



## Clinical trial results:

### An Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Baloxavir Marboxil 2% Granules after Administration of a Single Dose to Otherwise Healthy Pediatric Patients with Influenza

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2021-001026-22 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 17 March 2020  |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 28 March 2021 |
| First version publication date | 28 March 2021 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | 1813T0835 |
|-----------------------|-----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Shionogi & Co., Ltd.   |
| Sponsor organisation address | 12F, Hankyu Terminal Bldg., 1-4, Shibata 1-chome, Osaka, Japan, 530-0012                           |
| Public contact               | Corporate Communications Department, Shionogi & Co., Ltd., shionogiclintrials-admin@shionogi.co.jp |
| Scientific contact           | Corporate Communications Department, Shionogi & Co., Ltd., shionogiclintrials-admin@shionogi.co.jp |

Notes:

#### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-002440-PIP01-18 |
| 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? | Yes                 |

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 17 March 2020 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 17 March 2020 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to assess the safety, tolerability, pharmacokinetics (PK), and efficacy of baloxavir marboxil 2% granules in otherwise healthy pediatric participants with influenza virus infection aged less than 12 years and weighing less than 20 kg at Screening.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 25 January 2019 |
| 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: 45 |
| Worldwide total number of subjects   | 45        |
| 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)  | 13 |
| Children (2-11 years)                     | 32 |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 15 study centers in Japan.

### Pre-assignment

Screening details:

Participants with a clinical diagnosis of influenza A and/or B virus infection were enrolled in each arm of the study based on weight. Participants in the <10 kg arm received a 1 mg/kg or 2 mg/kg dose based on age. Participants aged <3 months were to receive a dose of 1 mg/kg. No participants in the study were <3 months of age.

### Period 1

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

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Baloxavir Marboxil (Participants' weight <10 kg) |

Arm description:

Participants who weighed <10 kilograms (kg) and were greater than or equal to ( $\geq$ ) 3 months of age received a single oral dose of 2 milligram per kilogram (mg/kg) baloxavir marboxil 2% granules on Day 1.

|  |                              |
|--|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Baloxavir marboxil           |
| Investigational medicinal product code |                              |
| Other name                             | S-033188, RO7191686, Xofluza |
| Pharmaceutical forms                   | Granules in sachet           |
| Routes of administration               | Oral use                     |

Dosage and administration details:

A single oral dose of 1 mg/kg or 2 mg/kg of baloxavir marboxil 2% granules was to be administered on Day 1 based on participants' age and body weight at Screening. All participants in this arm received 2 mg/kg of baloxavir marboxil 2% granules.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Baloxavir Marboxil (Participants' weight $\geq$ 10 kg to <20 kg) |
|------------------|--|

Arm description:

Participants who weighed between 10 to <20 kg received 20 mg of baloxavir marboxil 2% granules as a single oral dose on Day 1 irrespective of their age.

|  |                              |
|--|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Baloxavir marboxil           |
| Investigational medicinal product code |                              |
| Other name                             | S-033188, RO7191686, Xofluza |
| Pharmaceutical forms                   | Granules in sachet           |
| Routes of administration               | Oral use                     |

Dosage and administration details:

A single oral dose of 20 mg of baloxavir marboxil 2% granules was administered on Day 1 based on participants' age and body weight at Screening.

| <b>Number of subjects in period 1</b> | Baloxavir Marboxil<br>(Participants' weight<br><10 kg) | Baloxavir Marboxil<br>(Participants' weight<br>≥10 kg to <20 kg) |
|---------------------------------------|--|--|
| Started                               | 9  | 36   |
| Completed                             | 9  | 36   |

## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Baloxavir Marboxil (Participants' weight <10 kg) |
|-----------------------|--|

Reporting group description:

Participants who weighed <10 kilograms (kg) and were greater than or equal to ( $\geq$ ) 3 months of age received a single oral dose of 2 milligram per kilogram (mg/kg) baloxavir marboxil 2% granules on Day 1.

|                       |  |
|-----------------------|--|
| Reporting group title | Baloxavir Marboxil (Participants' weight $\geq$ 10 kg to <20 kg) |
|-----------------------|--|

Reporting group description:

Participants who weighed between 10 to <20 kg received 20 mg of baloxavir marboxil 2% granules as a single oral dose on Day 1 irrespective of their age.

| Reporting group values                                | Baloxavir Marboxil<br>(Participants' weight<br><10 kg) | Baloxavir Marboxil<br>(Participants' weight<br>$\geq$ 10 kg to <20 kg) | Total |
|---|--|--|-------|
| Number of subjects                                    | 9  | 36   | 45    |
| Age Categorical<br>Units: Subjects                    |  |  |       |
| In utero  | 0  | 0  | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0  | 0  | 0     |
| Newborns (0-27 days)                                  | 0  | 0  | 0     |
| Infants and toddlers (28 days-23<br>months)           | 9  | 4  | 13    |
| Children (2-11 years)                                 | 0  | 32   | 32    |
| Adolescents (12-17 years)                             | 0  | 0  | 0     |
| Adults (18-64 years)                                  | 0  | 0  | 0     |
| From 65-84 years                                      | 0  | 0  | 0     |
| 85 years and over                                     | 0  | 0  | 0     |
| Age Continuous<br>Units: years                        |  |  |       |
| arithmetic mean                                       | 0.4  | 3.4  |       |
| standard deviation                                    | $\pm$ 0.5  | $\pm$ 1.5  | -     |
| Gender Categorical<br>Units: Subjects                 |  |  |       |
| Female  | 3  | 17   | 20    |
| Male  | 6  | 19   | 25    |

## End points

### End points reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Baloxavir Marboxil (Participants' weight <10 kg) |
|-----------------------|--|

Reporting group description:

Participants who weighed <10 kilograms (kg) and were greater than or equal to ( $\geq$ ) 3 months of age received a single oral dose of 2 milligram per kilogram (mg/kg) baloxavir marboxil 2% granules on Day 1.

|                       |  |
|-----------------------|--|
| Reporting group title | Baloxavir Marboxil (Participants' weight $\geq$ 10 kg to <20 kg) |
|-----------------------|--|

Reporting group description:

Participants who weighed between 10 to <20 kg received 20 mg of baloxavir marboxil 2% granules as a single oral dose on Day 1 irrespective of their age.

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | Baloxavir marboxil 2 mg/kg dose |
|----------------------------|---------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

The PK concentration population consisted of all participants who received at least one dose of the study drug and had at least one evaluable PK assay result.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | Baloxavir marboxil 20 mg dose |
|----------------------------|-------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

The PK concentration population consisted of all participants who received at least one dose of the study drug and had at least one evaluable PK assay result.

### Primary: Time to Alleviation of Influenza Illness

|                 |   |
|-----------------|---|
| End point title | Time to Alleviation of Influenza Illness <sup>[1]</sup> |
|-----------------|---|

End point description:

Time to alleviation of influenza illness was defined as time taken from the start of treatment to the point at which all of the following criteria were met, and these clinical conditions persisted for at least 21.5 hours (90% of 24 hours): i) In the participant diary, cough and nasal discharge/nasal congestion were both rated as 0=absent or 1=mild; ii) Axillary temperature was < 37.5 degree Celsius [ $^{\circ}$ C]. Intent-to-treat infected (ITTI) population included all participants who received study drug with a confirmed diagnosis of influenza virus infection on Day 1 and complied with Good Clinical Practice (GCP).

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to Day 14

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 analyses were planned for this endpoint.

| End point values                 | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight $\geq$ 10 kg to <20 kg) |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed      | 8  | 35   |  |  |
| Units: hours                     |  |  |  |  |
| median (confidence interval 95%) | 26.4 (12.1 to 51.6)                              | 42.1 (28.6 to 54.8)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Influenza Virus Titer

|                 |                       |
|-----------------|-----------------------|
| End point title | Influenza Virus Titer |
|-----------------|-----------------------|

End point description:

Influenza virus titer is the quantity of influenza virus in a given volume within the samples obtained from nasopharyngeal swabs. A lower value indicates lower viral load. Influenza virus titer was reported in log-transformed units i.e. log of the 50% tissue culture infective dose per millilitre (log[TCID/mL]). Participants with positive virus titer at baseline in the ITTI population were included in the analysis.

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

End point timeframe:

Predose on Day 1, Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6, and 9

| End point values                     | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed          | 8  | 35   |  |  |
| Units: log[TCID/mL]                  |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Day 1 (n=8, 34)                      | 4.68 (± 1.05)                                    | 5.53 (± 1.73)  |  |  |
| Day 2 (n=8, 34)                      | 0.70 (± 0.00)                                    | 1.03 (± 0.73)  |  |  |
| Day 3 (n=6, 18)                      | 0.70 (± 0.00)                                    | 1.15 (± 1.18)  |  |  |
| Day 4 (n=3, 23)                      | 0.70 (± 0.00)                                    | 1.30 (± 1.06)  |  |  |
| Day 6 (n=8, 34)                      | 1.99 (± 1.36)                                    | 2.02 (± 1.69)  |  |  |
| Day 9 (n=8, 34)                      | 0.70 (± 0.00)                                    | 1.24 (± 1.11)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Amount of Virus RNA Determined by Reverse Transcription Polymerase Chain Reaction (RT-PCR)

|                 |  |
|-----------------|--|
| End point title | Amount of Virus RNA Determined by Reverse Transcription Polymerase Chain Reaction (RT-PCR) |
|-----------------|--|

End point description:

The amount of virus ribonucleic acid (RNA) observed at each time point including Baseline was reported in log-transformed units i.e. log of viral particles per millilitre (log[vp/mL]). Participants in the ITTI population were included in the analysis.

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

End point timeframe:

Predose on Day 1, Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6 and 9

| End point values                     | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed          | 8  | 35   |  |  |
| Units: log[vp/mL]                    |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Day 1 (n=8, 35)                      | 6.50 (± 0.80)                                    | 6.39 (± 0.94)  |  |  |
| Day 2 (n=8, 35)                      | 4.57 (± 0.93)                                    | 5.26 (± 0.98)  |  |  |
| Day 3 (n=6, 18)                      | 3.52 (± 0.76)                                    | 4.25 (± 1.22)  |  |  |
| Day 4 (n=3, 24)                      | 2.57 (± 0.37)                                    | 4.15 (± 1.24)  |  |  |
| Day 6 (n=8, 35)                      | 5.04 (± 1.55)                                    | 4.52 (± 1.37)  |  |  |
| Day 9 (n=8, 35)                      | 2.75 (± 0.79)                                    | 3.66 (± 1.41)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Influenza Virus Titer

|   |   |
|---|---|
| End point title   | Change From Baseline in Influenza Virus Titer |
| End point description:  |   |
| Influenza virus titer is the quantity of influenza virus in a given volume within the samples obtained from nasopharyngeal swabs. A lower value indicates a lower viral load. The change from Baseline in influenza virus titer at each time point was reported in log-transformed units i.e. log of the 50% tissue culture infective dose per mL (log[TCID <sub>50</sub> /mL]). Participants with positive virus titer at baseline in the ITTI population were included in the analysis. |   |
| End point type  | Secondary                                     |
| End point timeframe:  |   |
| Baseline and Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6 and 9   |   |

| End point values                        | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|---|--|--|--|--|
| Subject group type                      | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed             | 8  | 34   |  |  |
| Units: log[TCID <sub>50</sub> /mL]      |  |  |  |  |
| arithmetic mean (standard deviation)    |  |  |  |  |
| Change from Baseline at Day 2 (n=8, 34) | -3.98 (± 1.05)                                   | -4.51 (± 1.72)   |  |  |
| Change from Baseline at Day 3 (n=6, 18) | -3.83 (± 1.14)                                   | -3.98 (± 1.91)   |  |  |
| Change from Baseline at Day 4 (n=3, 23) | -4.27 (± 0.64)                                   | -4.11 (± 2.30)   |  |  |
| Change from Baseline at Day 6 (n=8, 34) | -2.69 (± 1.03)                                   | -3.51 (± 2.46)   |  |  |
| Change from Baseline at Day 9 (n=8, 34) | -3.98 (± 1.05)                                   | -4.29 (± 1.80)   |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the Amount of Virus RNA Determined by RT-PCR

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the Amount of Virus RNA Determined by RT-PCR |
|-----------------|--|

End point description:

The change from Baseline in the amount of virus RNA at each time point was reported in log-transformed units i.e. log of viral particles per mL (log[vp/mL]). Participants in the ITTI population were included in the analysis.

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

End point timeframe:

Baseline and Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6 and 9

| End point values                        | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|---|--|--|--|--|
| Subject group type                      | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed             | 8  | 35   |  |  |
| Units: log[vp/mL]                       |  |  |  |  |
| arithmetic mean (standard deviation)    |  |  |  |  |
| Change from Baseline at Day 2 (n=8, 35) | -1.93 (± 0.56)                                   | -1.13 (± 1.18)   |  |  |
| Change from Baseline at Day 3 (n=6, 18) | -3.12 (± 0.50)                                   | -1.96 (± 1.42)   |  |  |
| Change from Baseline at Day 4 (n=3, 24) | -3.45 (± 0.87)                                   | -2.19 (± 1.54)   |  |  |
| Change from Baseline at Day 6 (n=8, 35) | -1.46 (± 1.52)                                   | -1.87 (± 1.63)   |  |  |
| Change from Baseline at Day 9 (n=8, 35) | -3.75 (± 1.24)                                   | -2.73 (± 1.64)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Positive For Influenza Virus Titer

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Positive For Influenza Virus Titer |
|-----------------|---|

End point description:

Influenza virus titer is the quantity of influenza virus in a given volume within the samples obtained

from nasopharyngeal swabs. A lower value indicates lower viral load. Positive influenza virus titer was defined as virus titer not less than the lower limit of quantification among those assessed for virus titer on Days 2, 3, 4, 6, and 9. Participants positive for influenza virus titer at Baseline in the ITTI population were included in the analyses.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6, and 9 |           |

| End point values                  | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed       | 8  | 34   |  |  |
| Units: percentage of participants |  |  |  |  |
| number (confidence interval 95%)  |  |  |  |  |
| Day 2 (n=8, 34)                   | 0.0 (0.0 to 36.9)                                | 29.4 (15.1 to 47.5)  |  |  |
| Day 3 (n=6, 18)                   | 0.0 (0.0 to 45.9)                                | 22.2 (6.4 to 47.6)   |  |  |
| Day 4 (n=3, 23)                   | 0.0 (0.0 to 70.8)                                | 34.8 (16.4 to 57.3)  |  |  |
| Day 6 (n=8, 34)                   | 62.5 (24.5 to 91.5)                              | 58.8 (40.7 to 75.4)  |  |  |
| Day 9 (n=8, 34)                   | 12.5 (0.3 to 52.7)                               | 32.4 (17.4 to 50.5)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Positive For Influenza Virus by RT-PCR

|  |   |
|--|---|
| End point title  | Percentage of Participants Positive For Influenza Virus by RT-PCR |
| End point description:   |   |
| The percentage of participants positive for influenza virus by RT-PCR on Days 2, 3, 4, 6, and 9 and not less than the lower limit of detection among the participants with detectable amounts of virus RNA at Baseline was analysed. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Days 2, 3, 4 (one visit on either Day 3 or Day 4 was mandatory), 6, and 9  |   |

| End point values                  | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed       | 8  | 35   |  |  |
| Units: percentage of participants |  |  |  |  |
| number (confidence interval 95%)  |  |  |  |  |
| Day 2 (n=8, 35)                   | 100.0 (63.1 to 100.0)                            | 100.0 (90.0 to 100.0)                                      |  |  |
| Day 3 (n=6, 18)                   | 100.0 (54.1 to 100.0)                            | 94.4 (72.7 to 99.9)  |  |  |
| Day 4 (n=3, 24)                   | 100.0 (29.2 to 100.0)                            | 95.8 (78.9 to 99.9)  |  |  |
| Day 6 (n=8, 35)                   | 100.0 (63.1 to 100.0)                            | 97.1 (85.1 to 99.9)  |  |  |
| Day 9 (n=8, 35)                   | 75.0 (34.9 to 96.8)                              | 77.1 (59.9 to 89.6)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Curve (AUC) in Virus Titer

|  |   |
|--|---|
| End point title  | Area Under the Curve (AUC) in Virus Titer |
| End point description:<br>The AUC in virus titer was calculated using the trapezoidal method. Participants in the ITTI population were included in the analysis. |   |
| End point type   | Secondary                                 |
| End point timeframe:<br>Baseline up to Day 9   |   |

| End point values                     | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed          | 8  | 34   |  |  |
| Units: log[TCID/mL]*hours            |  |  |  |  |
| arithmetic mean (standard deviation) | -659.1 (± 190.5)                                 | -711.4 (± 357.0)   |  |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: Area Under the Curve (AUC) in the Amount of Virus RNA Determined by RT-PCR**

|   |  |
|---|--|
| End point title   | Area Under the Curve (AUC) in the Amount of Virus RNA Determined by RT-PCR |
| End point description:<br>The AUC in the amount of virus RNA determined by RT-PCR was calculated using the trapezoidal method. Participants in the ITTI population were included in the analysis. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline up to Day 9  |  |

| End point values                     | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed          | 8  | 35   |  |  |
| Units: log[vp/mL]*hours              |  |  |  |  |
| arithmetic mean (standard deviation) | -478.4 (± 165.0)                                 | -357.9 (± 226.7)   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to Cessation of Viral Shedding by Virus Titer**

|  |  |
|--|--|
| End point title  | Time to Cessation of Viral Shedding by Virus Titer |
| End point description:<br>Time to cessation of viral shedding by influenza virus titer was defined as the time from initiation of the study treatment until the virus titer was for the first time less than the lower limit of quantification. Participants in the ITTI population were included in the analysis. '0.9999' or '99999' means the limit of confidence interval was not calculated because there was no observation value corresponding the limit of confidence interval to ensure the 95% confidence coefficient. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Day 1 up to Day 9  |  |

| End point values                 | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed      | 8  | 34   |  |  |
| Units: hours                     |  |  |  |  |
| median (confidence interval 95%) | 24 (0.9999 to 99999)                             | 24 (0.9999 to 99999)                                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Cessation of Viral Shedding by RT-PCR

|                 |   |
|-----------------|---|
| End point title | Time to Cessation of Viral Shedding by RT-PCR |
|-----------------|---|

End point description:

Time to cessation of viral shedding by RT-PCR was defined as the time from initiation of the study treatment until the amount of virus RNA was for the first time less than the lower limit of detection. Participants in the ITTI population were included in the analysis. '0.9999' or '99999' means the limit of confidence interval was not calculated because there was no observation value corresponding the limit of confidence interval to ensure the 95% confidence coefficient.

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

End point timeframe:

Day 1 up to Day 9

| End point values                 | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed      | 8  | 35   |  |  |
| Units: hours                     |  |  |  |  |
| median (confidence interval 95%) | 300.0 (216.0 to 384.0)                           | 240.0 (216.0 to 99999)                                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Resolution of Fever

|                 |                             |
|-----------------|-----------------------------|
| End point title | Time to Resolution of Fever |
|-----------------|-----------------------------|

End point description:

Time to resolution of fever was defined as the time from the initiation of the study treatment until first experience of fever resolution. Resolution of fever was defined as the time point when the participant's self-measured axillary temperature had become less than 37.5°C and remained below 37.5°C for at least 12 hours. Participants in the ITTI population were included in the analysis.

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

End point timeframe:

Day 1 up to Day 14

| <b>End point values</b>          | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed      | 8  | 35   |  |  |
| Units: hours                     |  |  |  |  |
| median (confidence interval 95%) | 22.3 (12.1 to 32.8)                              | 22.0 (20.2 to 29.1)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Who Reported Normal Body Temperature

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Who Reported Normal Body Temperature |
|-----------------|---|

End point description:

Percentage of participants whose axillary temperature was below 37.5°C in the ITTI population at each time point were analysed.

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

End point timeframe:

Postdose: 12 hours (h), 24 h, 36 h, 48 h, 72 h, 76 h, 120 h, 144 h, 168 h, 192 h and 216 h (up to Day 10)

| <b>End point values</b>           | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed       | 8  | 35   |  |  |
| Units: percentage of participants |  |  |  |  |
| number (confidence interval 95%)  |  |  |  |  |
| 12 h postdose (n=8, 35)           | 50.0 (15.7 to 84.3)                              | 22.9 (10.4 to 40.1)  |  |  |
| 24 h postdose (n=8, 35)           | 87.5 (47.3 to 99.7)                              | 65.7 (47.8 to 80.9)  |  |  |
| 36 h postdose (n=8, 34)           | 87.5 (47.3 to 99.7)                              | 85.3 (68.9 to 95.0)  |  |  |
| 48 h postdose (n=8, 35)           | 100.0 (63.1 to 100.0)                            | 100.0 (90.0 to 100.0)                                      |  |  |
| 72 h postdose (n=8, 35)           | 100.0 (63.1 to 100.0)                            | 100.0 (90.0 to 100.0)                                      |  |  |
| 96 h postdose (n=8, 35)           | 87.5 (47.3 to 99.7)                              | 91.4 (76.9 to 98.2)  |  |  |

|                          |                     |                       |  |  |
|--------------------------|---------------------|-----------------------|--|--|
| 120 h postdose (n=8, 34) | 87.5 (47.3 to 99.7) | 94.1 (80.3 to 99.3)   |  |  |
| 144 h postdose (n=8, 35) | 62.5 (24.5 to 91.5) | 97.1 (85.1 to 99.9)   |  |  |
| 168 h postdose (n=8, 33) | 87.5 (47.3 to 99.7) | 97.0 (84.2 to 99.9)   |  |  |
| 192 h postdose (n=8, 34) | 75.0 (34.9 to 96.8) | 97.1 (84.7 to 99.9)   |  |  |
| 216 h postdose (n=8, 35) | 87.5 (47.3 to 99.7) | 100.0 (90.0 to 100.0) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Body Temperature at Each Timepoint

|   |                                    |
|---|------------------------------------|
| End point title   | Body Temperature at Each Timepoint |
| End point description:<br>Body temperature observed at each time point including Baseline was evaluated. Participants in the ITTI population were included in the analysis. |                                    |
| End point type  | Secondary                          |
| End point timeframe:<br>Baseline (0h, Day 1) and postdose 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 192 h, and 216 h (up to Day 10)                          |                                    |

| End point values                     | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed          | 8  | 35   |  |  |
| Units: degree Celsius (°C)           |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Baseline (n=8, 35)                   | 39.06 (± 0.77)                                   | 38.59 (± 0.60)   |  |  |
| 12 h postdose (n=8, 35)              | 37.78 (± 1.20)                                   | 38.16 (± 1.03)   |  |  |
| 24 h postdose (n=8, 35)              | 36.99 (± 0.55)                                   | 37.32 (± 0.93)   |  |  |
| 36 h postdose (n=8, 34)              | 36.86 (± 0.79)                                   | 36.85 (± 0.72)   |  |  |
| 48 h postdose (n=8, 35)              | 36.61 (± 0.22)                                   | 36.51 (± 0.42)   |  |  |
| 72 h postdose (n=8, 35)              | 36.64 (± 0.41)                                   | 36.40 (± 0.52)   |  |  |
| 96 h postdose (n=8, 35)              | 36.84 (± 0.53)                                   | 36.63 (± 0.66)   |  |  |
| 120 h postdose (n=8, 34)             | 36.98 (± 0.85)                                   | 36.56 (± 0.45)   |  |  |
| 144 h postdose (n=8, 35)             | 36.99 (± 0.70)                                   | 36.49 (± 0.42)   |  |  |
| 168 h postdose (n=8, 33)             | 36.96 (± 0.81)                                   | 36.47 (± 0.46)   |  |  |
| 192 h postdose (n=8, 34)             | 36.98 (± 0.43)                                   | 36.57 (± 0.38)   |  |  |
| 216 h postdose (n=8, 35)             | 36.86 (± 0.49)                                   | 36.49 (± 0.33)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Alleviation of Cough Symptoms

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Time to Alleviation of Cough Symptoms |
|-----------------|---------------------------------------|

End point description:

Time to alleviation of cough symptoms was defined as the time from initiation of the study treatment until the alleviation of cough symptoms. The alleviation of a symptom was defined as the time point when a symptom was assessed as 0=absent or 1=mild, for at least 21.5 hours (90% of 24 hours). Participants in the ITTI population, whose symptom scores at baseline were moderate or severe, were included in the analysis. '0.9999' or '99999' means the limit of confidence interval was not calculated because there was no observation value corresponding the limit of confidence interval to ensure the 95% confidence coefficient.

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

End point timeframe:

Day 1 up to Day 14

| End point values                 | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed      | 1  | 10   |  |  |
| Units: hours                     |  |  |  |  |
| median (confidence interval 95%) | 30.8 (0.9999 to 99999)                           | 3.8 (0.3 to 6.7)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Alleviation of Nasal Discharge/Nasal Congestion Symptoms

|                 |  |
|-----------------|--|
| End point title | Time to Alleviation of Nasal Discharge/Nasal Congestion Symptoms |
|-----------------|--|

End point description:

Time to alleviation of nasal discharge/ nasal congestion symptoms was defined as the time from initiation of the study treatment until the alleviation of nasal discharge/nasal congestion symptoms. The alleviation of a symptom was defined as the time point when a symptom was assessed as 0=absent or 1=mild, for at least 21.5 hours (90% of 24 hours). Participants in the ITTI population, whose symptom scores at baseline were moderate or severe, were included in the analysis.

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

End point timeframe:

Day 1 up to Day 14



| End point values                 | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed      | 3  | 16   |  |  |
| Units: hours                     |  |  |  |  |
| median (confidence interval 95%) | 30.8 (2.0 to 246.0)                              | 30.3 (3.7 to 68.0)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Resumption of Normal Activity

|   |                                       |
|---|---------------------------------------|
| End point title   | Time to Resumption of Normal Activity |
| End point description:  |                                       |
| Time to resumption of normal activity was defined as the time from initiation of the study treatment until the time when the participant's guardian assessed the participant's daily activities as 10. The participant's ability to perform daily activities was assessed by the participant's guardian on a scale of 0 (Unable to perform daily activities at all) to 10 (Able to perform all daily activities as usual). Participants in the ITTI population whose usual activity at Baseline was not 10 were included in the analyses. |                                       |
| End point type  | Secondary                             |
| End point timeframe:  |                                       |
| Day 1 up to Day 14  |                                       |

| End point values                 | Baloxavir Marboxil (Participants' weight <10 kg) | Baloxavir Marboxil (Participants' weight ≥10 kg to <20 kg) |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                                  | Reporting group  |  |  |
| Number of subjects analysed      | 8  | 35   |  |  |
| Units: hours                     |  |  |  |  |
| median (confidence interval 95%) | 78.9 (48.8 to 194.0)                             | 81.4 (55.3 to 105.2)                                       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Influenza-related Complications

|   |   |
|---|---|
| End point title   | Percentage of Participants With Influenza-related Complications |
| End point description:  |   |
| The percentage of participants who developed influenza-related complications such as death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, and otitis media after initiation of the study treatment was analysed. Participants in the ITTI population were included in the analysis. |   |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Day 1 up to Day 22   |           |

| End point values                   | Baloxavir Marboxil<br>(Participants' weight <10 kg) | Baloxavir Marboxil<br>(Participants' weight ≥10 kg to <20 kg) |  |  |
|------------------------------------|---|---|--|--|
| Subject group type                 | Reporting group                                     | Reporting group   |  |  |
| Number of subjects analysed        | 8   | 35  |  |  |
| Units: percentage of participants  |   |   |  |  |
| number (confidence interval 95%)   |   |   |  |  |
| Any Influenza-related Complication | 0 (0.0 to 36.9)                                     | 8.6 (1.8 to 23.1)   |  |  |
| Death                              | 0 (0.0 to 36.9)                                     | 0 (0.0 to 10.0)   |  |  |
| Hospitalization                    | 0 (0.0 to 36.9)                                     | 0 (0.0 to 10.0)   |  |  |
| Pneumonia                          | 0 (0.0 to 36.9)                                     | 0 (0.0 to 10.0)   |  |  |
| Bronchitis                         | 0 (0.0 to 36.9)                                     | 5.7 (0.7 to 19.2)   |  |  |
| Sinusitis                          | 0 (0.0 to 36.9)                                     | 0 (0.0 to 10.0)   |  |  |
| Otitis media                       | 0 (0.0 to 36.9)                                     | 2.9 (0.1 to 14.9)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Influenza-related Complications Particularly Seen in the Pediatric Population

|   |   |
|---|---|
| End point title   | Percentage of Participants With Influenza-related Complications Particularly Seen in the Pediatric Population |
| End point description:  |   |
| The percentage of participants who developed influenza-related complications particularly seen in the pediatric population such as influenza-associated encephalitis or encephalopathy, febrile seizures, and myositis was analysed. Participants in the ITTI population were included in the analysis. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Day 1 up to Day 22  |   |

| End point values                  | Baloxavir Marboxil<br>(Participants' weight <10 kg) | Baloxavir Marboxil<br>(Participants' weight ≥10 kg to <20 kg) |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Reporting group                                     | Reporting group   |  |  |
| Number of subjects analysed       | 8   | 35  |  |  |
| Units: percentage of participants |   |   |  |  |

|  |                 |                 |  |  |
|--|-----------------|-----------------|--|--|
| number (confidence interval 95%)                   |                 |                 |  |  |
| Any pediatric influenza- related complication      | 0 (0.0 to 36.9) | 0 (0.0 to 10.0) |  |  |
| Influenza associated encephalitis / encephalopathy | 0 (0.0 to 36.9) | 0 (0.0 to 10.0) |  |  |
| Febrile seizure                                    | 0 (0.0 to 36.9) | 0 (0.0 to 10.0) |  |  |
| Myositis   | 0 (0.0 to 36.9) | 0 (0.0 to 10.0) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration of S-033447

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Plasma Concentration of S-033447 |
|-----------------|----------------------------------|

End point description:

S-033447 or baloxavir is the active metabolite of baloxavir marboxil. The observed plasma concentration of baloxavir at 24 hours postdose (C24) was analysed. The PK concentration population consisted of all participants who received at least one dose of the study drug and had at least one evaluable PK assay result.

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

End point timeframe:

0.5 to 2 hours postdose at Day 1, Day 2, at one time point during the period from Day 6 to 22, and at Day 3 and/or Day 4 as needed

| End point values                                    | Baloxavir marboxil 2 mg/kg dose | Baloxavir marboxil 20 mg dose |  |  |
|---|---------------------------------|-------------------------------|--|--|
| Subject group type                                  | Subject analysis set            | Subject analysis set          |  |  |
| Number of subjects analysed                         | 7                               | 26                            |  |  |
| Units: nanogram/mL (ng/mL)                          |                                 |                               |  |  |
| geometric mean (geometric coefficient of variation) | 100 ( $\pm$ 43.4)               | 87.7 ( $\pm$ 44.0)            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Adverse Events (AEs)

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Adverse Events (AEs) |
|-----------------|--|

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant who was administered a pharmaceutical product (including an investigational drug) during the course of a clinical investigation. An AE could therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease that was temporally associated with the use of the investigational product, regardless of whether it was considered to be related to the investigational product or not. The safety population consisted of all participants who received at least one dose of the study drug and complied with GCP.

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

---

End point timeframe:

Day 1 up to Day 22

---

| <b>End point values</b>           | Baloxavir<br>Marboxil<br>(Participants'<br>weight <10 kg) | Baloxavir<br>Marboxil<br>(Participants'<br>weight ≥10 kg<br>to <20 kg) |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 9   | 36   |  |  |
| Units: percentage of participants |   |  |  |  |
| number (confidence interval 95%)  | 55.6 (21.2 to<br>86.3)                                    | 52.8 (35.5 to<br>69.6)   |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time of informed consent up to Day 22

Adverse event reporting additional description:

The safety population consisted of all participants who received at least one dose of the study drug and complied with GCP.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Baloxavir Marboxil (Participants' weight <10 kg) |
|-----------------------|--|

Reporting group description:

Participants who weighed <10 kg and were greater than or equal to ( $\geq$ ) 3 months of age received a single oral dose of 2 mg/kg baloxavir marboxil 2% granules on Day 1.

|                       |   |
|-----------------------|---|
| Reporting group title | Baloxavir Marboxil (Participants' weight $\geq$ 10 kg to < 20 kg) |
|-----------------------|---|

Reporting group description:

Participants who weighed between 10 to < 20 kg received 20 mg of baloxavir marboxil 2% granules as a single oral dose on Day 1 irrespective of their age.

| Serious adverse events                            | Baloxavir Marboxil<br>(Participants' weight<br><10 kg) | Baloxavir Marboxil<br>(Participants' weight<br>$\geq$ 10 kg to < 20 kg) |  |
|---|--|---|--|
| Total subjects affected by serious adverse events |  |   |  |
| subjects affected / exposed                       | 0 / 9 (0.00%)  | 0 / 36 (0.00%)  |  |
| number of deaths (all causes)                     | 0  | 0   |  |
| number of deaths resulting from adverse events    | 0  | 0   |  |

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

| Non-serious adverse events                            | Baloxavir Marboxil<br>(Participants' weight<br><10 kg) | Baloxavir Marboxil<br>(Participants' weight<br>$\geq$ 10 kg to < 20 kg) |  |
|---|--|---|--|
| Total subjects affected by non-serious adverse events |  |   |  |
| subjects affected / exposed                           | 5 / 9 (55.56%)   | 13 / 36 (36.11%)  |  |
| Gastrointestinal disorders                            |  |   |  |
| Diarrhoea   |  |   |  |
| subjects affected / exposed                           | 0 / 9 (0.00%)  | 5 / 36 (13.89%)   |  |
| occurrences (all)                                     | 0  | 5   |  |
| Respiratory, thoracic and mediastinal disorders       |  |   |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| Rhinorrhoea                            |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 0 / 36 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Upper respiratory tract inflammation   |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 0 / 36 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Skin and subcutaneous tissue disorders |                |                 |  |
| Skin fissures                          |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 0 / 36 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Infections and infestations            |                |                 |  |
| Bronchitis                             |                |                 |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  | 2 / 36 (5.56%)  |  |
| occurrences (all)                      | 0              | 2               |  |
| Influenza                              |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 0 / 36 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Nasopharyngitis                        |                |                 |  |
| subjects affected / exposed            | 2 / 9 (22.22%) | 6 / 36 (16.67%) |  |
| occurrences (all)                      | 2              | 6               |  |
| Enterocolitis viral                    |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 1 / 36 (2.78%)  |  |
| occurrences (all)                      | 1              | 1               |  |
| Rotavirus infection                    |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 0 / 36 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Upper respiratory tract infection      |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 2 / 36 (5.56%)  |  |
| occurrences (all)                      | 1              | 2               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 16 April 2019 | The original study protocol was amended as follows: 1) The planned duration of the study was increased by one year; 2) Shionogi & Co., Ltd. Was added to the Study Monitoring section. |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported