# Clinical trial results:
# Open-Label, Single-Arm, Multicenter, Long-Term Study to Evaluate Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Pediatric Subjects with Epilepsy

## Summary

| | |
|---|---|
| EudraCT number | 2011-000374-60 |
| Trial protocol | BE CZ ES PL Outside EU/EEA IE GB DE HU NL FR IT |
| Global end of trial date | 03 February 2022 |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 13 August 2022 |
| First version publication date | 13 August 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | N01266 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01364597 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | UCB Pharma SA |
| Sponsor organisation address | Allée de la Recherche 60, Brussels, Belgium, 1070 |
| Public contact | Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com |
| Scientific contact | Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000332-PIP01-08 |
| 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 | 09 March 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 February 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Document the long-term safety and tolerability of BRV

Protection of trial subjects:

During the conduct of the study all participants were closely monitored

Background therapy:

Background therapy as permitted in the protocol

Evidence for comparator:

N/A

| | |
|---|---|
| Actual start date of recruitment | 01 August 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Belgium: 12 |
| Country: Number of subjects enrolled | Czechia: 12 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Hungary: 30 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | Mexico: 61 |
| Country: Number of subjects enrolled | Poland: 56 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | United States: 55 |
| Worldwide total number of subjects | 257 |
| EEA total number of subjects | 141 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| wk | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 36 |
| Children (2-11 years) | 156 |
| Adolescents (12-17 years) | 65 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study started to enroll participants in August 2011 and concluded in February 2022.

### Pre-assignment

Screening details:

The Participant Flow refers to the enrolled set.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Age Cohort: ≥1 month to <2 years |

Arm description:

Participants from core study (LTFU [Long term follow-up] participants from N01263 [NCT00422422], EP0065 [NCT03405714] or N01349 [NCT03325439]) aged greater than or equal to (≥) 1 month to less than (<) 2 years entered evaluation period (EP) and received individualized Brivaracetam (BRV) dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 milligrams per kilogram per day (mg/kg/day) (0.5, 1, 2, and 2.5 mg/kg twice daily[bid]), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the investigational medicinal product (IMP) development was stopped by the Sponsor.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Brivaracetam |
| Investigational medicinal product code | UCB 34714 |
| Other name | |
| Pharmaceutical forms | Oral solution, Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received BRV at pre-specified dose and time points.

| | |
|---|---|
| **Arm title** | Age Cohort: ≥2 to <4 years |

Arm description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥2 Years to <4 years entered EP and received individualized BRV dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Brivaracetam |
| Investigational medicinal product code | UCB 34714 |
| Other name | |
| Pharmaceutical forms | Oral solution, Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received BRV at pre-specified dose and time points..

| **Arm title** | Age Cohort: ≥4 to <12 years |
|---|---|

Arm description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥4 Years to <12 years entered EP and received individualized BRV dose as they were receiving at completion of core study and Directly Enrolled (DE) participants in this study aged ≥4 years to <12 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Brivaracetam |
| Investigational medicinal product code | UCB 34714 |
| Other name | |
| Pharmaceutical forms | Oral solution, Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received BRV at pre-specified dose and time points.

| **Arm title** | Age Cohort: ≥12 to <17 years |
|---|---|

Arm description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥12 Years to <17 years entered EP and received individualized BRV dose as they were receiving at completion of core study and DE participants in this study aged ≥12 years to <17 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5 mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Brivaracetam |
| Investigational medicinal product code | UCB 34714 |
| Other name | |
| Pharmaceutical forms | Oral solution, Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received BRV at pre-specified dose and time points.

| **Number of subjects in period 1** | Age Cohort: ≥1 month to <2 years | Age Cohort: ≥2 to <4 years | Age Cohort: ≥4 to <12 years |
|---|---|---|---|
| Started | 36 | 15 | 141 |
| Directly Enrolled (DE) Participants | 0 [1] | 0 [2] | 85 |
| Long-term Follow-up (LTFU) Participants | 36 | 15 | 56 [3] |
| Completed | 18 | 4 | 65 |
| Not completed | 18 | 11 | 76 |
| Patient became seizure-free after surgery | - | - | 1 |
| Patient cured from Epilepsy | - | - | 1 |
| Seizures resolved | - | - | 1 |

| | | | |
|---|---|---|---|
| Cure | 1 | - | - |
| Lack of compliance | 1 | - | - |
| Lack of reliability from the subject's caregiver | 1 | - | - |
| Sponsor recommended discontinuation | - | - | - |
| Patient was moving | - | 1 | - |
| End of treatment epilepsy | 1 | - | - |
| 5 year without seizures. Treatment is finish | - | - | 1 |
| Consent withdrawn by subject | 4 | 1 | 18 |
| Adverse event, non-fatal | 4 | 5 | 16 |
| Dropout | - | - | 3 |
| Non compliance | 1 | - | 1 |
| Unknown | - | - | - |
| No Seizures | 1 | - | - |
| Investigator decision | - | - | 1 |
| Parents went abroad with the patient | - | - | 1 |
| Lost to follow-up | - | - | 5 |
| Unreliable subject | - | - | - |
| Lack of efficacy | 4 | 4 | 23 |
| Protocol deviation | - | - | 2 |
| BRV discontinued as no seizures during 2 years | - | - | 1 |
| BRV administration dropout | - | - | 1 |

| **Number of subjects in period 1** | Age Cohort: ≥12 to <17 years |
|---|---|
| Started | 65 |
| Directly Enrolled (DE) Participants | 35 [4] |
| Long-term Follow-up (LTFU) Participants | 30 [5] |
| Completed | 37 |
| Not completed | 28 |
| Patient became seizure-free after surgery | - |
| Patient cured from Epilepsy | - |
| Seizures resolved | - |
| Cure | - |
| Lack of compliance | - |
| Lack of reliability from the subject's caregiver | - |
| Sponsor recommended discontinuation | 1 |
| Patient was moving | - |
| End of treatment epilepsy | - |

