Clinical trial results:
An open-label, multicenter, follow-up trial to evaluate long-term safety and efficacy of brivaracetam used as adjunctive treatment at a flexible dose up to a maximum of 200 mg/day in subjects aged 16 years or older suffering from Epilepsy

Summary

EudraCT number	2004-002140-10
Trial protocol	BE CZ DE GB FI ES IT SE HU AT
Global end of trial date	28 May 2019

Results information

Result version number	v1
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	N01125

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00175916
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma S.A.
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, B-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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2019
Global end of trial reached?	Yes
Global end of trial date	28 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses with a maximum of 200mg/day in subjects suffering from epilepsy

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:

Not applicable

Actual start date of recruitment	08 September 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 24
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Czech Republic: 52
Country: Number of subjects enrolled	Finland: 30
Country: Number of subjects enrolled	France: 99
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Poland: 141
Country: Number of subjects enrolled	Russian Federation: 47
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Korea, Republic of: 79
Country: Number of subjects enrolled	Spain: 23

Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	Tunisia: 10
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	853
EEA total number of subjects	591

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	7
Adults (18-64 years)	834
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in September 2005 and concluded in May 2019.

Pre-assignment

Screening details:

Participants Flow refers to the Safety Set (SS).

Period 1

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

Arms

Arm title	Brivaracetam

Arm description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down- Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period.

Arm type	Experimental
Investigational medicinal product name	BRIVARACETAM
Investigational medicinal product code	BRV
Other name	UCB34714
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg and 25 mg tablets. Flexible dosing up to 200 mg/day, twice daily.

Number of subjects in period 1	Brivaracetam
Started	853
Completed	234
Not completed	619
Adverse event, serious fatal	19
Moved overseas	1
Lack of compliance	8
Sponsor decision	17
Patient's request	2
Vigabatrin intake	1
Site was closed	9
Consent withdrawn by subject	1
Suicidal behaviour	1
Loss of job and economic burden	1

Adverse event, non-fatal	81
Subject Choice	98
Pregnancy	1
Patient went to prison	1
Treating physiciant's choice	1
Lost to follow-up	17
Seizure - free	4
Lack of efficacy	354
Patient cannot record seizures	1
Administrative reason	1

Baseline characteristics

Reporting groups	
Reporting group title	Brivaracetam

Reporting group description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down- Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period.

Reporting group values	Brivaracetam	Total	
Number of subjects	853	853	
Age categorical Units: Subjects			
<=18 years	14	14	
Between 18 and 65 years	827	827	
>=65 years	12	12	
Age continuous Units: years			
arithmetic mean	37.5		
standard deviation	± 11.8	-	
Gender categorical Units: Subjects			
Male	435	435	
Female	418	418	

End points

End points reporting groups

Reporting group title	Brivaracetam

Reporting group description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down- Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period.

Subject analysis set title	Brivaracetam (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down- Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period. Participants formed the Safety Set (SS).

Subject analysis set title	Brivaracetam (POS Efficacy)
Subject analysis set type	Per protocol

Subject analysis set description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down- Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period. Participants formed the Partial Onset Seizure Efficacy Set (POS Efficacy).

Primary: Percentage of participants with at least one treatment-emergent adverse event (TEAE)

End point title	Percentage of participants with at least one treatment-emergent adverse event (TEAE)[1]

End point description:

Treatment-emergent adverse events (TEAEs) were defined as those events which started on or after the date of first dose of investigational medicinal product (IMP), or events in which severity worsened on or after the date of first dose of study medication. The event does not necessarily have a causal relationship with that treatment or usage.

End point type	Primary

End point timeframe:

From entry Visit 1 through End of Treatment (up to a maximum of 13 and a half years - 162 months)

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 as descriptive statistics only.

End point values	Brivaracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	853			
Units: Percentage of participants				
number (not applicable)	84.4			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants who withdrew due to an adverse event (AE)

End point title	Percentage of participants who withdrew due to an adverse event (AE)[2]

End point description:

An AE is any untoward medical occurrence in a participant or trial participant that is administered a drug or biologic (medicinal product) or that is using a medical device. The event does not necessarily have a causal relationship with that treatment or usage.

End point type	Primary

End point timeframe:

From entry Visit 1 through End of Treatment (up to a maximum of 13 and a half years - 162 months)

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 as descriptive statistics only.

End point values	Brivaracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	853			
Units: Percentage of participants				
number (not applicable)	11.6			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with at least one serious adverse event (SAE)

End point title	Percentage of participants with at least one serious adverse event (SAE)[3]

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening
- Requires in patient hospitalization or prolongation of existing hospitalization
- Is a congenital anomaly or birth defect
- Is an infection that requires treatment parenteral antibiotics
- Other important medical events which based on medical or scientific judgement may jeopardize the patients or may require medical or surgical intervention to prevent any of the above.

End point type	Primary

End point timeframe:

From entry Visit 1 through End of Treatment (up to a maximum of 13 and a half years - 162 months)

Notes:

[3] - 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 as descriptive statistics only.

End point values	Brivaracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	853			
Units: Percentage of participants				
number (not applicable)	29.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial onset seizure (POS) (type I) frequency per 28 days during the Evaluation Period

End point title	Partial onset seizure (POS) (type I) frequency per 28 days during the Evaluation Period

End point description:

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.

End point type	Secondary

End point timeframe:

From Baseline of the previous study to the Evaluation Period (up to a maximum of 13 and a half years - 162 months)

End point values	Brivaracetam (POS Efficacy)			
Subject group type	Subject analysis set			
Number of subjects analysed	729			
Units: Seizures per 28 days				
median (inter-quartile range (Q1-Q3))				
Baseline	8.4 (5.0 to 16.1)			
On Treatment	4.9 (2.1 to 10.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Partial Onset Seizure (POS) (Type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period

End point title	Percent change in Partial Onset Seizure (POS) (Type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period

End point description:

The percent change from the previous study baselines, in Partial Onset Seizure (POS) (Type I) frequency per 28 days is defined as:
(the value at the previous study baselines) minus (the value at each time-points during the evaluation period) divided by the value at the previous study baselines.

End point type	Secondary

End point timeframe:

From Baseline of the previous study to the Evaluation Period (up to a maximum of 13 and a half years - 162 months)

End point values	Brivaracetam (POS Efficacy)			
Subject group type	Subject analysis set			
Number of subjects analysed	729			
Units: Percent change				
median (inter-quartile range (Q1-Q3))	43.1 (9.9 to 71.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Responder rate in POS (type I) frequency over the Evaluation Period

End point title	Responder rate in POS (type I) frequency over the Evaluation Period

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.

End point type	Secondary

End point timeframe:

From Baseline of the previous study to the Evaluation Period (up to a maximum of 13 and a half years - 162 months)

End point values	Brivaracetam (POS Efficacy)			
Subject group type	Subject analysis set			
Number of subjects analysed	729			
Units: Percentage of participants				
number (not applicable)	43.6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the Entry Visit, at Month 0 and up to the Last Visit at Year 11.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Brivaracetam (SS)

Reporting group description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down- Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period. Participants formed the Safety Set (SS).

Serious adverse events	Brivaracetam (SS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	248 / 853 (29.07%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	4 / 853 (0.47%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Astrocytoma			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast cancer metastatic				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic lymphocytic leukaemia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon cancer				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ependymoma				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibroma				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mesothelioma				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mixed oligo-astrocytoma				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm prostate				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian neoplasm				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer recurrent				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Testicular neoplasm				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Circulatory collapse				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haematoma				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Artificial urinary sphincter implant				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cataract operation				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystectomy				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder operation				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hernia repair				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radiotherapy				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shoulder operation				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillectomy				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheostomy				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urethral repair				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Pregnancy				
subjects affected / exposed	4 / 853 (0.47%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Abortion				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abortion complete				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foetal growth restriction				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pregnancy on contraceptive				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pregnancy on oral contraceptive				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	5 / 853 (0.59%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	4 / 853 (0.47%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	1 / 4			
Fatigue				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Unevaluable event				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device failure				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drowning				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gait disturbance				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic cyst				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Implant site haematoma				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Irritability				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immunodeficiency				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Reproductive system and breast disorders				
Ovarian cyst				
subjects affected / exposed	4 / 853 (0.47%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Menometrorrhagia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Menorrhagia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Menstrual disorder				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fluid collection				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postmenopausal haemorrhage				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine polyp				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asthma				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia aspiration				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vocal cord polyp				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Suicidal ideation				
subjects affected / exposed	7 / 853 (0.82%)			
occurrences causally related to treatment / all	5 / 7			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	6 / 853 (0.70%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 1			
Psychotic disorder				
subjects affected / exposed	3 / 853 (0.35%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Aggression				
subjects affected / exposed	3 / 853 (0.35%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	1 / 1			
Suicide attempt				
subjects affected / exposed	3 / 853 (0.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Abnormal behaviour				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Acute psychosis				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Anxiety				

subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Depressed mood				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dysthymic disorder				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Suicidal behaviour				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Agitation				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Conversion disorder				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Decreased interest				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Delirium tremens				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dissociative disorder				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Insomnia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mental disorder				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Panic attack				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Panic disorder				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polydipsia psychogenic				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Restlessness				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholelithiasis				

subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Biliary colic			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Investigation			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid function test abnormal			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	10 / 853 (1.17%)		
occurrences causally related to treatment / all	3 / 11		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	5 / 853 (0.59%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		

Contusion			
subjects affected / exposed	5 / 853 (0.59%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	4 / 853 (0.47%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	4 / 853 (0.47%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Femur fracture			
subjects affected / exposed	4 / 853 (0.47%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	4 / 853 (0.47%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Extradural haematoma			
subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Hand fracture			

subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Meniscus lesion			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Poisoning			

subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Skull fracture				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skull fractured base				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Accident				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Accidental exposure				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bursa injury				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cartilage injury				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest injury				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Craniocerebral injury				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Face injury				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Forearm fracture				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incorrect dose administered				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle rupture				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Near drowning				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Open wound				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative hernia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Spinal column injury				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic haematoma				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				

subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Baltic myoclonic epilepsy			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorder			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Coronary artery disease				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Convulsion				
subjects affected / exposed	36 / 853 (4.22%)			
occurrences causally related to treatment / all	10 / 54			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	11 / 853 (1.29%)			
occurrences causally related to treatment / all	2 / 13			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	10 / 853 (1.17%)			
occurrences causally related to treatment / all	2 / 12			
deaths causally related to treatment / all	0 / 1			
Grand mal convulsion				
subjects affected / exposed	8 / 853 (0.94%)			
occurrences causally related to treatment / all	4 / 12			
deaths causally related to treatment / all	0 / 1			
Myoclonus				
subjects affected / exposed	9 / 853 (1.06%)			
occurrences causally related to treatment / all	1 / 20			
deaths causally related to treatment / all	0 / 0			
Myoclonic epilepsy				

subjects affected / exposed	4 / 853 (0.47%)		
occurrences causally related to treatment / all	3 / 11		
deaths causally related to treatment / all	0 / 0		
Seizure cluster			
subjects affected / exposed	4 / 853 (0.47%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Complex partial seizures			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Partial seizures with secondary generalisation			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Altered state of consciousness			

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ataxia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Aura				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Balance disorder				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brachial plexopathy				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haematoma				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Coordination abnormal				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hemiplegia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychomotor hyperactivity				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Radiculitis lumbosacral				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Status migrainosus				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxic encephalopathy				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia macrocytic				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	4 / 853 (0.47%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Hypoacusis				

subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tinnitus			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertigo positional			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Corneal erosion			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Opsoclonus myoclonus			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visual impairment			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	5 / 853 (0.59%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 853 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Nausea			

subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis ulcerative				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric polyps				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Proctocolitis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatomyositis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hidradenitis				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Swelling face				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	3 / 853 (0.35%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Bladder pain				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Calculus bladder				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Calculus ureteric				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Calculus urinary				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysuria				

subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract disorder			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroiditis			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	7 / 853 (0.82%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	4 / 853 (0.47%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Intervertebral disc disorder			
subjects affected / exposed	2 / 853 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoroacetabular impingement			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Groin pain			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemarthrosis			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic lupus erythematosus				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	9 / 853 (1.06%)			
occurrences causally related to treatment / all	2 / 14			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	6 / 853 (0.70%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Upper respiratory tract infection				
subjects affected / exposed	4 / 853 (0.47%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	4 / 853 (0.47%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				

subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Skin infection				
subjects affected / exposed	2 / 853 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear infection				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incision site infection				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected bites				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia mycoplasmal				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vestibular neuronitis				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyponatraemia				
subjects affected / exposed	6 / 853 (0.70%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 853 (0.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				

subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Histamine intolerance			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 853 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Brivaracetam (SS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	569 / 853 (66.71%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Somnolence			
subjects affected / exposed	73 / 853 (8.56%)		
occurrences (all)	104		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	47 / 853 (5.51%)		
occurrences (all)	62		
Contusion			
subjects affected / exposed	45 / 853 (5.28%)		
occurrences (all)	68		
Vascular disorders			
Hypertension			
subjects affected / exposed	43 / 853 (5.04%)		
occurrences (all)	53		
Nervous system disorders			
Headache			

subjects affected / exposed	186 / 853 (21.81%)		
occurrences (all)	419		
Dizziness			
subjects affected / exposed	123 / 853 (14.42%)		
occurrences (all)	191		
Convulsion			
subjects affected / exposed	112 / 853 (13.13%)		
occurrences (all)	158		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	84 / 853 (9.85%)		
occurrences (all)	106		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	58 / 853 (6.80%)		
occurrences (all)	114		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	78 / 853 (9.14%)		
occurrences (all)	112		
Nausea			
subjects affected / exposed	55 / 853 (6.45%)		
occurrences (all)	78		
Vomiting			
subjects affected / exposed	53 / 853 (6.21%)		
occurrences (all)	89		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	71 / 853 (8.32%)		
occurrences (all)	95		
Depression			
subjects affected / exposed	65 / 853 (7.62%)		
occurrences (all)	80		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	77 / 853 (9.03%)		
occurrences (all)	99		
Arthralgia			
subjects affected / exposed	52 / 853 (6.10%)		
occurrences (all)	73		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	157 / 853 (18.41%)		
occurrences (all)	332		
Urinary tract infection			
subjects affected / exposed	75 / 853 (8.79%)		
occurrences (all)	125		
Influenza			
subjects affected / exposed	66 / 853 (7.74%)		
occurrences (all)	104		
Upper respiratory tract infection			
subjects affected / exposed	50 / 853 (5.86%)		
occurrences (all)	127		
Bronchitis			
subjects affected / exposed	47 / 853 (5.51%)		
occurrences (all)	68		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2005	Limitation of the maximal dose to 150 mg/day.
07 April 2006	Issued to fulfill requirements by the German Central Ethics Committee; however, the amendment was not country-specific, but applied to all study sites. Updates made to several sections of the protocol to clarify wording used and study procedures.
05 May 2006	Allowed the inclusion of study participants with genetically ascertained Unverricht-Lundborg Disease (ULD) who might have benefited from BRV as adjunctive treatment in a previous confirmatory study. Furthermore, specific sections related to treatment of study participants with ULD were added.
02 February 2007	• Updated the exclusion criteria (suppression of exclusion criteria linked to laboratory values on the basis of favorable Phase 2 data). • Updated BRV background information. • Expanded study by including study participants with POS and study participants with generalized epilepsy coming from BRV Phase 3 studies (N01252, N01254, and possibly N01253), as well as collection and analysis of their data. • Allowed the Investigator to adjust dosage of concomitant antiepileptic drug(s) (AED(s)). Withdrawal of concomitant AED(s) resulting in monotherapy with BRV was permitted. • Addition of long-term exploratory data, namely Hospital Anxiety and Depression Scale (HADS) for study participants coming from N01114, and HADS, EuroQol 5 Dimensions (EQ-5D) and socioprofessional data for study participants coming from N01252, N01254, and possibly N01253.
01 June 2007	Issued as a follow up to the Food and Drug Administration (FDA) feedback received on N01253, where the FDA specifically requested to add an additional down-titration step for study participants with POS taking BRV 50 mg/day or more—a last down-titration step at 20 mg/day for 1 week was recommended prior to the Study Post-Treatment Period.
01 June 2007	Update to Amendment 6; was issued as a follow up to the FDA feedback received on N01253 requesting that an additional down-titration step for study participants taking 50 mg/day or more be added. The amendment also did the following: • Harmonized the duration of N01125 with the BRV program for study participants with ULD. The program was to continue until an FDA approval for the indication of ULD was obtained, or until the development program for the indication was stopped by the sponsor. • Clarified the use of 10 and 50 mg oral tablets. • Modified the instructions on the study drug storage conditions. • Clarified study procedures.
26 October 2007	Update to Amendment 6 and Amendment 9; was issued to remove some restrictions imposed on study participants switching from their previous study to this long-term follow-up (LTFU) study. The amendment also did the following: • Clarified the inclusion criterion for birth control methods. • Clarified end of study conditions. • Modified study drug discontinuation procedures as described in Amendment 9.

04 April 2008	Amendment to Amendment 8. Updates made to several sections of the protocol to clarify study procedures and FDA warning for suicidality and suicidal thoughts for study participants taking AEDs. The amendment also did the following: • Clarified the study objective. • Clarified the inclusion criterion regarding contraceptive methods (female study participants with childbearing potential were allowed to enter the study if their sexual inactivity was judged to be reliable by the Investigator). • Specified that doses beyond 40 mg/day increments were only to be made using 10 or 25 mg tablets.
03 January 2011	Amendments reduced the number of assessments for the study participants in view of the quantity of data already collected, the good safety profile of the drug, the extension of the study and the focus on safety aspects. Amendment 24 is the amendment to Protocol Amendment 18 for study participants with POS/PGS. Amendment 25 is the amendment to Protocol Amendment 10 for study participants with ULD. Integrated Amendment 25 combined Amendment 24 and 25, as well as specified the following: • Study participants were not allowed to convert to BRV monotherapy. • The maximum allowable daily dose of BRV was increased from 150 mg/day to 200 mg/day to align with more recent LTFU studies. The maximum dose was chosen following consultation with regulatory authorities. • Removed 2.5 mg BRV tablets and all capsules. • Introduced the Partner Pregnancy Consent form.
25 October 2011	• Addition of the suicidality assessment and the requirements per the Food and Drug Administration (FDA) Final Rule and update of the study variables. • Updated procedures for reporting serious adverse events (SAEs). • Specified that BRV packaging was updated (80 tablet containers no longer supplied).
12 March 2015	• Updated contact information. • Addition of procedures for study participants enrolling from another study (N01315). • Deletion of outdated exposure numbers. • Addition of language allowing all participants to enroll into a managed access program (or similar). • Updated protocol adherence language. • Added Sponsor declaration page.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported