



## Clinical trial results:

### A Phase 3, Multicenter, Open-label Study to Determine the Efficacy, Safety, and Pharmacokinetics of Buccally Administered MHOS/SHP615 in Pediatric Subjects With Status Epilepticus (Convulsive) in the Hospital or Emergency Room

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2020-000226-26 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 19 August 2019 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1            |
| This version publication date  | 01 March 2020 |
| First version publication date | 01 March 2020 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | SHP615-301 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03336645 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Shire  |
| Sponsor organisation address | 300 Shire Way, Lexington, United States, MA 02421                    |
| Public contact               | Study Director, Shire, 1 866-8425335, ClinicalTransparency@shire.com |
| Scientific contact           | Study Director, Shire, 1 866-8425335, ClinicalTransparency@shire.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 19 August 2019 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 19 August 2019 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was conducted in accordance with current applicable industry regulations, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996) and any updates, European Union (EU) Directive 2001/20/EC and its updates, the ethical principles in the Declaration of Helsinki, and local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 23 October 2017 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 25 |
| Worldwide total number of subjects   | 25        |
| EEA total number of subjects         | 0         |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 5  |
| Children (2-11 years)                     | 18 |
| Adolescents (12-17 years)                 | 2  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 28 study centers in the Japan between 23 October 2017 (first subject first visit) and 19 August 2019 (last subject last visit).

### Pre-assignment

Screening details:

A total of 25 subjects were enrolled, received treatment and completed the study.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|           |        |
|-----------|--------|
| Arm title | SHP615 |
|-----------|--------|

Arm description:

Subjects received an oromucosal single fixed age-specific dose (2.5 mg: 3 months to less than [ $<$ ] 1 year, 5 mg: 1 to  $<$ 5 years, 7.5 mg: 5 to  $<$ 10 years and 10 mg: 10 to  $<$ 18 years) of MHOS/SHP615 solution on Day 1.

|  |   |
|--|---|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | Midazolam Hydrochloride Oromucosal Solution |
| Investigational medicinal product code | SHP615                                      |
| Other name                             |   |
| Pharmaceutical forms                   | Oromucosal solution                         |
| Routes of administration               | Buccal use                                  |

Dosage and administration details:

Subjects received MHOS/SHP615 oromucosal solution through buccal route.

|                                       |        |
|---------------------------------------|--------|
| <b>Number of subjects in period 1</b> | SHP615 |
| Started                               | 25     |
| Completed                             | 25     |

## Baseline characteristics

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | SHP615 |
|-----------------------|--------|

Reporting group description:

Subjects received an oromucosal single fixed age-specific dose (2.5 mg: 3 months to less than [ $<$ ] 1 year, 5 mg: 1 to  $<$ 5 years, 7.5 mg: 5 to  $<$ 10 years and 10 mg: 10 to  $<$ 18 years) of MHOS/SHP615 solution on Day 1.

| Reporting group values | SHP615 | Total |  |
|------------------------|--------|-------|--|
| Number of subjects     | 25     | 25    |  |
| Age categorical        |        |       |  |
| Units: Subjects        |        |       |  |

|   |             |    |  |
|---|-------------|----|--|
| Age continuous                            |             |    |  |
| Units: years                              |             |    |  |
| arithmetic mean                           | 4.63        |    |  |
| standard deviation                        | $\pm 4.033$ | -  |  |
| Gender categorical                        |             |    |  |
| Units: Subjects                           |             |    |  |
| Female                                    | 16          | 16 |  |
| Male                                      | 9           | 9  |  |
| Race (NIH/OMB)                            |             |    |  |
| Units: Subjects                           |             |    |  |
| American Indian or Alaska Native          | 0           | 0  |  |
| Asian                                     | 25          | 25 |  |
| Native Hawaiian or Other Pacific Islander | 0           | 0  |  |
| Black or African American                 | 0           | 0  |  |
| White                                     | 0           | 0  |  |
| More than one race                        | 0           | 0  |  |
| Unknown or Not Reported                   | 0           | 0  |  |
| Ethnicity (NIH/OMB)                       |             |    |  |
| Units: Subjects                           |             |    |  |
| Hispanic or Latino                        | 0           | 0  |  |
| Not Hispanic or Latino                    | 25          | 25 |  |
| Unknown or Not Reported                   | 0           | 0  |  |