| | |
|---|---|
| 5 year without seizures. Treatment is finish | - |
| Consent withdrawn by subject | 6 |
| Adverse event, non-fatal | 7 |
| Dropout | 1 |
| Non compliance | - |
| Unknown | 1 |
| No Seizures | - |
| Investigator decision | - |
| Parents went abroad with the patient | - |
| Lost to follow-up | 3 |
| Unreliable subject | 1 |
| Lack of efficacy | 8 |
| Protocol deviation | - |
| BRV discontinued as no seizures during 2 years | - |
| BRV administration dropout | - |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of participants at this arm is the sum of both the milestones 'Directly Enrolled (DE) Participants and Long-term Follow-up (LTFU) Participants' and equals to the started participants only. Hence the number of participants at each of intermediate milestones were lesser.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of participants at this arm is the sum of both the milestones 'Directly Enrolled (DE) Participants and Long-term Follow-up (LTFU) Participants' and equals to the started participants only. Hence the number of participants at each of intermediate milestones were lesser.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of participants at this arm is the sum of both the milestones 'Directly Enrolled (DE) Participants and Long-term Follow-up (LTFU) Participants' and equals to the started participants only. Hence the number of participants at each of intermediate milestones were lesser.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of participants at this arm is the sum of both the milestones 'Directly Enrolled (DE) Participants and Long-term Follow-up (LTFU) Participants' and equals to the started participants only. Hence the number of participants at each of intermediate milestones were lesser.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of participants at this arm is the sum of both the milestones 'Directly Enrolled (DE) Participants and Long-term Follow-up (LTFU) Participants' and equals to the started participants only. Hence the number of participants at each of intermediate milestones were lesser.

## Baseline characteristics

### Reporting groups

| Reporting group title | Age Cohort: ≥1 month to <2 years |
|---|---|

Reporting group description:

Participants from core study (LTFU [Long term follow-up] participants from N01263 [NCT00422422], EP0065 [NCT03405714] or N01349 [NCT03325439]) aged greater than or equal to (≥) 1 month to less than (<) 2 years entered evaluation period (EP) and received individualized Brivaracetam (BRV) dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 milligrams per kilogram per day (mg/kg/day) (0.5, 1, 2, and 2.5 mg/kg twice daily[bid]), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the investigational medicinal product (IMP) development was stopped by the Sponsor.

| Reporting group title | Age Cohort: ≥2 to <4 years |
|---|---|

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥2 Years to <4 years entered EP and received individualized BRV dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| Reporting group title | Age Cohort: ≥4 to <12 years |
|---|---|

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥4 Years to <12 years entered EP and received individualized BRV dose as they were receiving at completion of core study and Directly Enrolled (DE) participants in this study aged ≥4 years to <12 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| Reporting group title | Age Cohort: ≥12 to <17 years |
|---|---|

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥12 Years to <17 years entered EP and received individualized BRV dose as they were receiving at completion of core study and DE participants in this study aged ≥12 years to <17 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5 mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| Reporting group values | Age Cohort: ≥1 month to <2 years | Age Cohort: ≥2 to <4 years | Age Cohort: ≥4 to <12 years |
|---|---|---|---|
| Number of subjects | 36 | 15 | 141 |
| Age Categorical<br>Units: Participants | | | |
| Infants and toddlers (28 days-23 months) | 36 | 0 | 0 |
| Children (2-11 years) | 0 | 15 | 141 |
| Adolescents (12-17 years) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 1.122 | 2.761 | 7.699 |
| standard deviation | ± 0.504 | ± 0.582 | ± 2.394 |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 19 | 5 | 62 |
| Male | 17 | 10 | 79 |

| **Reporting group values** | Age Cohort: ≥12 to <17 years | Total | |
|---|---|---|---|
| Number of subjects | 65 | 257 | |
| Age Categorical | | | |
| Units: Participants | | | |
| Infants and toddlers (28 days-23 months) | 0 | 36 | |
| Children (2-11 years) | 0 | 156 | |
| Adolescents (12-17 years) | 65 | 65 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 13.824 | | |
| standard deviation | ± 1.274 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 30 | 116 | |
| Male | 35 | 141 | |

## End points

### End points reporting groups

| Reporting group title | Age Cohort: ≥1 month to <2 years |
|---|---|

Reporting group description:

Participants from core study (LTFU [Long term follow-up] participants from N01263 [NCT00422422], EP0065 [NCT03405714] or N01349 [NCT03325439]) aged greater than or equal to (≥) 1 month to less than (<) 2 years entered evaluation period (EP) and received individualized Brivaracetam (BRV) dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 milligrams per kilogram per day (mg/kg/day) (0.5, 1, 2, and 2.5 mg/kg twice daily[bid]), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the investigational medicinal product (IMP) development was stopped by the Sponsor.

| Reporting group title | Age Cohort: ≥2 to <4 years |
|---|---|

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥2 Years to <4 years entered EP and received individualized BRV dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| Reporting group title | Age Cohort: ≥4 to <12 years |
|---|---|

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥4 Years to <12 years entered EP and received individualized BRV dose as they were receiving at completion of core study and Directly Enrolled (DE) participants in this study aged ≥4 years to <12 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| Reporting group title | Age Cohort: ≥12 to <17 years |
|---|---|

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥12 Years to <17 years entered EP and received individualized BRV dose as they were receiving at completion of core study and DE participants in this study aged ≥12 years to <17 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5 mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| Subject analysis set title | Brivaracetam (BRV): Participants ≥ 2 years to <17 years |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants from core study (LTFU participants from N01263 [NCT00422422]) aged ≥2 Years to <17 years entered EP and received individualized BRV dose as they were receiving at completion of core study and DE participants in this study aged ≥4 years to <17 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5 mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| Subject analysis set title | Brivaracetam (BRV): Participants ≥1 month to <2 years |
|---|---|

| Subject analysis set type | Full analysis |
|---|---|

Subject analysis set description:

Participants from core study (LTFU [Long term follow-up] participants from N01263 [NCT00422422] or N01349 [NCT03325439]) aged ≥1 month to <2 years entered EP and received individualized BRV dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5 mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

## Primary: Percentage of participants with treatment-emergent adverse events (TEAEs) during the study

| End point title | Percentage of participants with treatment-emergent adverse events (TEAEs) during the study[1] |
|---|---|

End point description:

TEAEs are defined as AEs that had onset on or after the day of first BRV dose. The Safety Set (SS) consisted of all enrolled participants who took at least 1 dose of study medication.

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

End point timeframe:

From Baseline to end of study (up to 10 years)

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 formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

| **End point values** | Age Cohort: ≥1 month to <2 years | Age Cohort: ≥2 to <4 years | Age Cohort: ≥4 to <12 years | Age Cohort: ≥12 to <17 years |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 36 | 15 | 141 | 65 |
| Units: percentage of participants | | | | |
| number (not applicable) | 94.4 | 93.3 | 93.6 | 92.3 |

### Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of participants with treatment-emergent serious adverse events (SAEs) during the study

| End point title | Percentage of participants with treatment-emergent serious adverse events (SAEs) during the study[2] |
|---|---|

End point description:

TEAEs: AEs that had onset on or after day of first BRV dose. SAE: an event that met 1 or more of below criteria: a) Death, b) Life-threatening, (excluding reaction that might caused death had it occurred in more severe form.) c) Significant or persistent disability/incapacity, d) Congenital anomaly/birth defect (including that occurring in fetus), e) Important medical event that, based upon appropriate medical judgment, may have jeopardized participant and required medical or surgical intervention to prevent 1 of other outcomes listed in definition of serious, (Important medical events may have included allergic bronchospasm requiring intensive treatment in an emergency room [ER] or at home) f) Initial inpatient hospitalization or prolongation of hospitalization. (Participant admitted to hospital, even if released on same day, met criteria for initial inpatient hospitalization). Safety Set (SS) consisted of all enrolled participants who took at least 1 dose of study medication.

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

End point timeframe:

From Baseline to end of study (up to 10 years)

Notes:

[2] - 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 formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

| **End point values** | Age Cohort: ≥1 month to <2 years | Age Cohort: ≥2 to <4 years | Age Cohort: ≥4 to <12 years | Age Cohort: ≥12 to <17 years |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 36 | 15 | 141 | 65 |
| Units: percentage of participants | | | | |
| number (not applicable) | 38.9 | 53.3 | 29.8 | 29.2 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change in 28-days adjusted partial-onset-seizure (POS) frequency for participants aged ≥2 years from Baseline to the end of the evaluation period in participants with POS only (based on daily record card [DRC])

| End point title | Absolute change in 28-days adjusted partial-onset-seizure (POS) frequency for participants aged ≥2 years from Baseline to the end of the evaluation period in participants with POS only (based on daily record card [DRC]) |
|---|---|

End point description:

Absolute change in seizure frequency per 28 days based on DRC data, is calculated as baseline seizure frequency per 28 days minus post-Baseline seizure frequency per 28 days. The 28-day adjusted seizure frequency was calculated by dividing number of POS by number of days for which the diary was completed and multiplying resulting value by 28. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM and it differs in both absolute and percent change because the percent change cannot be calculated for participants with 0 baseline ADF. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded. This OM was analyzed in participants ≥2 years (per DRC data) only.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous study N01263 [NCT00422422]; and DE participants: Baseline of current study) to the end of the evaluation period (up to 10 years)

| **End point values** | Brivaracetam (BRV): Participants ≥ 2 years to <17 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 134 | | | |
| Units: seizure frequency per 28-days | | | | |
| arithmetic mean (standard deviation) | -37.48 (± 628.34) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percent change in 28-days adjusted partial-onset-seizure (POS) frequency for participants aged ≥2 years from Baseline to the end of the evaluation period in participants with POS only (based on DRC data)

| End point title | Percent change in 28-days adjusted partial-onset-seizure (POS) frequency for participants aged ≥2 years from Baseline to the end of the evaluation period in participants with POS only (based on DRC data) |
|---|---|

End point description:

Percent change is calculated as absolute change in seizure frequency per 28 days divided by baseline seizure frequency per 28 days multiplied to 100. The 28 day adjusted seizure frequency was calculated by dividing the number of partial seizures by the number of days for which the diary was completed, and multiplying the resulting value by 28. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM and it differs in both absolute and percent change because the percent change cannot be calculated for participants with 0 baseline ADF. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded. This OM was analyzed in participants ≥2 years (per DRC data) only.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous study N01263 [NCT00422422]; and DE participants: Baseline of current study) to the end of the evaluation period (up to 10 years)

| **End point values** | Brivaracetam (BRV): Participants ≥ 2 years to <17 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 105 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 26.57 (± 123.06) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: 50% responder rate for participants ≥2 years of age for total seizures (all types) (based on DRC data)

| End point title | 50% responder rate for participants ≥2 years of age for total seizures (all types) (based on DRC data) |
|---|---|

End point description:

A responder is defined as a participant with a ≥ 50% reduction in seizure frequency from the baseline period of the previous study for LTFU participants or during this study for DE participants. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded. This OM was analyzed in participants ≥2 years (per DRC data) only.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous study N01263 [NCT00422422]; and DE participants: Baseline of current study) to the end of the evaluation period (up to 10 years)

| **End point values** | Brivaracetam (BRV): Participants ≥ 2 years to <17 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 167 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 50.9 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change in average daily frequency (ADF) of partial-onset-seizures (POS) in participants <2 years of age with POS only (based on EEG data)

| End point title | Absolute change in average daily frequency (ADF) of partial-onset-seizures (POS) in participants <2 years of age with POS only (based on EEG data) |
|---|---|

End point description:

Absolute change in ADF is calculated as the baseline ADF minus post-baseline ADF. ADF is calculated as (number of seizures from central reader divided by stop date and time of EEG minus start date and time of EEG) multiplied to 60, multiplied to 24. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM and it differs in both absolute and percent change because the percent change cannot be calculated for participants with 0 baseline ADF. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded. This OM was analyzed in participants <2 years (per EEG data) only.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous studies N01263 [NCT00422422], or N01349 [NCT03325439]) to the end of the evaluation period (up to 10 years)

| End point values | Brivaracetam (BRV): Participants ≥1 month to <2 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: seizures per day | | | | |
| arithmetic mean (standard deviation) | 2.56 (± 4.44) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent change in average daily frequency (ADF) of partial-onset-seizures (POS) in participants <2 years of age with POS only (based on EEG data)

| End point title | Percent change in average daily frequency (ADF) of partial-onset-seizures (POS) in participants <2 years of age with POS only (based on EEG data) |
|---|---|

End point description:

Percent change in average daily frequency (ADF) is calculated as absolute change in ADF divided by baseline ADF multiplied to 100. ADF is calculated as (number of seizures from central reader divided by stop date and time of EEG minus start date and time of EEG) multiplied to 60, multiplied to 24. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM and it differs in both absolute and percent change because the percent change cannot be calculated for participants with 0 baseline ADF. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded. This OM was analyzed in participants <2 years (per EEG data) only.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous studies N01263 [NCT00422422], or N01349 [NCT03325439]) to the end of the evaluation period (up to 10 years)

| End point values | Brivaracetam (BRV): Participants ≥1 month to <2 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 3 | | | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | 98.72 (± 2.22) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: 50% responder rate for participants <2 years of age for total seizures

## (all types) (based on EEG data)

| | |
|---|---|
| End point title | 50% responder rate for participants <2 years of age for total seizures (all types) (based on EEG data) |

End point description:

A responder is defined as a participant with a ≥ 50% reduction in seizure frequency from the baseline period of the previous study for LTFU participants. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded. This OM was analyzed in participants <2 years (per EEG data) only.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous studies N01263 [NCT00422422], or N01349 [NCT03325439]) to the end of the evaluation period (up to 10 years)

| **End point values** | Brivaracetam (BRV): Participants ≥1 month to <2 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 8 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 75.0 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change in average daily frequency of POS in participants <2 years of age with Typical Absence Seizures (based on EEG data)

| | |
|---|---|
| End point title | Absolute change in average daily frequency of POS in participants <2 years of age with Typical Absence Seizures (based on EEG data) |

End point description:

Absolute change in ADF is calculated as the baseline ADF minus post-baseline ADF. ADF is calculated as (number of seizures from central reader divided by stop date and time of EEG minus start date and time of EEG) multiplied to 60, multiplied to 24. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous studies N01263 [NCT00422422], or N01349 [NCT03325439]) to the end of the evaluation period (up to 10 years)

| End point values | Brivaracetam (BRV): Participants ≥1 month to <2 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 2[3] | | | |
| Units: Seizure per day | | | | |
| arithmetic mean (standard deviation) | 99999 (± 99999) | | | |

Notes:

[3] - 99999 indicates that typical absence seizures data was not collected and analyzed.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percent change in average daily frequency of POS in participants <2 years of age with Typical Absence Seizures (based on EEG data)

| End point title | Percent change in average daily frequency of POS in participants <2 years of age with Typical Absence Seizures (based on EEG data) |
|---|---|

End point description:

Percent change in average daily frequency (ADF) is calculated as absolute change in ADF divided by baseline ADF multiplied to 100. ADF is calculated as (number of seizures from central reader divided by stop date and time of EEG minus start date and time of EEG) multiplied to 60, multiplied to 24. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous studies N01263 [NCT00422422] or N01349 [NCT03325439]) to the end of the evaluation period (up to 10 years)

| End point values | Brivaracetam (BRV): Participants ≥1 month to <2 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 2[4] | | | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | 99999 (± 99999) | | | |

Notes:

[4] - 99999 indicates that typical absence seizures data was not collected and analyzed.

### Statistical analyses

No statistical analyses for this end point

## Secondary: 50% responder rate for total seizures (all types) in participants <2 years of age with Typical Absence Seizures (based on EEG data)

| End point title | 50% responder rate for total seizures (all types) in participants <2 years of age with Typical Absence Seizures (based on EEG data) |
|---|---|

End point description:

A responder is defined as a participant with a ≥ 50% reduction in seizure frequency from the baseline period of the previous study for LTFU participants. Full Analysis Set: all enrolled participants who took at least 1 dose of study drug in this Long-term study and had at least 1 completed post-baseline DRC or EEG. Overall number of participants analyzed included all participants evaluable for this OM. Per planned analysis, participants were grouped as per cohort linked to source (DRC for ≥2 years /EEG for <2 years) from which their seizure data is recorded.

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

End point timeframe:

From Baseline (LTFU participants: Baseline of previous studies N01263 [NCT00422422] or N01349 [NCT03325439]) to the end of the evaluation period (up to 10 years)

| **End point values** | Brivaracetam (BRV): Participants ≥1 month to <2 years | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 2[5] | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 99999 | | | |

Notes:

[5] - 99999 indicates that typical absence seizures data was not collected and analyzed.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline to end of Study (up to 10 years)

Adverse event reporting additional description:

TEAEs are defined as AEs that had onset on or after the day of first BRV dose.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Age Cohort: ≥1 month to <2 years |

Reporting group description:

Participants from core study (LTFU [Long term follow-up] participants from N01263 [NCT00422422], EP0065 [NCT03405714] or N01349 [NCT03325439]) aged greater than or equal to (≥) 1 month to less than (<) 2 years entered evaluation period (EP) and received individualized Brivaracetam (BRV) dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 milligram per kilogram per day (mg/kg/day) (0.5, 1, 2, and 2.5 mg/kg twice daily[bid]), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the investigational medicinal product (IMP) development was stopped by the Sponsor.

| | |
|---|---|
| Reporting group title | Age Cohort: ≥4 to <12 years |

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥4 Years to <12 years entered EP and received individualized BRV dose as they were receiving at completion of core study and Directly Enrolled (DE) participants in this study aged ≥4 years to <12 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| | |
|---|---|
| Reporting group title | Age Cohort: ≥12 to <17 years |

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥12 Years to <17 years entered EP and received individualized BRV dose as they were receiving at completion of core study and DE participants in this study aged ≥12 years to <17 years of age received BRV dose based on tolerability confirmed during screening period. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5 mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5 mg/kg bid), not to exceed a dose of 200 mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| | |
|---|---|
| Reporting group title | Age Cohort: ≥2 to <4 years |

Reporting group description:

Participants from core study (LTFU participants from N01263 [NCT00422422] and EP0065 [NCT03405714]) aged ≥2 Years to <4 years entered EP and received individualized BRV dose as they were receiving at completion of core study. For all participants, the approximate BRV doses to be administered are 1 to 5 mg/kg/day (0.5, 1, 2, and 2.5mg/kg bid), tablet or oral solution and can be up-titrated or down-titrated based on investigator decision with a maximum allowable BRV dose of 5.0 mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day. The duration of the treatment for each participant was planned to be at least 3 years, until BRV received approval for pediatric participants in their age range or until the IMP development was stopped by the Sponsor.

| **Serious adverse events** | Age Cohort: ≥1 month to <2 years | Age Cohort: ≥4 to <12 years | Age Cohort: ≥12 to <17 years |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 36 (38.89%) | 42 / 141 (29.79%) | 19 / 65 (29.23%) |
| number of deaths (all causes) | 2 | 2 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Astrocytoma, low grade | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Haemodynamic instability | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Brain operation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrostomy | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteotomy | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 3 / 141 (2.13%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device extrusion | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Testicular torsion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 141 (1.42%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Apnoea | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspiration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Asthmatic crisis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Affect lability | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aggression | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anger | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Homicidal ideation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood bicarbonate decreased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laparoscopy | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Greenstick fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iatrogenic injury | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Cryptorchism | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Developmental hip dysplasia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Spina bifida | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phimosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 12 / 141 (8.51%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 20 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 7 / 141 (4.96%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 12 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 4 / 141 (2.84%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 141 (1.42%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 141 (2.13%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complex partial seizures | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Partial seizures with secondary | | | |

| | | | |
|---|---|---|---|
| generalisation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Simple partial seizures | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ataxia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Petit mal epilepsy | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural hygroma | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 141 (2.13%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Faecaloma | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth deposit | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Volvulus | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Skin reaction | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal tubular acidosis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Juvenile idiopathic arthritis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scoliosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 4 / 141 (2.84%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 11 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 141 (2.13%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 141 (1.42%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 141 (1.42%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Corona virus infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Epididymitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurocysticercosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital cellulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 141 (2.13%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperammonaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Underweight | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Age Cohort: ≥2 to <4 years | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 15 (53.33%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Astrocytoma, low grade | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemodynamic instability | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Brain operation | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrostomy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteotomy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypothermia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inflammation | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device extrusion | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Testicular torsion | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Respiratory distress | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute respiratory failure | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Apnoea | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Aspiration | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Asthmatic crisis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic respiratory failure | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoxia | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sleep apnoea syndrome | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |
| Suicidal ideation | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Affect lability | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aggression | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anger | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Depression | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Homicidal ideation | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Suicide attempt | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood bicarbonate decreased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laparoscopy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Greenstick fracture | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Iatrogenic injury | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|---|---|---|---|
| Toxicity to various agents | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Procedural pain | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper limb fracture | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Congenital, familial and genetic disorders | | | | |
| Cryptorchism | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Developmental hip dysplasia | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spina bifida | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Phimosis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Seizure | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

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|---|---|---|---|
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Complex partial seizures | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Partial seizures with secondary generalisation | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Simple partial seizures | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hydrocephalus | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Loss of consciousness | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Petit mal epilepsy | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subdural hygroma | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| **Blood and lymphatic system disorders** | | | | |
| Anaemia | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune thrombocytopenic purpura | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutropenia | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thrombocytopenia | | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth deposit | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Toothache | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Volvulus | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin and subcutaneous tissue disorders | | | | |
| Skin reaction | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal and urinary disorders | | | | |
| Chronic kidney disease | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hydronephrosis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal tubular acidosis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal and connective tissue disorders | | | | |
| Juvenile idiopathic arthritis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

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|---|---|---|---|---|
| Scoliosis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchitis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral infection | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Appendicitis | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clostridium difficile colitis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Corona virus infection | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epididymitis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neurocysticercosis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Periorbital cellulitis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory syncytial virus infection | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory tract infection | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tuberculosis | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral upper respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |
| Dehydration | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Decreased appetite | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyperammonaemia | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoglycaemia | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyponatraemia | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Underweight | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Age Cohort: ≥1 month to <2 years | Age Cohort: ≥4 to <12 years | Age Cohort: ≥12 to <17 years |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 36 (83.33%) | 120 / 141 (85.11%) | 51 / 65 (78.46%) |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Device occlusion | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 5 / 141 (3.55%) | 6 / 65 (9.23%) |
| occurrences (all) | 1 | 6 | 10 |
| Gait disturbance | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 15 / 36 (41.67%) | 37 / 141 (26.24%) | 7 / 65 (10.77%) |
| occurrences (all) | 84 | 63 | 9 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 141 (1.42%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | 19 / 141 (13.48%) | 5 / 65 (7.69%) |
| occurrences (all) | 8 | 26 | 8 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 6 / 141 (4.26%) | 5 / 65 (7.69%) |
| occurrences (all) | 0 | 7 | 7 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 10 / 141 (7.09%) | 0 / 65 (0.00%) |
| occurrences (all) | 5 | 11 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 6 / 141 (4.26%) | 2 / 65 (3.08%) |
| occurrences (all) | 2 | 8 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 3 / 141 (2.13%) | 1 / 65 (1.54%) |
| occurrences (all) | 18 | 4 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 141 (1.42%) | 1 / 65 (1.54%) |
| occurrences (all) | 1 | 3 | 1 |
| Asthma | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Adenoidal hypertrophy | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Asthmatic crisis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Aspiration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 14 / 141 (9.93%) | 1 / 65 (1.54%) |
| occurrences (all) | 0 | 18 | 1 |
| Irritability | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 14 / 141 (9.93%) | 4 / 65 (6.15%) |
| occurrences (all) | 8 | 15 | 4 |
| Insomnia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 11 / 141 (7.80%) | 0 / 65 (0.00%) |
| occurrences (all) | 3 | 14 | 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 5 / 141 (3.55%) | 4 / 65 (6.15%) |
| occurrences (all) | 0 | 5 | 4 |
| Anxiety | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 4 / 141 (2.84%) | 2 / 65 (3.08%) |
| occurrences (all) | 2 | 5 | 2 |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hallucination, visual | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 10 / 141 (7.09%) | 2 / 65 (3.08%) |
| occurrences (all) | 3 | 13 | 2 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 3 / 141 (2.13%) | 1 / 65 (1.54%) |
| occurrences (all) | 2 | 3 | 1 |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Laceration | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 4 / 141 (2.84%) | 6 / 65 (9.23%) |
| occurrences (all) | 0 | 6 | 10 |
| Fall | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 6 / 141 (4.26%) | 8 / 65 (12.31%) |
| occurrences (all) | 1 | 8 | 11 |
| Congenital, familial and genetic disorders | | | |
| Arnold-Chiari malformation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 21 / 141 (14.89%) | 16 / 65 (24.62%) |
| occurrences (all) | 0 | 58 | 75 |
| Seizure | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 17 / 141 (12.06%) | 11 / 65 (16.92%) |
| occurrences (all) | 9 | 29 | 17 |
| Somnolence | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 15 / 141 (10.64%) | 5 / 65 (7.69%) |
| occurrences (all) | 4 | 25 | 5 |
| Complex partial seizures | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 3 / 141 (2.13%) | 1 / 65 (1.54%) |
| occurrences (all) | 3 | 3 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 7 / 141 (4.96%) | 8 / 65 (12.31%) |
| occurrences (all) | 0 | 13 | 16 |
| Partial seizures with secondary generalisation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 141 (1.42%) | 1 / 65 (1.54%) |
| occurrences (all) | 0 | 2 | 1 |
| Ataxia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Hypotonia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle spasticity | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 5 | 0 | 2 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 6 / 141 (4.26%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Eye disorders | | | |
| Strabismus | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypermetropia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 11 / 36 (30.56%) | 34 / 141 (24.11%) | 4 / 65 (6.15%) |
| occurrences (all) | 19 | 61 | 4 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 36 (19.44%) | 21 / 141 (14.89%) | 8 / 65 (12.31%) |
| occurrences (all) | 16 | 33 | 8 |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 12 / 141 (8.51%) | 3 / 65 (4.62%) |
| occurrences (all) | 4 | 20 | 9 |
| Constipation | | | |
| subjects affected / exposed | 7 / 36 (19.44%) | 10 / 141 (7.09%) | 2 / 65 (3.08%) |
| occurrences (all) | 11 | 12 | 4 |

| | | | |
|---|---|---|---|
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 9 / 141 (6.38%) | 8 / 65 (12.31%) |
| occurrences (all) | 1 | 10 | 10 |
| Nausea | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 5 / 141 (3.55%) | 3 / 65 (4.62%) |
| occurrences (all) | 4 | 5 | 3 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 4 / 141 (2.84%) | 0 / 65 (0.00%) |
| occurrences (all) | 6 | 5 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 5 / 141 (3.55%) | 1 / 65 (1.54%) |
| occurrences (all) | 21 | 5 | 1 |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Enteritis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 2 | 0 | 1 |
| Teething | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hiatus hernia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 10 / 141 (7.09%) | 1 / 65 (1.54%) |
| occurrences (all) | 2 | 15 | 1 |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 141 (0.71%) | 1 / 65 (1.54%) |
| occurrences (all) | 1 | 1 | 1 |
| Dermatitis diaper | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hair growth abnormal | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 141 (2.13%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 10 | 0 |
| Neurogenic bladder | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 6 / 141 (4.26%) | 1 / 65 (1.54%) |
| occurrences (all) | 0 | 6 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Facial asymmetry | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Pharyngitis | | | |
| subjects affected / exposed | 10 / 36 (27.78%) | 39 / 141 (27.66%) | 8 / 65 (12.31%) |
| occurrences (all) | 21 | 60 | 8 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 10 / 36 (27.78%) | 23 / 141 (16.31%) | 8 / 65 (12.31%) |
| occurrences (all) | 19 | 38 | 12 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 21 / 141 (14.89%) | 10 / 65 (15.38%) |
| occurrences (all) | 34 | 64 | 20 |
| Gastroenteritis | | | |
| subjects affected / exposed | 8 / 36 (22.22%) | 16 / 141 (11.35%) | 5 / 65 (7.69%) |
| occurrences (all) | 14 | 30 | 6 |

| | | | |
|---|---|---|---|
| Influenza | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 16 / 141 (11.35%) | 6 / 65 (9.23%) |
| occurrences (all) | 7 | 18 | 6 |
| Bronchitis | | | |
| subjects affected / exposed | 7 / 36 (19.44%) | 16 / 141 (11.35%) | 1 / 65 (1.54%) |
| occurrences (all) | 18 | 29 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 16 / 141 (11.35%) | 2 / 65 (3.08%) |
| occurrences (all) | 8 | 47 | 6 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 11 / 36 (30.56%) | 44 / 141 (31.21%) | 16 / 65 (24.62%) |
| occurrences (all) | 44 | 114 | 41 |
| Ear infection | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 10 / 141 (7.09%) | 4 / 65 (6.15%) |
| occurrences (all) | 3 | 18 | 4 |
| Tonsillitis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 13 / 141 (9.22%) | 2 / 65 (3.08%) |
| occurrences (all) | 2 | 21 | 3 |
| Otitis media | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 10 / 141 (7.09%) | 0 / 65 (0.00%) |
| occurrences (all) | 13 | 24 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 6 / 141 (4.26%) | 4 / 65 (6.15%) |
| occurrences (all) | 3 | 11 | 5 |
| Varicella | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 9 / 141 (6.38%) | 0 / 65 (0.00%) |
| occurrences (all) | 4 | 10 | 0 |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 8 / 141 (5.67%) | 2 / 65 (3.08%) |
| occurrences (all) | 3 | 9 | 3 |
| Viral infection | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 7 / 141 (4.96%) | 1 / 65 (1.54%) |
| occurrences (all) | 6 | 19 | 2 |
| Conjunctivitis | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 4 / 141 (2.84%) | 1 / 65 (1.54%) |
| occurrences (all) | 6 | 5 | 1 |

| | | | |
|---|---|---|---|
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 6 / 141 (4.26%) | 1 / 65 (1.54%) |
| occurrences (all) | 3 | 11 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 7 / 141 (4.96%) | 1 / 65 (1.54%) |
| occurrences (all) | 3 | 12 | 1 |
| Otitis media acute | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 4 / 141 (2.84%) | 2 / 65 (3.08%) |
| occurrences (all) | 4 | 5 | 2 |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 4 / 141 (2.84%) | 1 / 65 (1.54%) |
| occurrences (all) | 3 | 4 | 1 |
| Viral pharyngitis | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 3 / 141 (2.13%) | 1 / 65 (1.54%) |
| occurrences (all) | 3 | 3 | 1 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 141 (2.13%) | 1 / 65 (1.54%) |
| occurrences (all) | 0 | 3 | 1 |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 141 (2.13%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Lice infestation | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 141 (0.71%) | 1 / 65 (1.54%) |
| occurrences (all) | 1 | 1 | 1 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 141 (0.71%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Gastroenteritis rotavirus | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral fungal infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 9 / 141 (6.38%) | 0 / 65 (0.00%) |
| occurrences (all) | 4 | 11 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | 16 / 141 (11.35%) | 7 / 65 (10.77%) |
| occurrences (all) | 7 | 18 | 8 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 141 (0.71%) | 1 / 65 (1.54%) |
| occurrences (all) | 2 | 1 | 1 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 141 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 2 | 0 | 1 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Underweight | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 141 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Age Cohort: ≥2 to <4 years | | |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 13 / 15 (86.67%) | | |
| Vascular disorders<br>Hypotension<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| General disorders and administration site conditions<br>Device occlusion<br>subjects affected / exposed<br>occurrences (all)<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br>Gait disturbance<br>subjects affected / exposed<br>occurrences (all)<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)<br>Influenza like illness<br>subjects affected / exposed<br>occurrences (all)<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0<br>2 / 15 (13.33%)<br>3<br>0 / 15 (0.00%)<br>0<br>4 / 15 (26.67%)<br>11<br>1 / 15 (6.67%)<br>1<br>1 / 15 (6.67%)<br>1 | | |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 15 (13.33%)<br>4<br>2 / 15 (13.33%)<br>2 | | |

| | | | |
|---|---|---|---|
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Asthma<br>subjects affected / exposed<br>occurrences (all) | 2 / 15 (13.33%)<br>2 | | |
| Adenoidal hypertrophy<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Asthmatic crisis<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Bronchospasm<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Aspiration<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Psychiatric disorders<br>Aggression<br>subjects affected / exposed<br>occurrences (all) | 2 / 15 (13.33%)<br>2 | | |
| Irritability<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Insomnia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 15 (20.00%) | | |
| occurrences (all) | 3 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hallucination, visual | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Congenital, familial and genetic disorders | | | |
| Arnold-Chiari malformation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|---|---|
| Cardiac disorders | | | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | |
| occurrences (all) | 2 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Complex partial seizures | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Partial seizures with secondary generalisation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Ataxia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hypotonia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 2 | | |
| Muscle spasticity | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---|---|---|
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Strabismus | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hypermetropia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | | |
| occurrences (all) | 6 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Toothache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>3 | | |
| Enteritis<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Teething<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Hiatus hernia<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Dermatitis diaper<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1 | | |
| Alopecia<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | | |
| Hair growth abnormal<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>2 | | |
| Renal and urinary disorders<br>Urinary incontinence | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all)<br><br>Neurogenic bladder<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>1<br><br><br>1 / 15 (6.67%)<br>1 | | |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 15 (6.67%)<br>1 | | |
| Musculoskeletal and connective tissue disorders<br>Facial asymmetry<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 15 (6.67%)<br>1 | | |
| Infections and infestations<br>Pharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Pharyngotonsillitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza<br>subjects affected / exposed<br>occurrences (all)<br><br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis | <br><br>2 / 15 (13.33%)<br>9<br><br><br>5 / 15 (33.33%)<br>15<br><br><br>0 / 15 (0.00%)<br>0<br><br><br>0 / 15 (0.00%)<br>0<br><br><br>2 / 15 (13.33%)<br>2<br><br><br>3 / 15 (20.00%)<br>11<br><br><br>2 / 15 (13.33%)<br>3 | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 4 / 15 (26.67%) | | | |
| occurrences (all) | 6 | | | |
| Ear infection | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences (all) | 2 | | | |
| Tonsillitis | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences (all) | 1 | | | |
| Otitis media | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences (all) | 1 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | | | |
| occurrences (all) | 3 | | | |
| Varicella | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Pharyngitis streptococcal | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Viral infection | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences (all) | 1 | | | |
| Conjunctivitis | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences (all) | 2 | | | |
| Respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | | |
| occurrences (all) | 37 | | | |
| Sinusitis | | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | | | |
| occurrences (all) | 2 | | | |
| Otitis media acute | | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Pharyngitis bacterial | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Viral pharyngitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 2 | | |
| Lice infestation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Gastroenteritis rotavirus | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Oral fungal infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | | |
| occurrences (all) | 16 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |
| Underweight | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | | |
| occurrences (all) | 1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 26 August 2011 | Protocol Amendment 1 was dated 26 Aug 2011 and the rationale was to include the Bayley Scales of Infant Development™, Second Edition (BSID-II™) in order to assess the cognitive development of children <18 months at Baseline in response to the European Pediatric Committee (PDCO) request. Withdrawal criteria were extended to include the consequences of any findings related to the results of liver function tests. Procedures for reporting serious adverse events (SAEs) were updated to implement the Food and Drug Administration (FDA) Final Rule requirements. The Columbia-Suicide Severity Rating Scale (C-SSRS) was added to address the request of the FDA that prospective assessments for suicidality are to be included in clinical studies involving all drugs for neurological indications. Some operational updates were also considered. Administrative changes included the update of the SAE reporting and CRO contact details. A few editorial changes were not listed in the specific changes section. |
| 09 December 2011 | Protocol Amendment 2 was dated 09 Dec 2011 and the rationale was to replace the children's version of the C-SSRS with the version validated in multiple languages for study participants ≥6 years of age. The BSID-II score was replaced by the Bayley-III scales in order to apply the most recent version of the cognition scale. In addition, it was clarified that the cognition scale was to be used only in English-speaking countries, since it is validated only in English. The efficacy variables for study participants <2 years of age and for study participants with absence seizures were updated and amended in response to the PDCO requirements. It was clarified that safety laboratory assessments included hepatic monitoring. Furthermore, an error in the mathematical symbols used for the presentation of the age limits of the EEG assessments was corrected, and the SAE reporting details were updated. Administrative changes included the update of the Clinical Project Manager contact details and typographical corrections. A few editorial changes were additionally listed in the specific changes section. |
| 26 September 2012 | Protocol Amendment 3 was dated 26 Sep 2012 and the rationale was to allow study participants who had not previously participated in a clinical study of BRV to enroll directly into N01266 (ie, DE study participants). Up to 100 study participants who were ≥4 years to <17 years of age with POS and met entry criteria were planned for direct enrollment, and overall planned enrollment increased from up to 500 study participants to up to 600 study participants. The purpose of direct enrollment was to obtain sufficient long-term safety exposure data in study participants ≥4 years to <17 years of age. With this amendment, the BRIEF-P/BRIEF and PedsQL were added to the assessments for study participants ≥2 years of age. These assessments were added to provide an additional means of assessing the effect of BRV on cognition and quality of life, respectively, in pediatric study participants ≥2 years of age. |
| 10 December 2013 | Protocol Amendment 4 was dated 10 Dec 2013. As a result of the PK analyses performed on the plasma samples collected at N01263 completion, the plasma concentrations approximating the concentrations for adults receiving BRV 200mg/day were not achieved by the dosing scheme initially included in N01266. Thus, N01266 was amended to allow a maximum BRV dose of 5.0mg/kg/day (not to exceed a total dose of BRV 200mg/day) for all study participants, irrespective of age. The number of DE study participants was increased from "up to" to "at least" 100 study participants with the planned total enrollment of approximately 600 study participants to allow flexibility in the number of study participants reaching 1 year of exposure. Demographics and childbearing potential were captured at the EV for LTFU study participants, instead of using the data recorded from either the Baseline or the FV of the core study. The handling of protocol deviations was made consistent with the updated statistical analysis process. In addition, it was clarified that although no formal interim analysis was planned, the data may be reported prior to the completion of this study to support ongoing data cleaning, annual reports, regulatory submissions, and publications. |

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|---|---|
| 14 December 2016 | Protocol Amendment 5 was dated 14 Dec 2016. The rationale for this amendment was to: • Add an updated list of Anticipated SAEs. • Add a section on adverse events (AEs) of special interest in accordance with the Sponsor template requirement. • Update the schema for down-titration to align with N01263 and provide uniformity across the BRV pediatric development program. • Remove the requirement that study participants <7 years of age receive oral solution and, as appropriate, study participants ≥7 years of age receive tablets in recognition of individual study participant preferences to allow study participants additional flexibility in treatment options. • Provide EV information specific to study participants who enroll from core studies under development. • Provide additional clarity regarding enrolled study participants who participate in EP0065 and then resume participation in N01266. Protocol Amendment 3 had allowed for study participants to participate in what was called a "substudy." • Clarify the requirement that study participants ≥2 years of age with typical absence seizures have at least a 24-hour EEG, instead of a 1-hour EEG. • Eliminate the EEG at the 3-month visit (Visit 4) and the requirement for study participants to have EEGs after they reach 2 years of age (exception: study participants with typical absence seizures), and allow the EDV EEGs to be done at the Investigator's discretion. This change was made due to the limited clinical utility of these assessments and to unburden the Investigator, study participant, and study participant's caregiver/family. • Replace serum pregnancy tests with urine pregnancy tests and include urine pregnancy tests at all MEVs. |
| 14 December 2016 | Protocol Amendment 5 Continued: • Update according to the current Sponsor protocol template. This included: − The addition of text regarding potential drug-induced liver injury (PDILI); these changes were strictly template-driven. They did not reflect a change in the liver safety signal for BRV and were included only for alignment with updated standard Sponsor text across programs. − The streamlining of the Introduction with reference to the availability of additional information in the Investigator's Brochure. • Update of the Introduction text to include more current literature references and to include information about the marketing authorization of BRV. • Revise the duration of the study for an individual study participant from approximately 3 years to at least 3 years, with the addition of the possibility of study participants entering a managed access program, if available. • Remove the BRV 1.0mg/mL oral solution from the description of the IMP as the BRV 10mg/mL oral solution is adequate for dosing. |
| 06 March 2018 | Protocol Amendment 6 was dated 06 Mar 2018 and the rationale was to: • Update language for Bayley-III scales to include countries where a validated translation was available. • Remove reference to central reading of EEGs to provide flexibility. • Remove EEG assessment for the EV (all study participants). • Update inclusion criteria to align language enhancements provided in country-specific amendment (Czech Republic) (ie, diagnosis of epilepsy and contraceptive language). • Update language in regards to partner pregnancy to align with Sponsor's Standard Operating Procedure (SOP) and protocol templates. • Add blood draw volumes for study participants <2 years of age. • Clarify PedsQL age range (≥2 years of age) as this assessment is not used in children <2 years of age. • Clarify for all other EEGs (ie, Visit 5 and yearly thereafter) the duration in study participants >2 years of age. |
| 18 April 2019 | Protocol Amendment 7 was dated 18 Apr 2019. This amendment was implemented to update the pregnancy text to clarify that the Pregnancy Report and Outcome form is to be completed for all pregnancies. |
| 25 June 2020 | Protocol Amendment 8 was dated 25 Jun 2020. This amendment was implemented to: • Reorganize the study variables into primary, secondary, other variables in compliance with reporting agencies. This change does not affect the type or processing of data collected and reported in the study report, as they will be assessed as initially planned. • Allow study participants to transition to another BRV study. • Add information regarding down-titration for study participants who do not continue BRV treatment after completing the study. • Clarify the text describing the maximum dose of BRV. • Modify the study conduct to ensure the safety of participants in response to the COVID-19 pandemic. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported