criteria were met. The seizure event(s) had to be accompanied by loss of consciousness and could be either generalized tonic-clonic seizures or could have started focally and then generalized.

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.

Treatments

The investigational product, MHOS/SHP615, was administered buccally by the investigator or subinvestigator as a single, fixed-dose product, banded by age, to subjects with CSE in the healthcare setting.

There were 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

For buccal administration, MHOS/SHP615 was administered into the space between the lower gum and the inside of the cheek. Only 1 syringe with the specified dose was given. The full amount of the prefilled dosing syringe was injected slowly into the buccal mucosa. In some cases, it might have been necessary to divide the dose so that half of the solution was injected into each side of mouth. Prior to administration of drug therapy, the airway was secured, and respiratory and cardiac function assessed.

CHMP comments:

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

Pharmacokinetics

Plasma midazolam (MDZ) and its active metabolite (1-hydroxymidazolam, 1-OH-MDZ)) concentrations were evaluated. Pharmacokinetic samples were collected at approximately 1 hour earliest and at 3, and 6 hours (or time of discharge, if earlier than 6 hours) after midazolam administration.

Bioanalytical

Determination of midazolam and 1-hydroxymidazolam in human K3EDTA plasma samples for study SHP615-301 was performed using a validated method of protein precipitation for sample preparation followed by liquid chromatography with tandem mass spectrometry.

Overall precision and bias for the QC samples were within 15% at all levels, indicating that the method performed reliably during the analysis of study samples. Samples were analysed within the established storage stability period of 362 days at -80°C. Valid concentrations were generated for all study samples analysed. The reproducibility of the validated analytical method when applied to incurred plasma samples (ISR) was also within the required acceptance limits for the re-analysis of incurred samples stored at -80°C.

Statistical Methods (Pop PK)

The PK data from study SHP615-301 were analysed using a previously established semi-mechanistic model that supported an age-based dosing paradigm. The previously developed popPK model was refined by supplementing data from study SHP615-301 to the existing study MID001 dataset. The analysis simultaneously models MDZ and 1-OH-MDZ data from both studies to assess drug exposure differences between Japanese and non-Japanese pediatric subjects.

Study MID001 is a PK study of buccal administered SHP615 in non-Japanese children undergoing routine elective surgery, dosed 0.2 mg/kg (5 mg/ml), in which sparse sampling was applied (N = 3-6 samples from 50 subjects, obtained from 0 to 8 h post dose or prior to cannula removal). Patients aged >3 months to <18 years (3 m to <1 y n=6, 1 y to <5 y n=20, 5 y to <10 y n=12 and 10 y to <18 y n= 12).

A number of Japanese pediatric subjects in study SHP615-301 (N=12) were administered MDZ via a route other than buccal. Of these, 8 subjects received concomitant MDZ as rescue treatment on the same day as SHP615 administration (i.e., occurring between approximately 40 min and 9 h after SHP615 treatment). These subjects were excluded from the PopPK analysis. A total of 16 subjects remained in the popPK evaluation (3m to <1y (n=3), 1y to <5y (n=8) and 5y to <10y (n=5)).

Overall, a total of 45 (Study SHP615-301) and 263 (Study MID001) concentration samples with quantifiable MDZ or 1-OH-MDZ were available for inclusion in the PopPK analysis. For all MDZ concentrations, corresponding 1-OH-MDZ observations were similarly available.

Plasma MDZ and 1-OH-MDZ concentration-time data were simultaneously analyzed using nonlinear mixed-effects modeling (NONMEM®, Version 7.3, ICON, Hanover, MD, USA). The first-order conditional estimation method with interaction was used for all modeling, and the ADVAN5 subroutine. R Version 3.4.4 was used for graphical exploration, goodness-of-fit (GOF), model evaluation, and descriptive statistics. All simulations were performed using the RxODE package in R (Version 3.4.4).

Standard GOF plots were used to assess whether the model appropriately described MDZ and 1-OH-MDZ observed concentrations. A prediction-corrected visual predictive check (pcVPC) was used to evaluate the performance of the final model. Bootstrap resampling methods were used to evaluate the precision of final estimates, including the estimation of confidence intervals (CIs) for model parameters. Individual

empirical Bayes estimates (EBEs) from the final model were used to derive secondary PK parameters for MDZ and 1-OH-MDZ. Non-compartmental analyses were performed on simulated data, to derive secondary PK parameters for each subject. These included the drug concentration at 10 min (C10), maximal drug concentration (Cmax), area under the concentration-time from 0 to infinity (AUC0-inf), AUC from 0 to 10 min (AUC0-10), AUC from 0 to 60 min (AUC0-60), AUC from 0 to 180 min (AUC0-180), time to maximal concentration (Tmax), and elimination half-life (t1/2) for both analytes.

Outcomes/endpoints

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

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

The secondary efficacy endpoints will include:

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

CHMP comments:

Treatment success was defined as cessation of visible seizure activity < 10 minutes with sustained absence for 30 minutes. This is shorter than the endpoints investigated in the studies discussed in the initial marketing authorisation for Buccolam, where 1 hour was used (see Buccolam EPAR). However, sustained absence is covered by the other endpoints.

If there was no response to Buccolam treatment after 10 minutes, rescue medication was administered. This is in line with the current posology of Buccolam in the SmPC.

Statistical Methods

Primary endpoint

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

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

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

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

Secondary endpoints

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

The same definition of therapeutic success as given in the CSR will be used except that the second condition will be modified to require sustained absence of visible seizure activity without the need for additional rescue medication for 1 hour, 4 hours or 6 hours, respectively, following a single dose of MHOS/SHP615. Two-sided, 95% Wald CI for the percentage of subjects reaching therapeutic success will be constructed on the FAS.

Time to Resolution of Seizures (Convulsions)

Time to resolution of seizures (convulsions) in minutes will be calculated as time from investigational product administration to the end of the initial seizure or administration of rescue anticonvulsant medication, whichever occurs first. The initial seizure refers to the seizure which triggered the use of the investigational product and which is captured on the "confirmation of status epilepticus" eCRF form. Note that, as per the definition of the FAS, there will be no censoring in this time to event analysis as all subjects will have a date and time captured for the initial seizure cessation. Administration of rescue anticonvulsant medication for ongoing initial seizure will be treated as a competing event. Cumulative incidence function (CIF) of resolution of seizures will be estimated and a plot will be provided. In addition, CIF estimates and 95% CI will be provided at several time points post dose.

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

Time to Recovery of Consciousness

Time to recovery of consciousness in minutes will be calculated only for subjects who lose consciousness pre-dose as time from investigational product administration to recovery of consciousness post-dose or administration of rescue anticonvulsant medication, whichever occurs first. Administration of rescue anticonvulsant medication prior to recovery of consciousness will be treated as a competing event. If the time of recovery of consciousness is missing and there is no administration of rescue anticonvulsant medication during the 24 hours treatment period, the time to recovery of consciousness will be censored at the latest time of any assessment captured in the eCRF up to hospital discharge during the 24 hours treatment period, i.e., vital signs, oxygen saturation, Riker SAS, buccal cavity assessment, laboratory or PK sample collection, ECG or time the subject was discharged from the hospital. CIF of recovery of consciousness will be estimated and a plot will be provided. In addition, CIF estimates and 95% CI will be provided at several time points post dose.

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

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

Anticonvulsant medication for ongoing SE (rescue treatment) are captured on the "prior and concomitant medications" eCRF form. The percentage of subjects who require additional anticonvulsant medication for ongoing SE 10 minutes after investigational product administration and before the end of the initial seizure will be presented along with the corresponding 95% Wald CI.

Percentage of Subjects Who Fail to Respond to Treatment

Responder is defined as subject with cessation of visible seizure activity within 10 minutes after a single dose of MHOS/SHP615. A Treatment failure/Non-responder is defined as a subject with continuing

seizure activity for more than 10 minutes after a single dose of MHOS/SHP615 or the need for any additional anticonvulsant rescue medication to treat the initial seizure any time after the single dose of MHOS/SHP615 according to the participating healthcare setting protocol or guideline. Any of the following events qualifies as a treatment failure:

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

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

Sensitivity Analyses

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

The 2-sided nominal p-value of the Wald test will be presented for the analysis of therapeutic success based on the PPS and no multiplicity adjustment will be performed for this sensitivity analysis. If the PPS and the FAS are identical, these sensitivity analyses will not be performed.

CHMP comments:

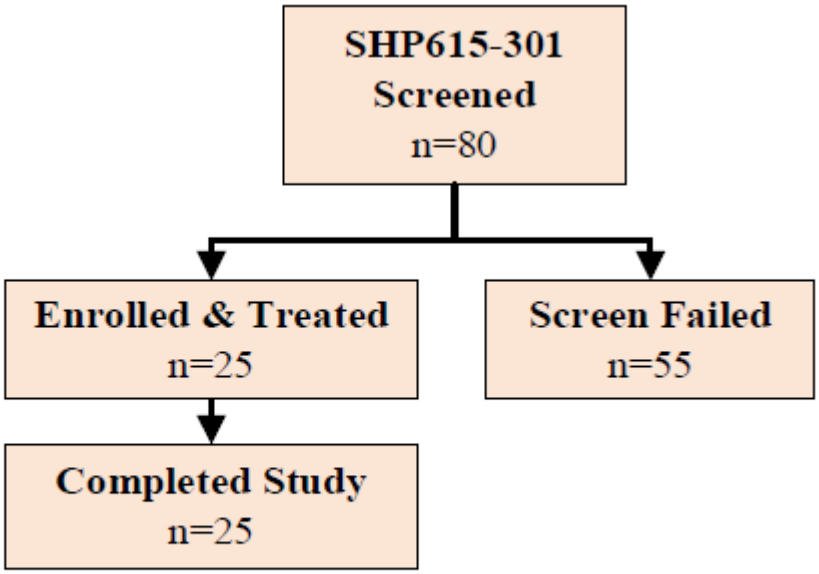
The statistical analyses proposed are descriptive, which is acceptable for this open-label single arm study. The proportion of patients with treatment success, and corresponding confidence interval will be compared to a threshold of 30%. No (clinical) justification could be found for this threshold, but since results are well away of the threshold, this is not further pursued

Results

Recruitment/ Number analysed

Of the 80 subjects screened, 25 subjects received the IP, and 25 subjects completed the study; no subjects withdrew from the study. A total of 55 subjects did not meet all of the inclusion and exclusion criteria and therefore failed screening (see Figure 2).

Figure 2 Subject Disposition



Source: Section 14, Table 14.1.1.

CHMP comments:

The relationship between (prior) screening and enrolment into the study is unclear, i.e. how by prior screening it is anticipated that a subject will experience status epilepticus in the future. This is issue, however, is not pursued.

Baseline data

Demographics

Of the 25 subjects who received the IP, 3 subjects were <1 year of age, 13 subjects were 1 to <5 years of age, 7 subjects were 5 to <10 years of age, and 2 subjects were 10 to <18 years of age. All subjects were Asian and none were from a Hispanic or Latino ethnic group; the majority (64.0%) was female. The mean body mass index was 15.73 kg/m2 among all subjects, and was generally consistent across the age groups. As expected, mean weight and mean height increased with increasing age group.

History of epilepsy

The most common epilepsy diagnosis was severe myoclonic epilepsy of infancy which was reported in 14 subjects (56.0%) overall, all of whom were <10 years of age (1, 9, and 4 subjects in the age groups <1 year, 1 to <5 years, and 5 to <10 years, respectively). There were no subjects with an epilepsy diagnosis of severe myoclonic epilepsy of infancy in the age group 10 to <18 years.

A diagnosis of epilepsy was reported in 1 subject in the age group 10 to <18 years, 3 subjects in the age group 1 to <5 years, and 2 subjects each in the age groups <1 year and 5 to 10 years. All other epilepsy diagnoses were reported in ≤2 subjects overall, irrespective of age group.

Overall, the mean duration of epilepsy history was 3.47 years and the mean number of years since diagnosis was 2.98 years. As expected, mean duration of epilepsy history and time since diagnosis increased with increasing age group. A total of 18 subjects (72.0%) had major epilepsy of genetic etiology, the majority of whom were 1 to <5 years of age. Major epilepsy of idiopathic etiology was reported in 4 subjects, all of whom were <10 years of age, while major epilepsy of structural etiology was reported in 3 subjects (1 subject each in the age groups <1 year, 1 to <5 years, and 10 to <18 years, respectively).

As per the study entry criteria, all 25 subjects had a current seizure (convulsive) accompanied by loss of consciousness, prior to IP administration. All 25 subjects were hospitalized prior to seizure onset . Time from seizure onset to IP administration ranged from 0 to 68 minutes for all except 1 subject, in whom time from seizure onset to IP administration was 116 minutes. The prolonged time to IP administration in 1 Subject did not appear to have a notable impact on the time to seizure cessation or recovery of consciousness, both of which occurred 2 minutes postdose.

Prior anti-epileptic medication

All 25 subjects had at least 1 prior medication. Thirteen subjects (52.0%) had prior anticonvulsant medications as rescue treatment for ongoing SE . The most frequently reported anticonvulsant medications as rescue treatment were diazepam (9 subjects [36.0%]) and midazolam (8 subjects [32.0%]).

Prior anticonvulsant medications as prophylaxis treatment were reported for all subjects. The most frequently reported were clobazam (17 subjects [68.0%]), valproate sodium (16 subjects [64.0%]), stiripentol (13 subjects [52.0%]), levetiracetam (10 subjects [40.0%]), and topiramate (9 subjects [36.0%]).

Concomitant medication

Concomitant medications were those taken between the time of IP administration and the end of the follow-up period (ie, 8 days after IP administration). No subjects had a protocol deviation related to prohibited medication.

All 25 subjects had at least 1 concomitant medication. Sixteen subjects (64.0%) had concomitant anticonvulsant medications as rescue treatment for ongoing SE. The most frequently reported were midazolam (9 subjects [36.0%]), diazepam (7 subjects [28.0%]), and fosphenytoin sodium (4 subjects [16.0%]). No subject received rescue treatment for the initial seizure within 10 minutes of IP administration. Four subjects received rescue anticonvulsant medication 10 minutes or more after IP administration and before the end of the initial seizure. The remaining rescue treatment was administered after the initial seizure.

Concomitant anticonvulsant medications as prophylaxis treatment were reported for all subjects.

As seen with the prior medications, the most frequently reported were clobazam (17 subjects [68.0%]), valproate sodium (16 subjects [64.0%]), stiripentol (13 subjects [52.0%]), and levetiracetam and topiramate (9 subjects [36.0%] each).

All subjects were reported with at least 1 other concomitant medication. The most frequently reported were in the classes of intravenous solutions (13 subjects [52.0%]; other alimentary tract and metabolism products (10 subjects [40.0%]); and drugs for constipation, and hypnotics and sedatives (9 subjects [36.0%] each).

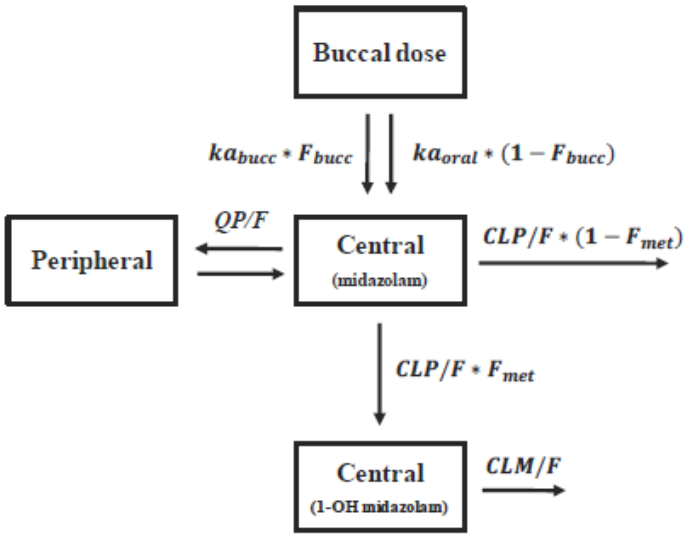
Concomitant therapies were administered to 20 subjects (80.0%); the most frequently reported were oxygen therapy (17 subjects [68.0%]); occupational therapy and physiotherapy (5 subjects [20.0%] each); and speech rehabilitation (4 subjects [16.0%]

Pharmacokinetic results

The final model retained the structure of the original Study MID001 model, including the age effects and random variability components. In addition, CYP3A4 inducers and Japanese origin were identified as influential covariates on the clearance of MDZ (CLP/F) and volume of 1-OH-MDZ (VCM/F), respectively.

MDZ PK was best described by a 2-compartment model where a fraction of the absorbed dose was assumed to be metabolized to 1-OH-MDZ and the remaining fraction metabolized to other metabolites, both as linear clearance terms. The absorption of MDZ was assumed to occur both buccally and intestinally (i.e. swallowed and absorbed in the intestinal tract). 1-OH-MDZ PK was best described as a 1-compartment model with linear clearance from the central compartment.

Figure: structure of the pharmacokinetic model



Abbreviations: *CLP/F*=apparent central clearance of the parent; *CLM/F*=apparent central clearance of the metabolite; F_{bucc}=fraction of dose absorbed via the buccal route; F_{met}=fraction of dose metabolized; ka_{bucc}=First-order rate constant for buccal absorption; ka_{oral}=first-order rate constant for oral absorption; *QP/F*=apparent intercompartmental clearance of the parent

The input after buccal dosing was described by a parallel absorption process. Drug disposition was characterized by a 2-compartment model for parent (midazolam) and 1-compartment model for metabolite (1-OH-MDZ).

Age was identified as covariate and was included on the fraction buccally absorbed and all central clearances and volumes of distribution.

CYP3A4 inducers and Japanese origin were identified as covariates on the clearance of MDZ (CLP/F) and volume of 1-OH-MDZ (VCM/F), respectively.

In subjects receiving a moderate to strong CYP3A4-effector agent as a concomitant medication (75% of the Japanese population, 0% of the non-Japanese population), MDZ clearance was estimated to be 2.28-fold greater than in those subjects not on a CYP3A4 effector.

Japanese pediatric subjects would be expected to have an approximately 2.42-fold higher 1-OH-MDZ volume of distribution; however, this should be interpreted with caution, as a result of the large portion of Japanese pediatric subjects which was also receiving a concomitantly administered CYP3A4 effector, which may be biasing the metabolite estimates for subjects in study SHP615-301.

Model diagnostics showed favourable results and relatively good precision in estimates was obtained (relative standard error <50%), with ETA shrinkage ranging from 3.75 to 33.5%, see table of the model parameters below.

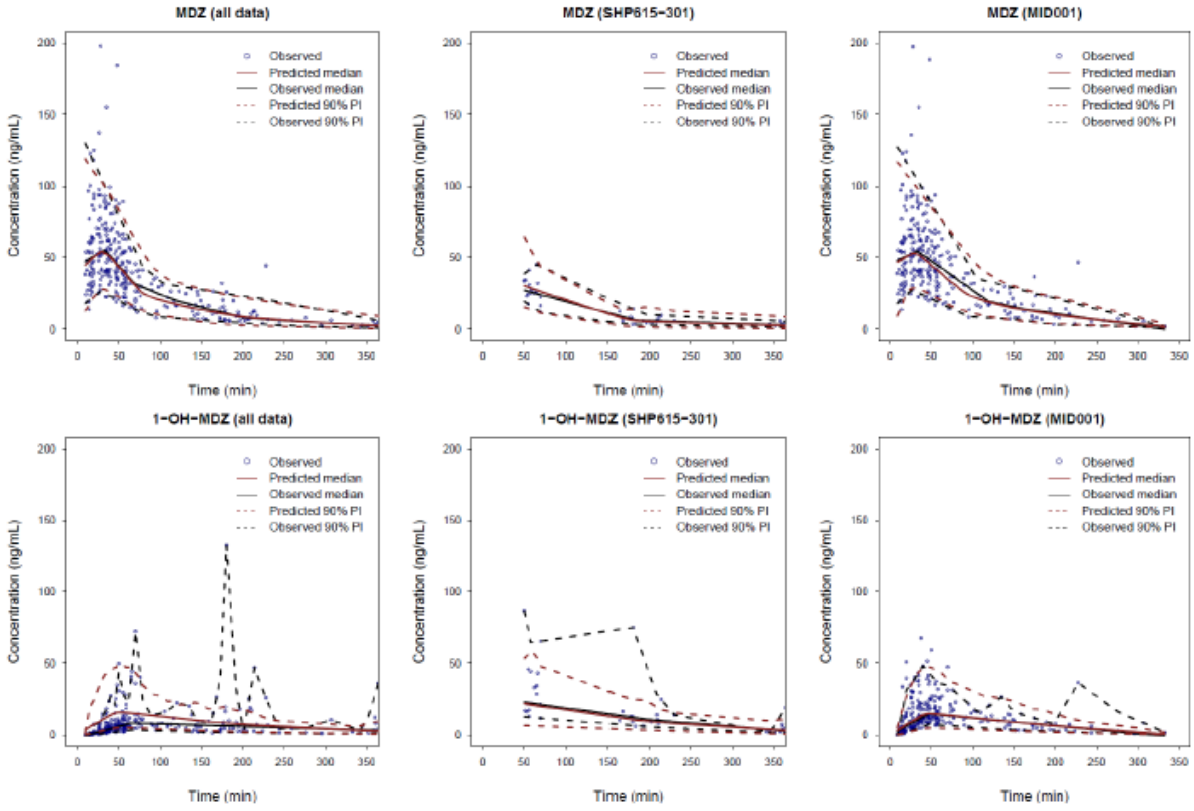
Table of population parameter estimates for the final model

Parameter (Units)	Population Mean Estimate (%RSE)	%BSV Estimate (%RSE)	ETA Shrinkage (%)
F_{bucc}	$0.548 \times (Age/3)^{0.285}$ (10.2)	211 (48.0)	33.5
ka_{bucc} (1/min)	0.133 (15.3)	-	-
ka_{oral} (1/min)	0.125 (17.2)	-	-
$Tlag_{bucc}$ (min)	11.3 (2.40)	-	-
CLP/F (L/min/3 y) CYP3A4 inductive effect	$0.495 \times (Age/3)^{0.390}$ $\times$ 2.28 (11.4)	46.9 (22.8)	3.75
VCP/F (L/3 y)	$37.8 \times (Age/3)^{0.527}$ (10.8)	45.4 (19.4)	9.61
QP/F (L/min)	0.511 (14.1)	68.0 (40.5)	21.5
VPP/F (L)	54.8 (21.6)	-	-
F_{met}	0.7 FIX	-	-
CLM/F (L/min/3 y)	$0.754 \times (Age/3)^{0.634}$ (10.8)	57.9 (24.1)	3.90
VCM/F (L/3 y) Japanese origin	$22.0 \times (Age/3)^{0.426}$ $\times$ 2.42 (12.8)	66.7 (18.0)	8.74
RUVP (CV)	0.170 (13.2)	-	23.6
RUVM (CV)	0.259 (8.24)	-	21.8

Abbreviations: 1-OH-MDZ=1-hydroxymidazolam; BSV=between-subject variability; CLP/F=apparent central clearance of the parent; CLM/F=apparent central clearance of the metabolite; CV=coefficient of variation; CYP=cytochrome P450; ETA=between-subject random effect; Fbucc=fraction of dose absorbed via the buccal route; Fmet=fraction of dose metabolized; kabucc=first-order rate constant for buccal absorption; kaoral=first-order rate constant for oral absorption; MDZ=midazolam; QP/F=apparent intercompartmental clearance of the parent; RSE=relative standard error; RUVP=residual variability for the parent MDZ; RUVM=residual variability for the metabolite 1-OH-MDZ; Tlagbucc=lag time of buccal route; fraction of dose absorbed via the buccal route; VCM/F=apparent central volume of distribution of the metabolite; VCP/F=apparent central volume of distribution of the parent; VPP/F=apparent peripheral volume of distribution of the parent; y=year; Dashes (-) denote not applicable

Good predictive performance was demonstrated when evaluating the model by pcVPC across alldata and when stratified by study. The pcVPC plots show that the final model describes both the central tendency and variability for MDZ and 1-OH-MDZ in Japanese subjects, see Figure below.

Figures of prediction-corrected visual predictive check of the final model



Secondary PK parameters for MDZ and 1-OH-MDZ were derived using the EBE from the final model. The exposure variables of interest included C10, Cmax, AUC0-inf, and partial AUC values up to 10 min (AUC0-10), 60 min (AUC0-60), and 180 min (AUC0-180) Model derived PK parameters of both MDZ and 1-OH-MDZ are depicted in the following figures and tables.

Figures of estimated exposure for MDZ

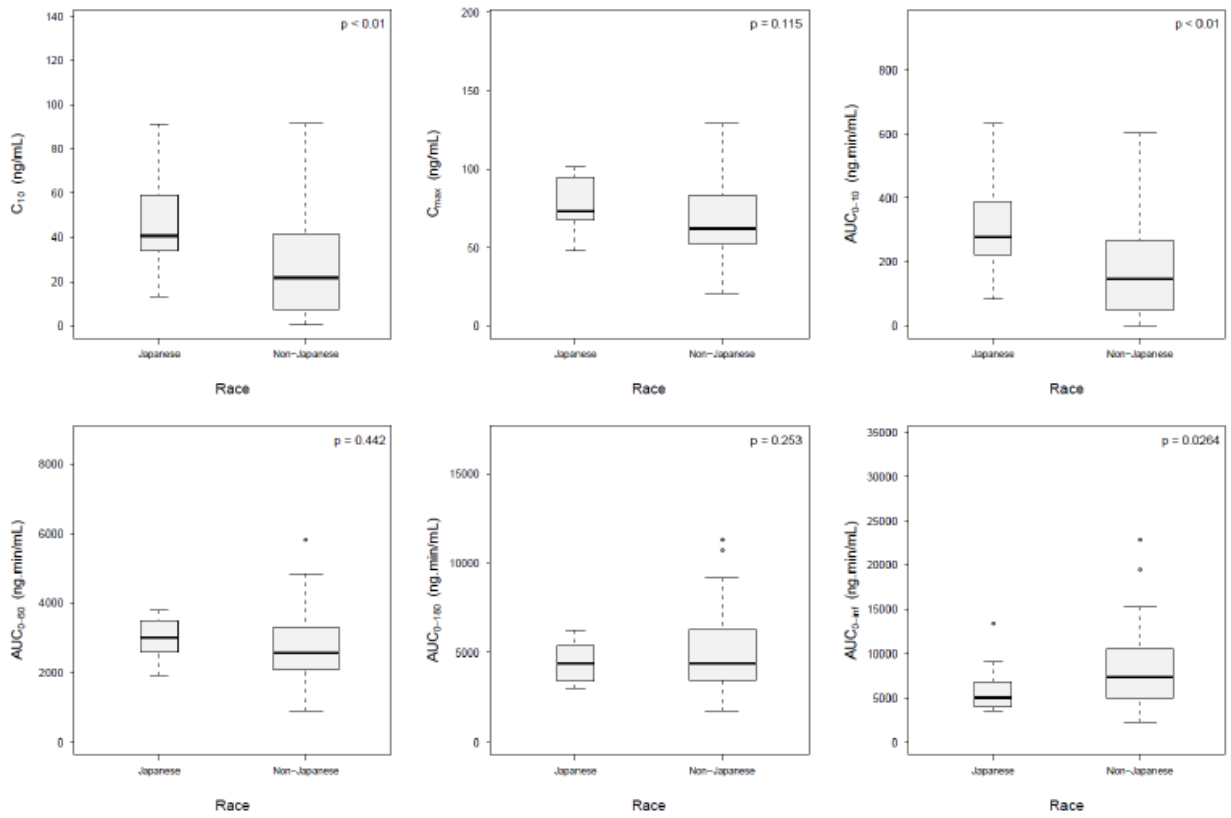


Table of statistical summary of MDZ exposures

Race	Analyte	Variable (Units)	Median	Mean	SD	Min	Max	CV	5% centile	95% centile
Japanese (N=16)	MDZ	C_{10} (ng/mL)	40.6	45.2	21.3	13.4	91.4	0.471	14.9	73.6
		C_{max} (ng/mL)	73.1	78.0	16.4	48.2	102	0.211	56.6	101
		$AUC_{0\text{-}10}$ (ng.min/mL)	276	304	149	83.6	635	0.489	97.2	510
		$AUC_{0\text{-}60}$ (ng.min/mL)	3011	2965	592	1925	3783	0.200	2067	3713
		$AUC_{0\text{-}180}$ (ng.min/mL)	4423	4411	1140	2989	6261	0.258	3001	6047
		$AUC_{0\text{-}inf}$ (ng.min/mL)	5046	5847	2599	3505	13455	0.444	3723	10241
		T_{max} (min)	20.5	20.5	3.31	15.5	28.0	0.161	15.5	26.5
		$t_{1/2}$ (min)	115	136	55.0	90.6	303	0.404	94.5	223
Non-Japanese (N=50)	MDZ	C_{10} (ng/mL)	21.7	27.1	23.1	0.465	91.8	0.852	1.38	67.4
		C_{max} (ng/mL)	62.1	67.7	24.0	21.0	129	0.355	33.7	110
		$AUC_{0\text{-}10}$ (ng.min/mL)	146	177	151	2.87	604	0.855	8.49	426
		$AUC_{0\text{-}60}$ (ng.min/mL)	2564	2756	1025	913	5834	0.372	1401	4439
		$AUC_{0\text{-}180}$ (ng.min/mL)	4409	5057	2137	1739	11348	0.423	2874	9160
		$AUC_{0\text{-}inf}$ (ng.min/mL)	7332	8389	4213	2210	22944	0.502	3961	14957
		T_{max} (min)	23.8	23.8	4.27	16.0	33.0	0.180	17.0	30.8
		$t_{1/2}$ (min)	191	214	106	91.5	655	0.497	103.4	409

Figure of estimated exposures for 1-OH-MDZ

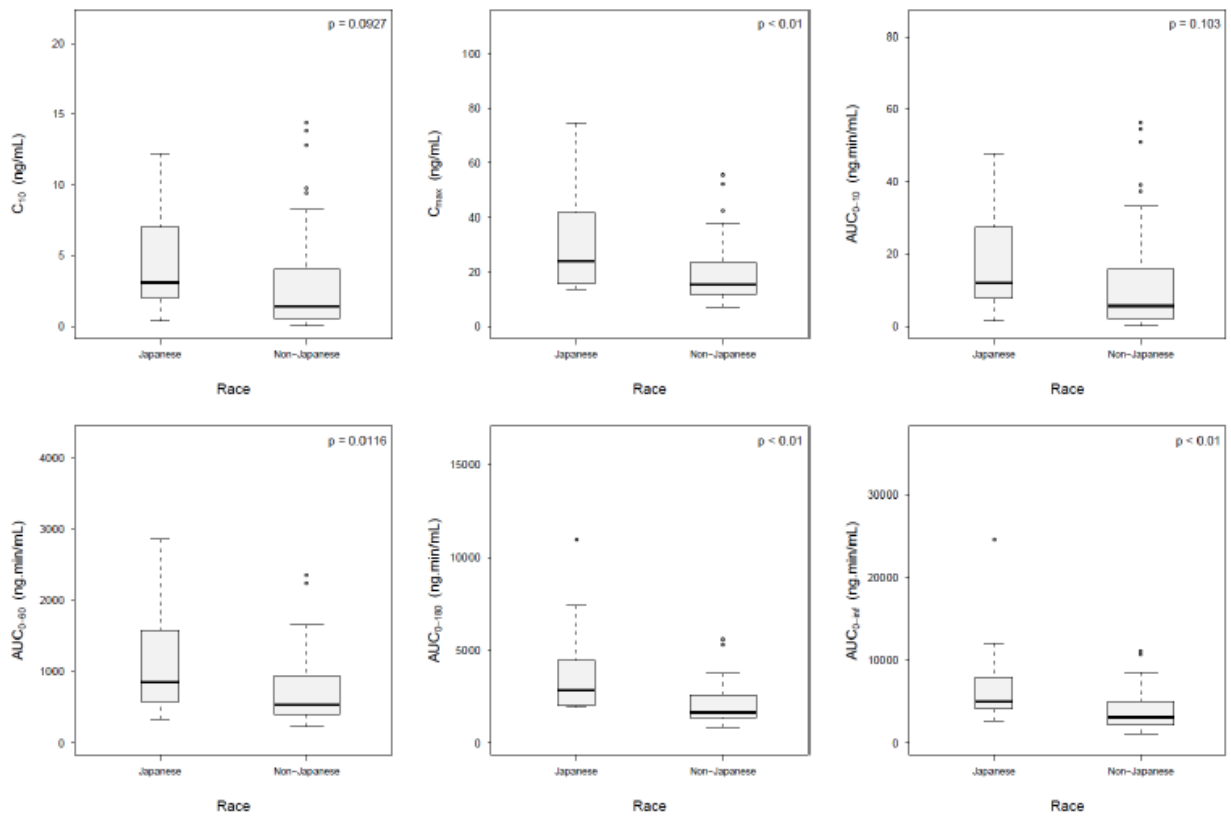


Table of statistical summary of 1-OH-MDZ exposures

Race	Analyte	Variable (Units)	Median	Mean	SD	Min	Max	CV	5% centile	95% centile
Japanese (N=16)	1-OH-MDZ	C_{10} (ng/mL)	3.10	4.75	3.79	0.405	12.2	0.798	1.13	11.9
		C_{max} (ng/mL)	23.8	31.3	19.6	13.6	74.6	0.626	13.6	73.4
		T_{max} (min)	12.0	18.5	14.9	1.52	47.7	0.803	4.39	46.3
		$AUC_{0\text{-}10}$ (ng.min/mL)	846	1157	769	328	2849	0.665	425	2743
		$AUC_{0\text{-}60}$ (ng.min/mL)	2852	3803	2450	1894	10946	0.644	1933	8293
		$AUC_{0\text{-}180}$ (ng.min/mL)	5004	6754	5391	2634	24577	0.798	2790	15164
		$AUC_{0\text{-}inf}$ (ng.min/mL)	59.5	63.6	15.6	45.0	106	0.245	46.5	86.5
		$t_{1/2}$ (min)	115	135	62.9	86.3	339	0.465	88.0	223
Non-Japanese (N=50)	1-OH-MDZ	C_{10} (ng/mL)	1.39	2.93	3.69	0.0366	14.4	1.26	0.110	11.4
		C_{max} (ng/mL)	15.3	19.3	11.3	6.79	55.5	0.586	7.98	40.3
		T_{max} (min)	5.52	11.6	14.6	0.140	56.1	1.26	0.425	45.6
		$AUC_{0\text{-}10}$ (ng.min/mL)	531	732	493	219	2346	0.674	280	1599
		$AUC_{0\text{-}60}$ (ng.min/mL)	1625	2022	1044	804	5576	0.516	983	3645
		$AUC_{0\text{-}180}$ (ng.min/mL)	3054	3754	2228	1084	11062	0.594	1489	8100
		$AUC_{0\text{-}inf}$ (ng.min/mL)	52.2	55.2	19.4	31.5	156	0.351	37.0	80.6
		$t_{1/2}$ (min)	186	210	101	90.6	593	0.480	103	411

Figure: statistical summary of MDZ exposures by age category (Study SHP615-301)

Age category	Analyte	Dose (mg)	Variable (Units)	Median	Mean	SD	Min	Max	CV	5% centile	95% centile
3m to <1y (N=3)	MDZ	2.5	C_{10} (ng/mL)	39.8	32.5	14.1	16.2	41.4	0.436	18.5	41.3
			C_{max} (ng/mL)	59.3	69.0	26.9	48.2	99.4	0.391	49.3	95.4
			AUC_{0-10} (ng.min/mL)	266	220	98.0	108	287	0.445	123	285
			AUC_{0-60} (ng.min/mL)	2115	2513	859	1925	3498	0.342	1944	3360
			AUC_{0-180} (ng.min/mL)	3005	3990	1720	2989	5976	0.431	2991	5679
			AUC_{0-inf} (ng.min/mL)	4133	7174	5441	3934	13455	0.758	3954	12523
			T_{max} (min)	20.5	20.2	2.52	17.5	22.5	0.125	17.8	22.3
			$t_{1/2}$ (min)	162	201	89.6	137	303	0.446	139.4	289
1y to <5y (N=8)	MDZ	5.0	C_{10} (ng/mL)	46.6	50.3	24.5	15.4	91.4	0.486	20.8	83.1
			C_{max} (ng/mL)	72.3	79.8	16.4	61.8	102	0.206	63.5	101
			AUC_{0-10} (ng.min/mL)	310	341	174	102	635	0.510	133	576
			AUC_{0-60} (ng.min/mL)	2808	2997	585	2236	3783	0.195	2348	3743
			AUC_{0-180} (ng.min/mL)	4197	4271	1013	3071	5502	0.237	3166	5427
			AUC_{0-inf} (ng.min/mL)	4948	5231	1559	3505	7454	0.298	3607	7231
			T_{max} (min)	20.5	20.1	3.57	15.5	26.0	0.178	15.5	24.9
			$t_{1/2}$ (min)	115	130	37.6	97.7	196	0.290	99.5	191
5y to <10y (N=5)	MDZ	7.5	C_{10} (ng/mL)	54.0	44.7	19.5	13.4	59.5	0.435	18.4	59.3
			C_{max} (ng/mL)	76.4	80.6	10.1	71.9	94.3	0.126	71.9	93.0
			AUC_{0-10} (ng.min/mL)	359	296	131	83.6	391	0.444	118	391
			AUC_{0-60} (ng.min/mL)	3065	3186	359	2755	3690	0.113	2811	3629
			AUC_{0-180} (ng.min/mL)	4670	4888	1069	3659	6261	0.219	3762	6144
			AUC_{0-inf} (ng.min/mL)	5363	6036	2037	4055	9170	0.337	4190	8709
			T_{max} (min)	20.0	21.5	3.74	18.5	28.0	0.174	18.8	26.6
			$t_{1/2}$ (min)	98.7	107	24.6	90.6	151	0.229	91.7	141

Figure: statistical summary of 1-OH-MDZ exposures by age category (Study SHP615-301)

Age category	Analyte	Dose (mg)	Variable (Units)	Median	Mean	SD	Min	Max	CV	5% centile	95% centile
3m to <1y (N=3)	1-OH-MDZ	2.5	C_{10} (ng/mL)	1.76	1.83	0.497	1.37	2.35	0.272	1.41	2.29
			C_{max} (ng/mL)	13.6	17.0	5.83	13.6	23.7	0.344	13.6	22.7
			AUC_{0-10} (ng.min/mL)	6.83	7.08	1.88	5.34	9.07	0.265	5.49	8.85
			AUC_{0-60} (ng.min/mL)	490	590	202	457	822	0.342	460	789
			AUC_{0-180} (ng.min/mL)	2026	2239	419	1970	2723	0.187	1975	2653
			AUC_{0-inf} (ng.min/mL)	4453	5606	2172	4255	8112	0.387	4275	7746
			T_{max} (min)	73.5	70.2	11.9	57.0	80.0	0.169	58.7	79.4
			$t_{1/2}$ (min)	160	214	109	143	339	0.508	144.4	321
1y to <5y (N=8)	1-OH-MDZ	5.0	C_{10} (ng/mL)	6.00	6.76	4.06	2.01	12.2	0.600	2.34	12.05
			C_{max} (ng/mL)	38.9	43.0	20.6	20.6	74.6	0.478	21.7	74.0
			AUC_{0-10} (ng.min/mL)	23.3	26.4	16.0	7.64	47.7	0.605	8.97	47.1
			AUC_{0-60} (ng.min/mL)	1505	1604	795	662	2849	0.495	735	2800
			AUC_{0-180} (ng.min/mL)	4424	5246	2734	2577	10946	0.521	2719	9708
			AUC_{0-inf} (ng.min/mL)	6459	9103	6818	4026	24577	0.749	4208	20184
			T_{max} (min)	59.0	60.6	11.3	45.0	75.5	0.186	46.4	74.6
			$t_{1/2}$ (min)	114.8	126	33.2	90.0	185	0.263	92.3	174
5y to <10y (N=5)	1-OH-MDZ	7.5	C_{10} (ng/mL)	2.76	3.29	2.79	0.405	7.86	0.849	0.728	6.97
			C_{max} (ng/mL)	15.8	21.4	11.7	14.6	42.1	0.549	14.7	37.5
			AUC_{0-10} (ng.min/mL)	10.6	12.8	11.0	1.52	30.8	0.857	2.77	27.26
			AUC_{0-60} (ng.min/mL)	584	782	526	328	1685	0.673	376	1497
			AUC_{0-180} (ng.min/mL)	1974	2433	998	1894	4210	0.410	1904	3797
			AUC_{0-inf} (ng.min/mL)	2944	3686	1221	2634	5250	0.331	2675	5152
			T_{max} (min)	59.5	64.6	23.8	47.0	106	0.369	47.7	96.8
			$t_{1/2}$ (min)	90.3	102	29.0	86.3	154	0.283	86.8	142

CHMP comments:

Overall, the PopPK analysis adequately described the PK of MDZ and 1-OH-MDZ in Japanese and non-Japanese pediatric subjects. The results do not indicate a marked difference of estimated exposure

between Japanese and non-Japanese pediatric subjects. Further, the age-based dosing regimen seems to result in a fairly consistent exposure of MDZ and 1-OH-MDZ over the different age categories.

Differences in estimated non-compartmental exposure comparisons between Japanese and non-Japanese pediatric subjects were not significant for most PK parameters. However, for the parent compound midazolam, Japanese pediatric patients are expected to demonstrate a significant higher exposure compared to non-Japanese pediatric patients for C10 (mean 45.2 versus 27.1 ng/ml) and AUC0-10 (mean 304 versus 177 ng/min/ml). For the metabolite 1-OH-MDZ, Japanese pediatric patients are expected to demonstrate a significant higher exposure compared to non-Japanese pediatric patients for Cmax (mean 31.1 versus 19.3 ng/ml), AUC0-180 (mean 6754 versus 3754 ng/min/ml) and AUC0-inf.

The results are confounded by the limited number of Japanese pediatric patients and concomitant use of CYP3A4 effector drugs (75% of the patients) in study SHP615-301, and late first blood sample draw (1 hour post dose) which is likely the origin of large variability (BSV) on the parameter for the fraction of the dose absorbed via the buccal route (F_{bucc}), and the estimated C10 and AUC0-10 values.

Therefore, some uncertainty remains with regard to the effect of race on the PK of MDZ and 1-OH-MDZ in pediatric patients and the estimated parameters of the absorption phase of the model, resulting in difficulty interpreting estimated C10 and AUC0-10 values.

Nonetheless, overall, it can be agreed with the MAH that the pop PK modeling results are sufficient to support the conclusion that a different pharmacokinetic profile for Japanese pediatric patients compared to non-Japanese pediatric patients is not expected.

However, it is not agreed with the MAH that results presented in this article 46 procedure do not need to be reflected in the SPC. First, it should be discussed by the MAH whether the current table on pharmacokinetic parameters in section 5.2 of the SPC should be updated based on the results of the refined pop PK study. Second, the newly gained information on the effect of race on the pharmacokinetics of midazolam should be included in section 5.2 of the SPC.

Efficacy results

Primary endpoint

The response rate, defined as the percentage of subjects with therapeutic success, was 80.0% (95% CI: 64.3, 95.7) in the full analysis set (FAS, see Table 1). The 95% CI showed that there was a 95% probability that the true percentage was between 64.3% and 95.7% of subjects. When the lower limit of the 95% CI was compared with the threshold of 30% (using the Wald test), the response was statistically significant (2-sided p-value <0.001).

The results were similar for the per protocol set (PPS) (79.2%; 95% CI: 62.9, 95.4; 2-sided p-value <0.001).

Table 1 Summary and Analysis of Therapeutic Success (Full Analysis Set)

	MHOS/SHP615 (N=25)		
Endpoint	**n (%)**	**95% CI**	**p-value**
Therapeutic success	20 (80.0)	64.3, 95.7	<0.001

CI-=confidence interval; MHOS/SHP615=midazolam hydrochloride oromucosal solution.
- Therapeutic success was defined as cessation of visible seizure activity within 10 minutes and sustained absence of visible seizure activity for 30 minutes after a single dose of the IP without the need for additional rescue medication.
- The 2-sided, 95% Wald CI for the percentage of subjects reaching therapeutic success is presented.
- The percentage of subjects reaching therapeutic success is compared to the threshold of 30% using the Wald test. The corresponding 2-sided p-value is presented.
Source: Section 14, Table 14.2.1.1.

A summary of therapeutic success by subgroup is presented for the FAS in Table 2. All 3 subjects in the <1 year age group reached therapeutic success as did all 4 subjects with an epilepsy etiology of idiopathic.

Table 2 Summary and Analysis of Therapeutic Success by Subgroup (Full Analysis Set)

Endpoint Subgroup	MHOS/SHP615 (N=25)		
	N	n (%)	95% CI
Therapeutic success			
Age[a]			
<1 year	3	3 (100)	29.2, 100
1 to <5 years	13	10 (76.9)	46.2, 95.0
5 to <10 years	7	6 (85.7)	42.1, 99.6
10 to <18 years	2	1 (50.0)	1.3, 98.7
Gender			
Male	9	8 (88.9)	51.8, 99.7
Female	16	12 (75.0)	47.6, 92.7
Epilepsy etiology			
Genetic	18	15 (83.3)	58.6, 96.4
Idiopathic	4	4 (100)	39.8, 100
Metabolic	0	-	- , -
Structural	3	1 (33.3)	0.8, 90.6

CI=confidence interval; MHOS/SHP615=midazolam hydrochloride oromucosal solution; N=number of subjects in each subgroup category; IP=investigational product.
[a]Age was calculated as the difference between date of birth and date of IP administration.
- n (%) refers to the number and percentage of subjects meeting the endpoint in each subgroup category.
- Percentages were calculated based on the number of subjects in each subgroup category (N).
- Therapeutic success was defined as cessation of visible seizure activity within 10 minutes and sustained absence of visible seizure activity for 30 minutes after a single dose of the IP without the need for additional rescue medication.
- The 2-sided, exact 95% Clopper-Pearson CI for the percentage of subjects reaching therapeutic success is presented.
Source: Section 14, Table 14.2.1.2.

CHMP comments

Eighty percent of the subjects enrolled in the study were a responder to treatment ("95% CI [64.3; 95.7]"). This is within the same order of effect as was observed with prior studies (Buccolam SmPC, Section 5.1). However, due to the open label and uncontrolled design of the study, no firm conclusions regarding efficacy can be drawn.

Secondary endpoints

Percentage of subjects whose seizure event(s) stopped within 10 minutes of Single dose of the ip and who had sustained absence of seizure activity for at Least 1 hour/4 hours/6 hours

The percentage of subjects with a cessation of seizures within 10 minutes (ie, ≤10 minutes) of IP administration and no seizure activity for at least 1 hour was 68.0%. The percentage of subjects with a cessation of seizures within 10 minutes and no seizure activity for at least 4 hours was 36.0% and for at least 6 hours was 32.0% (see Table 3).

The results were similar for the PPS (70.8%, 37.5% and 33.3% of subjects with a cessation of seizures within 10 minutes of IP administration and no seizure activity at least 1 hour, 4 hours, and 6 hours, respectively).

Table 3 Summary and Analysis of Seizure Cessation Within 10 Minutes of Investigational Product Administration and Sustained Absence of Seizure Activity (Full Analysis Set)

	MHOS/SHP615 (N=25)	
Endpoint	**n (%)**	**95% CI**
Seizure cessation within 10 minutes of IP administration and:		
No seizure activity for at least 1 hour	17 (68.0)	49.7, 86.3
No seizure activity for at least 4 hours	9 (36.0)	17.2, 54.8
No seizure activity for at least 6 hours	8 (32.0)	13.7, 50.3

CI=confidence interval; MHOS/SHP615=midazolam hydrochloride oromucosal solution; IP=investigational product.
- The 2-sided, 95% Wald CI for the percentage of subjects reaching the efficacy endpoint is presented.
Source: Section 14, Table 14.2.2.1.1.

Time to resolution of seizures (convulsions)

Seizure resolution without the need for rescue anticonvulsant medication occurred in 21 out of 25 subjects (84.0%). Of these 21 subjects, 1 subject had seizure recurrence within 30 minutes after the initial seizure stopped

Overall, an estimated 20% of subjects had resolution of their initial seizure at 1 minute after IP administration, 80.0% at 7 minutes after IP administration, and 84.0% at 10 minutes after IP administration.

Four subjects (16.0%) had a competing event (the subjects were administered a rescue anticonvulsant medication for their ongoing initial seizure).

Results were similar in the PPS (20 out of 24 subjects had seizure resolution without the need for rescue anticonvulsant medication; an estimated 20.8%, 79.2%, and 83.3% of subjects had resolution of their initial seizure at 1, 7 and 10 minutes after IP administration, respectively).

Time to recovery of consciousness

Of the 25 subjects who lost consciousness predose, 19 subjects (76.0%) recovered consciousness postdose without the need for rescue anticonvulsant medication. Overall, an estimated 60.0% of subjects had recovered consciousness at 10 minutes after IP administration, 68.0% at 30 minutes after IP administration, and 76.0% at 2 hours after IP administration.

Six subjects (24.0%) had a competing event (subjects were administered rescue anticonvulsant medication before recovering consciousness).

Results were similar in the PPS (18 out of 24 subjects recovered consciousness without the need for rescue anticonvulsant medication; an estimated 58.3%, 66.7%, and 75.0% of subjects had recovered consciousness at 10 minutes, 30 minutes, and 2 hours after IP administration, respectively).

CHMP comments:

Most subjects (84%) had seizure resolution without the need for rescue medication. Sixty-eight percent of subjects had resolution of their initial seizure within 10 minutes after administration and had no seizure activity for at least an hour. These results are in line with results previously obtained, where cessation of visible signs of seizures within 10 minutes without recurrence within 1 hour after administration was observed in 56% to 70% of children (Buccolam SmPC, section 5.1). However, due to the open label, uncontrolled design of the study, no firm conclusions on efficacy can be drawn.

Safety results

A total of 24 out of 25 subjects (96.0%) received the correct and complete dose of the IP.

One subject received the full dose of the IP into each side of the mouth but some of the drug leaked out. The subject initially responded to treatment (the initial seizure was stopped within 10 minutes of IP administration and an absence of seizure activity was sustained for 30 minutes); however, the subject had seizure recurrence within 1 hour after IP administration that required treatment with rescue anticonvulsant medication.Among the 24 subjects who received a complete dose of the IP, mean (SD) actual dose increased proportionately with increasing age group: 2.50 (0.000) mg in the age group <1 year, 5.00 (0.000) mg in the age group 1 to <5 years, 7.50 (0.000) mg in the age group 5 to <10 years, and 10.00 (-) mg in the age group 10 to <18 years.

<u>Adverse events</u>

Overall, 9 subjects (36.0%) experienced a total of 13 TEAEs. Three subjects reported serious TEAEs during the study; 2 subjects (15.4%) in the age group 1 to <5 years, and 1 subject (50.0%) in the age group 10 to <18 years. A total of 2 subjects (8.0%) reported severe TEAEs, and 3 subjects (12.0%)

reported a TEAE that was considered by the investigator to be related to IP. No subjects died during the study, and no subjects reported TEAEs leading to discontinuation from the study.

Treatment-emergent AEs occurred most frequently in the SOC of nervous system disorders, which was reported in 4 subjects (16.0%) overall; 2 subjects (15.4%) in the age group 1 to <5 years, 1 subject (14.3%) in the age group 5 to <10 years, and 1 subject (50%) in the age group 10 to <18 years. All other TEAEs by SOC were reported in ≤2 subjects overall, irrespective of age group

The most frequent TEAE by PT occurring in ≥10% of subjects in any age group was respiratory depression (2 subjects [8.0%]). All other TEAEs by PT occurring in ≥10% of subjects in any age group were reported in 1 subject overall (see Table 4).

Table 4 Frequently Occurring (>=10%) Treatment-Emergent Adverse Events by Preferred Term and Age Group (Safety Set)

	MHOS/SHP615									
	Age group[a]									
Category	<1 year (N=3)		1 to <5 years (N=13)		5 to <10 years (N=7)		10 to <18 years (N=2)		Total (N=25)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Respiratory depression	0	0	1 (7.7)	1	0	0	1 (50.0)	1	2 (8.0)	2
Amylase increased	0	0	0	0	1 (14.3)	1	0	0	1 (4.0)	1
Dermatitis diaper	0	0	0	0	1 (14.3)	1	0	0	1 (4.0)	1
Diarrhoea	1 (33.3)	1	0	0	0	0	0	0	1 (4.0)	1
Face oedema	0	0	0	0	1 (14.3)	1	0	0	1 (4.0)	1
Seizure	0	0	0	0	1 (14.3)	1	0	0	1 (4.0)	1
Status epilepticus	0	0	0	0	0	0	1 (50.0)	2	1 (4.0)	2

AE=adverse event; IP=investigational product; MHOS/SHP615=midazolam hydrochloride oromucosal solution; n=number of subjects experiencing the event; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.
[a]Age was calculated as the difference between date of birth and date of IP administration.
- Percentages were calculated based on the number of subjects in each age group and total group, respectively.
- Treatment-emergent AEs were defined as AEs whose onset occurred, severity worsened, or intensity increased on or after the date of IP administration. Events which occurred more than one week after the IP administration were not considered treatment emergent.
- Adverse events were classified into PT using version 20.0 of MedDRA.
- Within each group, subjects were counted once per PT.
- Treatment-emergent AEs occurring in ≥10% of subjects in any group are presented.
- Preferred terms are sorted by descending incidence using counts from the total column.
Source: Section 14, Table 14.3.1.2.3.

The majority of TEAEs were considered mild in intensity. Overall, 2 subjects (8.0%) reported severe TEAEs; 1 subject (4.0%) reported a severe TEAE of SE and 1 subject (4.0%) reported a severe TEAE of respiratory depression.

All TEAEs reported during the study occurred before hospital discharge. No subjects reported TEAEs after hospital discharge.

A total of 3 subjects (12.0%) reported a total of 3 serious TEAEs during the study, including SE, seizure cluster, and respiratory depression. Of these, 1 SAE was considered by the investigator to be related to the IP (respiratory depression); the event was severe in intensity and occurred on the same day as treatment failure. The other 2 SAEs were not considered by the investigator to be related to the IP.

Severe TEAEs of respiratory depression (1 event; serious and considered related to the IP, and SE (2 events in 1 subject; 1 serious event and 1 nonserious event, both considered unrelated to the IP) were also reported.

A total of 2 subjects (8.0%) reported a TEAE of respiratory depression during the study:

- 1 subject reported a TEAE of respiratory depression on Day 5 of the study that was mild in intensity and was not considered by the investigator to be related to the IP. No action was taken in response to the event, which resolved 3 days after onset.

1 subject reported a serious TEAE of respiratory depression on Day 1 of the study that was severe in intensity and was considered by the investigator to be related to the IP. Of note, the subject had decreased oxygen saturation at baseline (82%) and failed to respond to treatment with the IP. Medical intervention (assisted ventilation) was required to treat the event which resolved on the same day. No events of aspiration pneumonia or buccal irritation were reported during the study.

Improvements in Riker SAS scores were observed following IP administration. Median Riker SAS scores increased from 1.0 (indicates "unarousable") at baseline to 4.0 (indicates "calm and cooperative") at 30 minutes postdose and remained at 4.0 at all subsequent timepoints evaluated.

No clinically relevant trends were apparent in mean changes from baseline in chemistry values, vital signs, or urinalysis parameters over time. Clinically significant abnormalities in individual chemistry values and vital signs were observed in a small number of subjects. Elevated ALT and elevated glucose were reported in 1 subject each. Vital signs abnormalities included elevated pulse rate, reported in 4 subjects; elevated temperature, reported in 3 subjects; and elevated respiratory rate, reported in 2 subjects.

Overall, 24 out of 25 subjects had at least 1 oxygen saturation on room air result recorded during the study. At all timepoints evaluated, overall mean oxygen saturation on room air was ≥94%. One subject had an oxygen saturation on room air measurement of 87% at baseline which persisted for at least 2 minutes.

No clinically relevant changes with time were observed for ECG results.

CHMP comments:

The amount of safety data is limited due to the number of subjects included in the study. Adverse events did not occur frequently, though what has been reported are known events associated with midazolam (Buccolam SmPC, section 4.8).

There were two cases of respiratory depression of which one was serious. Subject 1's seizure activity did not resolve 10 minutes after Buccolam administration and was regarded as a treatment failure and subsequently received rescue medication (thiopental sodium). Approximately half an hour after Buccolam/rescue medication administration, the subject experienced a serious case of respired depression and needed to be intubated. The subject had Dravet Syndrome and took the following concomitant anti-epileptic drugs: stiripentol, levetiracetam, valproate and clobazam. The Applicant

considers the event related to the study medication, more specifically the result of various drug-drug interactions due to the concomitant drugs the subject had taken. This conclusion is supported as it is known that combining midazolam with other anti-epileptic drugs increases the risk for respiratory depression.

2.3.3. Discussion on clinical aspects

Study SHP615-301 was an open-label study to evaluate oromucosal midazolam as an acute treatment for status epilepticus.

The pop PK modelling results are sufficient to support the conclusion that a different pharmacokinetic profile for Japanese pediatric patients compared to non-Japanese pediatric patients is not expected. However, it should be discussed by the MAH whether section 5.2 of SPC should updated, based on the current results. .

Regarding efficacy results, 80% of the subjects enrolled in the study were a responder to treatment. Furthermore, 68% percent of subjects had resolution of their initial seizure within 10 minutes after administration and had no seizure activity for at least an hour. These results are within the same order of magnitude as results previously obtained (Buccolam SmPC, Section 5.1). However, due to the open label, uncontrolled design of the studies, no firm conclusions on efficacy can be drawn.

No new safety signals have been identified in the study population. Adverse events were infrequent and what was reported is similar to what was previously observed (Buccolam SmPC, section 4.8).

3. Rapporteur's updated overall conclusion and recommendation

☒ **Fulfilled:**

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. It has not sufficiently been justified that results presented in this article 46 procedure do not need to be reflected in the SPC. First, it should be discussed by the Applicant whether the current table on pharmacokinetic parameters in section 5.2 of the SPC should be updated based on the results of the refined pop PK study. Second, it should be discussed if the newly gained information on the effect of race on the pharmacokinetics of midazolam should be included in section 5.2 of the SPC.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

The Applicant acknowledges the rapporteurs request and proposes to update section 5.2 of the SmPC with the following wording:

Race:

Clinical studies have included patients from Japanese and non-Japanese groups, and no differences in the pharmacokinetic profile have been identified on exposure to Buccolam.

No dose adjustment is warranted.

CHMP comments:

The Applicant partially responded to the assessor's request for supplementary information. The proposed addition to section 5.2 of the SmPC is agreed. The issue on the table on pharmacokinetic parameters in section 5.2, is not further pursued.

No further issues.