## End points

### End points reporting groups

|  |        |
|--|--------|
| Reporting group title  | SHP615 |
| Reporting group description:   |        |
| Subjects received an oromucosal single fixed age-specific dose (2.5 mg: 3 months to less than [ $<$ ] 1 year, 5 mg: 1 to $<$ 5 years, 7.5 mg: 5 to $<$ 10 years and 10 mg: 10 to $<$ 18 years) of MHOS/SHP615 solution on Day 1. |        |

### Primary: Percentage of Subjects with Response Rate

|  |  |
|--|--|
| End point title  | Percentage of Subjects with Response Rate <sup>[1]</sup> |
| End point description:   |  |
| Response rate was defined as the percentage of subjects with therapeutic success. Therapeutic success was defined as the cessation of visible seizure activity within 10 minutes (mins) with a sustained absence of visible seizure activity for 30 minutes following a single dose of MHOS/SHP615 without the need for additional rescue medication. Percentage of subjects with response rate were reported. Full Analysis Set (FAS) consisted of all subjects in the safety set who had at least 1 assessment for determination of therapeutic success (date and time of the investigational product [IP] administration and seizure cessation for the initial seizure; subjects with no recurrence of seizure within 30 minutes post-dose) performed after the administration of the IP. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| From start of study drug administration up to 30 minutes post-dose   |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical and comparison analysis were performed for this endpoint.

| End point values              | SHP615          |  |  |  |
|-------------------------------|-----------------|--|--|--|
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 25              |  |  |  |
| Units: Percentage of subjects |                 |  |  |  |
| number (not applicable)       | 80.0            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who had Sustained Absence of Seizure Activity for at Least 1, 4 and 6 Hours

|  |  |
|--|--|
| End point title  | Percentage of Subjects Who had Sustained Absence of Seizure Activity for at Least 1, 4 and 6 Hours |
| End point description:   |  |
| Percentage of subject whose seizure event stopped within 10 mins of a single dose administration of SHP615 and who had sustained absence of seizure activity for at least 1, 4, and 6 hours were reported. FAS consisted of all subjects in the safety set who had at least 1 assessment for determination of therapeutic success (date and time of the IP administration and seizure cessation for the initial seizure; subjects with no recurrence of seizure within 30 minutes post-dose) performed after the administration of the IP. |  |
| End point type   | Secondary  |

End point timeframe:

From start of study drug administration up to 1, 4 and 6 hours post-dose

|                               |                 |  |  |  |
|-------------------------------|-----------------|--|--|--|
| <b>End point values</b>       | SHP615          |  |  |  |
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 25              |  |  |  |
| Units: Percentage of subjects |                 |  |  |  |
| number (not applicable)       |                 |  |  |  |
| At least 1 hour               | 68.0            |  |  |  |
| At least 4 hours              | 36.0            |  |  |  |
| At least 6 hours              | 32.0            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Time to Resolution of Seizures (Convulsions)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects with Time to Resolution of Seizures (Convulsions) |
|-----------------|--|

End point description:

Time to resolution of seizures (convulsions) was calculated as time from IP administration to the end of the initial seizure or administration of rescue anticonvulsant medication, whichever occurs first, the initial seizure referred to the seizure that triggered the use of the IP and that was captured. Number of subjects with time to resolution of seizures (convulsions) was reported. FAS consisted of all subjects in the safety set who had at least 1 assessment for determination of therapeutic success (date and time of the IP administration and seizure cessation for the initial seizure; subjects with no recurrence of seizure within 30 minutes post-dose) performed after the administration of the IP.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From start of study drug administration to follow-up (8 days)

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | SHP615          |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 25              |  |  |  |
| Units: subjects             | 21              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Time to Recovery of Consciousness

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with Time to Recovery of Consciousness |
|-----------------|---|

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**End point description:**

Time to recovery of consciousness (in minutes) was calculated only for subjects who lost consciousness pre-dose as time from IP administration to recovery of consciousness post-dose or administration of rescue anticonvulsant medication, whichever occurs first. Number of subjects with time to recovery of consciousness was reported. FAS consisted of all subjects in the safety set who had at least 1 assessment for determination of therapeutic success (date and time of the IP administration and seizure cessation for the initial seizure; subjects with no recurrence of seizure within 30 minutes post-dose) performed after the administration of the IP.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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**End point timeframe:**

From start of study drug administration to follow-up (8 days)

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|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | SHP615          |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 25              |  |  |  |
| Units: subjects             | 19              |  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Percentage of Subjects Who Required Additional Anticonvulsant Medication for Ongoing Status Epilepticus (SE)**

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|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Who Required Additional Anticonvulsant Medication for Ongoing Status Epilepticus (SE) |
|-----------------|--|

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**End point description:**

Percentage of subjects who required additional anticonvulsant medication for ongoing SE 10 minutes after a single dose of SHP615 were reported. FAS consisted of all subjects in the safety set who had at least 1 assessment for determination of therapeutic success (date and time of the IP administration and seizure cessation for the initial seizure; subjects with no recurrence of seizure within 30 minutes post-dose) performed after the administration of the IP.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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**End point timeframe:**

10 minutes post-dose

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|                               |                 |  |  |  |
|-------------------------------|-----------------|--|--|--|
| <b>End point values</b>       | SHP615          |  |  |  |
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 25              |  |  |  |
| Units: Percentage of Subjects |                 |  |  |  |
| number (not applicable)       | 16.0            |  |  |  |

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**Statistical analyses**



No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Failed to Respond to the Treatment with SHP615

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Failed to Respond to the Treatment with SHP615 |
|-----------------|---|

End point description:

Treatment failure/non-responder was defined as subjects with continuing seizure activity and/or the need for any additional rescue medication according to the participating healthcare setting protocol or guideline, for 10 minutes or more after a single dose of the IP. FAS consisted of all subjects in the safety set who had at least 1 assessment for determination of therapeutic success (date and time of the IP administration and seizure cessation for the initial seizure; subjects with no recurrence of seizure within 30 minutes post-dose) performed after the administration of the IP.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

10 minutes post-dose

| End point values              | SHP615          |  |  |  |
|-------------------------------|-----------------|--|--|--|
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 25              |  |  |  |
| Units: Percentage of subjects |                 |  |  |  |
| number (not applicable)       | 16.0            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Concentration of SHP615 in Plasma at 10 Minutes (C10)

|                 |   |
|-----------------|---|
| End point title | Concentration of SHP615 in Plasma at 10 Minutes (C10) |
|-----------------|---|

End point description:

Concentration of SHP615 in plasma at 10 minutes was reported. Pharmacokinetic (PK) set consisted of all subjects who received a single dose of the IP and for whom at least 1 PK blood sample was collected post-dose. Here the number of subjects analyzed signifies subjects who were evaluable for this measure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

10 minutes post-dose

| End point values                       | SHP615          |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 16              |  |  |  |
| Units: nanogram per milliliter (ng/mL) |                 |  |  |  |
| arithmetic mean (standard deviation)   | 45.2 (± 21.3)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Plasma Concentration (C<sub>max</sub>) of SHP615

|  |  |
|--|--|
| End point title  | Maximum Plasma Concentration (C <sub>max</sub> ) of SHP615 |
| End point description:<br>C <sub>max</sub> of SHP615 in plasma was reported. PK set consisted of all subjects who received a single dose of the IP and for whom at least 1 PK blood sample was collected post-dose. Here the number of subjects analyzed signifies subjects who were evaluable for this measure. |  |
| End point type   | Secondary  |
| End point timeframe:<br>1, 3, 6 hours post-dose  |  |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | SHP615          |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 16              |  |  |  |
| Units: ng/mL                         |                 |  |  |  |
| arithmetic mean (standard deviation) | 78.0 (± 16.4)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to 10 Minutes (AUC<sub>0-10</sub>) of SHP615 in Plasma

|  |   |
|--|---|
| End point title  | Area Under the Concentration-time Curve From Time Zero to 10 Minutes (AUC <sub>0-10</sub> ) of SHP615 in Plasma |
| End point description:<br>AUC <sub>0-10</sub> of SHP615 in plasma was reported. Here min ng/mL is minutes nanogram per milliliter. PK set consisted of all subjects who received a single dose of the IP and for whom at least 1 PK blood sample was collected post-dose. Here the number of subjects analyzed signifies subjects who were evaluable for this measure. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Pre-dose, 10 minutes post-dose   |   |

|                                      |                  |  |  |  |
|--------------------------------------|------------------|--|--|--|
| <b>End point values</b>              | SHP615           |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 16               |  |  |  |
| Units: min ng/mL                     |                  |  |  |  |
| arithmetic mean (standard deviation) | 304 ( $\pm$ 149) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to 60 Minutes (AUC0-60) of SHP615 in Plasma

|                 |  |
|-----------------|--|
| End point title | Area Under the Concentration-time Curve From Time Zero to 60 Minutes (AUC0-60) of SHP615 in Plasma |
|-----------------|--|

End point description:

AUC0-60 of SHP615 in plasma was reported. PK set consisted of all subjects who received a single dose of the IP and for whom at least 1 PK blood sample was collected post-dose. Here the number of subjects analyzed signifies subjects who were evaluable for this measure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 60 minutes post-dose

|                                      |                   |  |  |  |
|--------------------------------------|-------------------|--|--|--|
| <b>End point values</b>              | SHP615            |  |  |  |
| Subject group type                   | Reporting group   |  |  |  |
| Number of subjects analysed          | 16                |  |  |  |
| Units: min ng/mL                     |                   |  |  |  |
| arithmetic mean (standard deviation) | 2965 ( $\pm$ 592) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to 180 Minutes (AUC0-180) of SHP615 in Plasma

|                 |  |
|-----------------|--|
| End point title | Area Under the Concentration-time Curve From Time Zero to 180 Minutes (AUC0-180) of SHP615 in Plasma |
|-----------------|--|

End point description:

AUC0-180 of SHP615 in plasma was reported. PK set consisted of all subjects who received a single dose of the IP and for whom at least 1 PK blood sample was collected post-dose. Here the number of subjects analyzed signifies subjects who were evaluable for this measure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 180 minutes post-dose

|                                      |                    |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| <b>End point values</b>              | SHP615             |  |  |  |
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 16                 |  |  |  |
| Units: min ng/mL                     |                    |  |  |  |
| arithmetic mean (standard deviation) | 4411 ( $\pm$ 1140) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity (AUC<sub>0-inf</sub>) of SHP615 in Plasma

|                 |  |
|-----------------|--|
| End point title | Area Under the Concentration-time Curve From Time Zero to Infinity (AUC <sub>0-inf</sub> ) of SHP615 in Plasma |
|-----------------|--|

End point description:

AUC(0-infinity) of SHP615 in plasma was reported. PK set consisted of all subjects who received a single dose of the IP and for whom at least 1 PK blood sample was collected post-dose. Here the number of subjects analyzed signifies subjects who were evaluable for this measure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 1, 3, and 6 hours post-dose

|                                      |                    |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| <b>End point values</b>              | SHP615             |  |  |  |
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 16                 |  |  |  |
| Units: min ng/mL                     |                    |  |  |  |
| arithmetic mean (standard deviation) | 5847 ( $\pm$ 2599) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time at Maximum Concentration (T<sub>max</sub>) of SHP615 in Plasma

|                 |   |
|-----------------|---|
| End point title | Time at Maximum Concentration (T <sub>max</sub> ) of SHP615 in Plasma |
|-----------------|---|

End point description:

T<sub>max</sub> of SHP615 in plasma was reported. PK set consisted of all subjects who received a single dose of the IP and for whom at least 1 PK blood sample was collected post-dose. Here the number of subjects analyzed signifies subjects who were evaluable for this measure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1, 3, and 6 hours post-dose

|                               |                     |  |  |  |
|-------------------------------|---------------------|--|--|--|
| <b>End point values</b>       | SHP615              |  |  |  |
| Subject group type            | Reporting group     |  |  |  |
| Number of subjects analysed   | 16                  |  |  |  |
| Units: minutes                |                     |  |  |  |
| median (full range (min-max)) | 20.5 (15.5 to 28.0) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Elimination Half-life (t<sub>1/2</sub>) of SHP615 in Plasma

