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 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		

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			

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				

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			

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			

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
Asthma			
subjects affected / exposed	3 / 36 (8.33%)	0 / 141 (0.00%)	0 / 65 (0.00%)
occurrences (all)	5	0	0
Nasal congestion			
subjects affected / exposed	1 / 36 (2.78%)	2 / 141 (1.42%)	1 / 65 (1.54%)
occurrences (all)	1	3	1
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			
Irritability			
subjects affected / exposed	5 / 36 (13.89%)	14 / 141 (9.93%)	4 / 65 (6.15%)
occurrences (all)	8	15	4
Aggression			
subjects affected / exposed	0 / 36 (0.00%)	14 / 141 (9.93%)	1 / 65 (1.54%)
occurrences (all)	0	18	1
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
Dizziness			
subjects affected / exposed	0 / 36 (0.00%)	7 / 141 (4.96%)	8 / 65 (12.31%)
occurrences (all)	0	13	16
Complex partial seizures			
subjects affected / exposed	3 / 36 (8.33%)	3 / 141 (2.13%)	1 / 65 (1.54%)
occurrences (all)	3	3	1
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			

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

Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Epistaxis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Asthma subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Nasal congestion subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Adenoidal hypertrophy subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Asthmatic crisis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Bronchospasm subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Aspiration subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Psychiatric disorders Irritability subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Aggression subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
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		
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Complex partial seizures			
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 occurrences (all)	1 / 15 (6.67%) 1		
Abdominal distension subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Dysphagia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 3		
Enteritis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Teething subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hiatus hernia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Dermatitis diaper subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Alopecia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hair growth abnormal subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Renal and urinary disorders Urinary incontinence			

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

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