|  |   |
|--|---|
| End point title  | Elimination Half-life (t <sub>1/2</sub> ) of SHP615 in Plasma |
| End point description:   |   |
| t <sub>1/2</sub> of SHP615 in plasma was reported. PK set consisted of all subjects who received a single dose of the IP and for whom at least 1 PK blood sample was collected post-dose. Here the number of subjects analyzed signifies subjects who were evaluable for this measure. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| 1, 3, and 6 hours post-dose  |   |

|                               |                   |  |  |  |
|-------------------------------|-------------------|--|--|--|
| <b>End point values</b>       | SHP615            |  |  |  |
| Subject group type            | Reporting group   |  |  |  |
| Number of subjects analysed   | 16                |  |  |  |
| Units: minutes                |                   |  |  |  |
| median (full range (min-max)) | 115 (90.6 to 303) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with Respiratory Depression

|   |  |
|---|--|
| End point title   | Number of Subjects with Respiratory Depression |
| End point description:  |  |
| Persistent decrease in oxygen saturation to <92 percent (%) measured at 10 minutes, 30 minutes, and 4, 6, and 24 hours post-dose (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]) and increase in respiratory effort such that assisted ventilation is used (bag-valve-mask ventilation or endotracheal intubation). Safety set consisted of all subjects who had received a single dose of the IP, regardless of whether IP administration was documented to be complete or not on the IP administration page of the electronic case report form (eCRF). |  |

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From start of study drug administration to follow-up (8 days) |           |

|  |                 |  |  |  |
|--|-----------------|--|--|--|
| <b>End point values</b>                  | SHP615          |  |  |  |
| Subject group type                       | Reporting group |  |  |  |
| Number of subjects analysed              | 25              |  |  |  |
| Units: subjects                          |                 |  |  |  |
| Persistent Decrease in Oxygen Saturation | 0               |  |  |  |
| Increase in Respiratory Effort           | 1               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Aspiration Pneumonia Reported as Treatment Emergent Adverse Events (TEAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Aspiration Pneumonia Reported as Treatment Emergent Adverse Events (TEAEs) |
|-----------------|--|

End point description:

Number of subjects with aspiration pneumonia were reported as TEAEs. Safety set consisted of all subjects who had received a single dose of the IP, regardless of whether IP administration was documented to be complete or not on the IP administration page of the eCRF.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From start of study drug administration to follow-up (8 days)

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | SHP615          |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 25              |  |  |  |
| Units: subjects             | 0               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Riker Sedation-Agitation Scale at 24 Hours Post-dose

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Riker Sedation-Agitation Scale at 24 Hours Post-dose |
|-----------------|--|

End point description:

Sedation - Agitation was assessed using the Riker Sedation-Agitation Scale (SAS) by the following 7-point scale: 7=dangerous agitation; 6=very agitated; 5=agitated; 4=calm, cooperative; 3=sedated; 2=very sedated; 1=un arousable. Change from baseline in riker sedation-agitation scale at 24 hours post-dose was reported. Safety set consisted of all subjects who had received a single dose of the IP, regardless of whether IP administration was documented to be complete or not on the IP administration page of the eCRF. Here the number of subjects analysed signifies subjects who were evaluable for this measure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 24 hours post-dose

| End point values                     | SHP615          |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 23              |  |  |  |
| Units: Score on the scale            |                 |  |  |  |
| arithmetic mean (standard deviation) | 2.2 (± 1.23)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation subjects administered a pharmaceutical product and that does not necessarily had a causal relationship with this treatment. TEAEs are defined as AEs that start or deteriorate on or after the date of the first dose of IP and no later than 3 days following the last dose of IP. Safety set consisted of all subjects who had received a single dose of the IP, regardless of whether IP administration was documented to be complete or not on the IP administration page of the eCRF.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From start of study drug administration to follow-up (8 days)

| End point values            | SHP615          |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 25              |  |  |  |
| Units: subjects             | 9               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Change From Baseline in Oxygen Saturation at 24 Hours Post-dose**

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|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Oxygen Saturation at 24 Hours Post-dose |
|-----------------|---|

End point description:

Oxygen saturation at baseline was measured and recorded on room air. The investigator had recorded the oxygen saturation, oxygen delivery system and amount of oxygen administered during the study. Change from baseline in oxygen saturation at 24 hours post-dose was reported. Safety set consisted of all subjects who had received a single dose of the IP, regardless of whether IP administration was documented to be complete or not on the IP administration page of the eCRF. Here the number of subjects analysed signifies subjects who were evaluable for this measure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 24 hours post-dose

---

| End point values                       | SHP615          |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 14              |  |  |  |
| Units: Percentage of oxygen saturation |                 |  |  |  |
| arithmetic mean (standard deviation)   | 3.7 (± 10.21)   |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration to follow up (8 days)

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | SHP615 |
|-----------------------|--------|

Reporting group description:

Subjects received an oromucosal single fixed age-specific dose (2.5 mg: 3 months to less than [ $<$ ] 1 year, 5 mg: 1 to  $<$ 5 years, 7.5 mg: 5 to  $<$ 10 years and 10 mg: 10 to  $<$ 18 years) of MHOS/SHP615 solution on Day 1.

| Serious adverse events                            | SHP615          |  |  |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 3 / 25 (12.00%) |  |  |
| number of deaths (all causes)                     | 0               |  |  |
| number of deaths resulting from adverse events    | 0               |  |  |
| Nervous system disorders                          |                 |  |  |
| Seizure cluster                                   |                 |  |  |
| subjects affected / exposed                       | 1 / 25 (4.00%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Status epilepticus                                |                 |  |  |
| subjects affected / exposed                       | 1 / 25 (4.00%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders   |                 |  |  |
| Respiratory depression                            |                 |  |  |
| subjects affected / exposed                       | 1 / 25 (4.00%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

|   |                |  |  |
|---|----------------|--|--|
| <b>Non-serious adverse events</b>                     | SHP615         |  |  |
| Total subjects affected by non-serious adverse events |                |  |  |
| subjects affected / exposed                           | 2 / 25 (8.00%) |  |  |
| Respiratory, thoracic and mediastinal disorders       |                |  |  |
| Respiratory depression                                |                |  |  |
| subjects affected / exposed                           | 2 / 25 (8.00%) |  |  |
| occurrences (all)                                     | 2              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 08 July 2017     | <p>Amendment 1</p> <ul style="list-style-type: none"><li>- To clarify that a subject should be excluded if their exact age is not known at the time of IP administration.</li><li>- To replace "drugs that inhibit or induce CYP3A" with "concomitant drugs determined by the investigator to have a contraindication to the use of benzodiazepines" in Exclusion Criterion 6.</li><li>- To change the schedule of assessments for oxygen saturation, 12-lead ECG, and hematology assessments.</li><li>- To add details on requirement for oxygen saturation to be measured on room air.</li><li>- To clarify responsibilities of investigator/sub-investigator versus qualified staff members.</li><li>- To add requirement for laboratory blood samples to be repeated every 6 months if no seizure occurred that resulted in IP administration.</li><li>- To add time windows for buccal cavity assessment.</li><li>- To add requirement to re-sign ICF at time of admission if more than 3 months have elapsed between initial informed consent and seizure.</li><li>- To update blood volume to be drawn.</li><li>- To change creatinine clearance calculation method from Cockcroft and Gault to Schwartz.</li></ul> |
| 28 August 2017   | <p>Amendment 2</p> <ul style="list-style-type: none"><li>- To clarify duration of condom use for 7 days after IP administration.</li><li>- To update footnotes for schedules of assessments and recommended prescreening procedures and assessments.</li><li>- To remove amylase from the clinical laboratory assessments</li></ul>  |
| 18 December 2017 | <p>Amendment 3</p> <ul style="list-style-type: none"><li>- To include an additional exclusion criterion to omit subjects with seizures due to severe cases of encephalitis or meningitis, as determined by the investigator.</li><li>- To remove assessment of Riker SAS and 12-lead ECG at 10 minutes after IP administration, and add collection of 12-lead ECG at 1 hour after IP administration.</li><li>- To remove AE monitoring at screening/baseline.</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported