



## Clinical trial results:

### **Efficacy and safety of Eslicarbazepine Acetate (BIA 2 093) as adjunctive therapy for refractory partial seizures in children: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial**

#### **Summary**

EudraCT number	2007-001887-55
Trial protocol	PT HU CZ AT FR SK IT ES GB DE
Global end of trial date	

#### **Results information**

Result version number	v1
This version publication date	08 April 2016
First version publication date	07 August 2015

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	BIA-2093-305
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00988156
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	BIAL - Portela & CA, S.A.
Sponsor organisation address	À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457
Public contact	André Garrido, BIAL - Portela & Cª, S.A., 00351 229866100, andre.garrido@bial.com
Scientific contact	José Francisco Rocha, BIAL - Portela & Cª, S.A., 00351 229866100, jose.rocha@bial.com

Notes:

##### **Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000696-PIP02-10
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	Interim
Date of interim/final analysis	03 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2012
Global end of trial reached?	No

Notes:

## General information about the trial

Main objective of the trial:

Primary: The primary objective of the study is to assess the efficacy of Eslicarbazepine Acetate as adjunctive therapy in children and adolescents with refractory partial seizures.

The primary analysis variables for the assessment of efficacy will be:

1. the responder rate, defined as the proportion of patients with at least a 50% decrease in the standardised seizure frequency
2. the relative reduction in the standardised seizure frequency

Protection of trial subjects:

The trial was conducted in accordance with the International Conference on Harmonisation (ICH), Good Clinical Practices (GCP), Good Manufacturing Practice (GMP), the ethical principles of the Declaration of Helsinki and with applicable local regulations. This trial was conducted by qualified persons who respected the rights and welfare of the subjects and after the review and approval of the protocol by an EC. Adverse events were collected throughout the trial and subject was followed by 4 weeks after last treatment visit in the double blind phase and 4 weeks after last treatment visit in the open blind phase.

Background therapy:

Concomitant AED therapy (1 or 2 AEDs).

Evidence for comparator: -

Actual start date of recruitment	07 December 2007
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: 3
Country: Number of subjects enrolled	Bosnia and Herzegovina: 4
Country: Number of subjects enrolled	Czech Republic: 31
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Hungary: 38
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Philippines: 17
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 20

Country: Number of subjects enrolled	Serbia: 37
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Ukraine: 63
Worldwide total number of subjects	304
EEA total number of subjects	160

Notes:

<b>Subjects enrolled per age group</b>	
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)	207
Adolescents (12-17 years)	96
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The patient recruitment period will last approximately 66 months. The actual overall study duration or patient recruitment period may vary.

### Pre-assignment

Screening details:

Subjects who met all the inclusion criteria and none of the exclusion criteria. 370 subjects were enrolled to the trial and 66 subjects were screening failures including 5 IMP recalls and 41 randomised subjects were IMP recall.

### Pre-assignment period milestones

Number of subjects started	370 <sup>[1]</sup>
Number of subjects completed	263

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Ineligibility: 44
Reason: Number of subjects	Treatment with > 2 conc. AEDs at the same time: 5
Reason: Number of subjects	IMP recall: 46
Reason: Number of subjects	Sponsor decision: 6

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported to have started the pre-assignment period is the number of enrolled subjects; The worldwide number is number of treated subjects.

### Period 1

Period 1 title	PART I: DOUBLE-BLIND TREATMENT
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Part I - Placebo
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Arm description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL placebo oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg placebo tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

**Dosage and administration details:**

The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily.

**Titration period:**

First 2 weeks: 10 mg/kg/day;

Next 4 weeks: 20 mg/kg/day (maximum 1200 mg/day) (if no AE occurred), 10 mg/kg/day (if AE occurred);

**Maintenance period:**

Next 12 weeks: 20 mg/kg/day (if acceptable tolerability), 30 mg/kg/day (maximum 1200 mg/day) (if unsatisfactory response), 10 mg/kg/day (if during the previous period will receive this dose)

**Tapering-off \follow-up period:**

After the 12-week maintenance period, the study treatment will be tapered off in 10 mg/kg/day steps every 2 weeks, followed by a 4 week observational follow-up period.

<b>Arm title</b>	Part I - ESL
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**Arm description:**

Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

Arm type	Active comparator
Investigational medicinal product name	Eslicarbazepine acetate
Investigational medicinal product code	BIA 2093
Other name	Zebinix
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

**Dosage and administration details:**

The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily.

**Titration period:**

First 2 weeks: 10 mg/kg/day;

Next 4 weeks: 20 mg/kg/day (maximum 1200 mg/day) (if no AE occurred), 10 mg/kg/day (if AE occurred);

**Maintenance period:**

Next 12 weeks: 20 mg/kg/day (if acceptable tolerability), 30 mg/kg/day (maximum 1200 mg/day) (if unsatisfactory response), 10 mg/kg/day (if during the previous period will receive this dose)

**Tapering-off \follow-up period:**

After the 12-week maintenance period, the study treatment will be tapered off in 10 mg/kg/day steps every 2 weeks, followed by a 4 week observational follow-up period.

<b>Number of subjects in period 1<sup>[2]</sup></b>	Part I - Placebo	Part I - ESL
Started	129	134
Completed	118	120
Not completed	11	14
Adverse event, serious fatal	1	1
Consent withdrawn by subject	5	5
Physician decision	2	2
Adverse event, non-fatal	1	2
Other reason	1	-
Adverse event, serious non-fatal	-	2

Not serious AE and lack of efficacy	-	1
Treatment with > 2 conc. AEDs at the same time	-	1
Lack of efficacy	1	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline period does not include 41 subjects with IMP recall.

## Period 2

Period 2 title	PART II: OPEN-LABEL EXTENSION PERIOD
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

<b>Arm title</b>	Part II - ESL
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Arm description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

Arm type	Active comparator
Investigational medicinal product name	Eslicarbazepine acetate
Investigational medicinal product code	BIA 2093
Other name	Zebinix
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily.

The starting dose will be 10 mg/kg/day or 800 mg/day for patients with high body weight. The daily dose will be titrated by the investigator according to clinical response in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to maximum 1200 mg/day for patients with high body weight). Down-titration will be allowed during Part II according to clinical response or in case of intolerable AEs.

<b>Number of subjects in period 2<sup>[3]</sup></b>	Part II - ESL
Started	226
Completed	163
Not completed	63
Consent withdrawn by subject	16
Physician decision	3
Adverse event, non-fatal	6
At the specific request of the sponsor	2

Other reason	3
Adverse event, serious non-fatal	3
Lack of efficacy	30

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Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Number of subjects 238 completed double blind part and 12 of them did not start open label part.

## Baseline characteristics

### Reporting groups

Reporting group title	Part I - Placebo
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Reporting group description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL placebo oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg placebo tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

Reporting group title	Part I - ESL
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Reporting group description:

Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.

Reporting group values	Part I - Placebo	Part I - ESL	Total
Number of subjects	129	134	263
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0
Newborns (0-27days)	0	0	0
Infants and toddlers (28days – 23months)	0	0	0
Children (2-11 years)	84	82	166
Adolescents (12-17 year)	45	51	96
From 18 - 64 years	0	1	1
From 65 – 84 years	0	0	0
Over 85 years	0	0	0
Age Continuous			
Age Continuous Characteristic			
Units: Years			
arithmetic mean	9.5	9.9	
standard deviation	± 3.85	± 4.22	-
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	67	70	137
Male	62	64	126



## End points

### End points reporting groups

Reporting group title	Part I - Placebo
Reporting group description: Patients aged 2–6 years will receive the study treatment as 50 mg/mL placebo oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg placebo tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.	
Reporting group title	Part I - ESL
Reporting group description: Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.	
Reporting group title	Part II - ESL
Reporting group description: Patients aged 2–6 years will receive the study treatment as 50 mg/mL Eslicarbazepine Acetate oral suspension. Patients aged 7 or over will receive the study treatment in the form of 200 mg Eslicarbazepine Acetate tablets. The study treatment should be administered once daily, preferably at the same time of the day. The maximum absolute dosage will be 1200 mg once daily. Subjects without IMP recall.	
Subject analysis set title	Part I - Placebo x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received at least one dose of double-blind study treatment excluding those stratum I patients who were randomised before the IMP recall	
Subject analysis set title	Part I - ESL x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received at least one dose of double-blind study treatment excluding those stratum I patients who were randomised before the IMP recall	
Subject analysis set title	Part I - Placebo x Intent-to-treat Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomised, treated with at least one dose of study medication after randomisation, and with at least one post-baseline seizure frequency assessment excluding those stratum I patients who were randomised before the IMP recall	
Subject analysis set title	Part I - ESL x Intent-to-treat Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomised, treated with at least one dose of study medication after randomisation, and with at least one post-baseline seizure frequency assessment excluding those stratum I patients who were randomised before the IMP recall	
Subject analysis set title	Part I - Placebo x Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: All patients of the ITT without any major protocol deviations	
Subject analysis set title	Part I - ESL x Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: All patients of the ITT without any major protocol deviations	
Subject analysis set title	Part II - ESL x Safety Set
Subject analysis set type	Safety analysis

#### Subject analysis set description:

All patients entering Part II who received at least one dose of Eslicarbazepine Acetate during the open-label extension period excluding stratum I patients randomised before the IMP recall irrespective of treatment with suspension or tablets in Part II

Subject analysis set title	Part II - ESL x Intent-to-treat Set
Subject analysis set type	Intention-to-treat

#### Subject analysis set description:

All patients entering Part II, treated with at least one dose of Eslicarbazepine Acetate during the open-label extension period, and with at least one seizure frequency assessment during the extension period excluding stratum I patients randomised before the IMP recall irrespective of treatment with suspension or tablets in Part II

### Primary: Responder rate

End point title	Responder rate
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#### End point description:

Responder rate defined as the number of patients with at least a 50% decrease in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period

End point type	Primary
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#### End point timeframe:

Baseline up to Visit 7 in the Part I

End point values	Part I - Placebo x Intent-to-treat Set	Part I - ESL x Intent-to-treat Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	134		
Units: Participants				
number (not applicable)				
Participants	40	41		

### Statistical analyses

Statistical analysis title	Cochran—Mantel—Haenszel—test strat. by age stratum
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#### Statistical analysis description:

The responder rate during the 12-week maintenance period were analysed by a Cochran-Mantel-Haenszel (CMH) test with age stratum as stratification factor.

Comparison groups	Part I - Placebo x Intent-to-treat Set v Part I - ESL x Intent-to-treat Set
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9017
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.63

### Primary: Relative Reduction From Baseline in Seizure Frequency

End point title	Relative Reduction From Baseline in Seizure Frequency
End point description: Relative reduction in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period	
End point type	Primary
End point timeframe: Baseline up to Visit 7 in the Part I	

End point values	Part I - Placebo x Intent-to-treat Set	Part I - ESL x Intent-to-treat Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	134		
Units: Seizures				
least squares mean (standard error)				
Seizures	-8.6 (± 5.93)	-18.1 (± 5.84)		

### Statistical analyses

Statistical analysis title	ANCOVA model for comparison
Statistical analysis description: ANCOVA model with treatment and stratum group as fixed effects and baseline seizure frequency as a covariate.	
Comparison groups	Part I - Placebo x Intent-to-treat Set v Part I - ESL x Intent-to-treat Set
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.249
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.71
upper limit	25.77

Variability estimate	Standard error of the mean
Dispersion value	8.25

### Primary: Relative Change From Baseline in Seizure Frequency

End point title	Relative Change From Baseline in Seizure Frequency <sup>[1]</sup>
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End point description:

Relative change in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period

End point type	Primary
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End point timeframe:

Baseline up to Visit 7 in the Part I

Notes:

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

Justification: No statistical analysis was performed.

End point values	Part I - Placebo x Intent-to- treat Set	Part I - ESL x Intent-to-treat Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	134		
Units: Seizures				
arithmetic mean (standard deviation)				
Seizures	-9.6 (± 70.15)	-19.2 (± 64.1)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the date of first study treatment up to 28 days after the last dose of study medication in the corresponding part.

Adverse event reporting additional description:

Part I: up to the date of visit FU1 for patients continuing if the visit occurs within these 28 days

Part II: up to 28 days after the last dose of study medication for patients discontinuing treatment during Part II or the date of Visit OL6 for patients continuing with treatment in Part III of the study

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	Part I - Placebo x Safety Set
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Reporting group description:

Subjects in the Safety Set treated with placebo during Part I

Reporting group title	Part I - ESL x Safety Set
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Reporting group description:

Subjects in the Safety Set treated with ESL during Part I

Reporting group title	Part II - ESL x Safety Set
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Reporting group description:

Subjects in the Safety Set treated with ESL during Part II

Serious adverse events	Part I - Placebo x Safety Set	Part I - ESL x Safety Set	Part II - ESL x Safety Set
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 129 (6.98%)	15 / 134 (11.19%)	23 / 226 (10.18%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Medical device change			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (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
General disorders and administration site conditions			

Device malfunction			
subjects affected / exposed	0 / 129 (0.00%)	2 / 134 (1.49%)	0 / 226 (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
Drug withdrawal syndrome			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritability			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (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
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (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
Psychiatric disorders			
Conduct disorder			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
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			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Brain herniation			

subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (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
Joint dislocation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (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
Convulsion			
subjects affected / exposed	2 / 129 (1.55%)	2 / 134 (1.49%)	6 / 226 (2.65%)
occurrences causally related to treatment / all	1 / 2	0 / 2	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dysarthria			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	0 / 226 (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
Hydrocephalus			

subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (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
Hypotonia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nystagmus			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures with secondary generalisation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 129 (0.00%)	3 / 134 (2.24%)	2 / 226 (0.88%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Otosalpingitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0



Gastrointestinal disorders			
Coeliac disease			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (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
Colitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash vesicular			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular purpura			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteochondrosis			

subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
Bronchopneumonia			
subjects affected / exposed	0 / 129 (0.00%)	2 / 134 (1.49%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (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
Lobar pneumonia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 129 (2.33%)	1 / 134 (0.75%)	4 / 226 (1.77%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
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 infection			

subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (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
<b>Metabolism and nutrition disorders</b>			
Dehydration			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Part I - Placebo x Safety Set	Part I - ESL x Safety Set	Part II - ESL x Safety Set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 129 (71.32%)	108 / 134 (80.60%)	172 / 226 (76.11%)
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
Oral papilloma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Sebaceous adenoma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Skin papilloma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	1	1
<b>Vascular disorders</b>			
Haematoma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	2	0	0
Hypertension			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1

Phlebitis subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Surgical and medical procedures			
Adenoidectomy subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Brain operation subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Plastic surgery to the face subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Suture insertion subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Tenotomy subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Tooth extraction subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	2 / 134 (1.49%) 2	3 / 226 (1.33%) 3
Chest pain subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Device malfunction subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Face oedema subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Fatigue			

subjects affected / exposed	3 / 129 (2.33%)	5 / 134 (3.73%)	6 / 226 (2.65%)
occurrences (all)	3	7	6
Feeling hot			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	4 / 226 (1.77%)
occurrences (all)	0	2	4
Hyperthermia			
subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	2 / 226 (0.88%)
occurrences (all)	1	2	2
Irritability			
subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	4 / 226 (1.77%)
occurrences (all)	1	2	4
Malaise			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	2	2
Oedema			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	7 / 129 (5.43%)	10 / 134 (7.46%)	20 / 226 (8.85%)
occurrences (all)	13	14	27
Sluggishness			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Thirst			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0

Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	3 / 226 (1.33%) 3
Immunodeficiency subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	2 / 134 (1.49%) 2	1 / 226 (0.44%) 2
Reproductive system and breast disorders			
Labia enlarged subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Menstruation irregular subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Pelvic pain subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Polycystic ovaries subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Vaginal discharge subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Respiratory, thoracic and mediastinal disorders			
Asthma subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	3 / 134 (2.24%) 6	1 / 226 (0.44%) 3
Cough subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 4	2 / 134 (1.49%) 3	6 / 226 (2.65%) 8
Epistaxis			

subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	3 / 226 (1.33%)
occurrences (all)	1	1	3
Laryngospasm			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	3	3
Nasal discomfort			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Nasal obstruction			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Nasal septum deviation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 129 (0.78%)	3 / 134 (2.24%)	4 / 226 (1.77%)
occurrences (all)	1	3	5
Respiratory disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	2 / 226 (0.88%)
occurrences (all)	0	3	2
Rhinitis allergic			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 129 (1.55%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	3	0	3
Tonsillar hypertrophy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Tonsillar inflammation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	3 / 226 (1.33%)
occurrences (all)	1	2	3

Agitation			
subjects affected / exposed	1 / 129 (0.78%)	5 / 134 (3.73%)	1 / 226 (0.44%)
occurrences (all)	1	5	1
Anxiety			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Apathy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	0	0	2
Attention deficit/Hyperactivity disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	1
Bradyphrenia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Bruxism			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Disorientation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Dyslogia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Dysthymic disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Inappropriate affect			



subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 2	0 / 226 (0.00%) 0
Insomnia			
subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	2 / 134 (1.49%) 4	1 / 226 (0.44%) 1
Listless			
subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Mood swings			
subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	2 / 134 (1.49%) 2	1 / 226 (0.44%) 1
Obsessive-compulsive disorder			
subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Panic attack			
subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Restlessness			
subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	1 / 134 (0.75%) 2	0 / 226 (0.00%) 0
Sleep disorder			
subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Sleep talking			
subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Blood bicarbonate decreased			
subjects affected / exposed	2 / 129 (1.55%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	2	0	0
Blood calcium decreased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	0	0	2
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 129 (1.55%)	2 / 134 (1.49%)	1 / 226 (0.44%)
occurrences (all)	2	2	1
Blood glucose decreased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	2 / 226 (0.88%)
occurrences (all)	1	2	2
Blood triglycerides increased			
subjects affected / exposed	2 / 129 (1.55%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	2	0	1
Body temperature increased			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	1	1	0
Breath sounds abnormal			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Ecg p wave inverted			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Electrocardiogram pr prolongation			

subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram qt prolonged			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	1	1
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Eosinophil count increased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	7 / 226 (3.10%)
occurrences (all)	1	1	7
Platelet count increased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Positive rombergism			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	3 / 226 (1.33%)
occurrences (all)	1	1	4
Rheumatoid factor increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Thyroxine decreased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Thyroxine increased			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	2
Weight decreased			

subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	2 / 129 (1.55%)	5 / 134 (3.73%)	3 / 226 (1.33%)
occurrences (all)	2	5	3
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Concussion			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	1 / 129 (0.78%)	3 / 134 (2.24%)	0 / 226 (0.00%)
occurrences (all)	1	3	0
Drug toxicity			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Excoriation			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	3 / 226 (1.33%)
occurrences (all)	2	1	3
Face injury			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	3
Fall			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	3 / 226 (1.33%)
occurrences (all)	1	0	7
Foot fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Hand fracture			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	1	1	0
Head injury			

subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	4 / 226 (1.77%)
occurrences (all)	1	2	4
Injury			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 129 (0.00%)	2 / 134 (1.49%)	1 / 226 (0.44%)
occurrences (all)	0	2	1
Lip injury			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Overdose			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Poisoning			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Radius fracture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Skin wound			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Tooth injury			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Traumatic haematoma			

subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Wound subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Wrist fracture subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	1 / 226 (0.44%) 1
Congenital, familial and genetic disorders			
Atrial septal defect subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Phimosis subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Cardiac disorders			
Arrhythmia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Tachycardia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 2	1 / 226 (0.44%) 1
Wolff-parkinson-white syndrome subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Nervous system disorders			
Ataxia subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	3 / 134 (2.24%) 4	2 / 226 (0.88%) 2
Balance disorder subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Cerebellar ataxia			

subjects affected / exposed	1 / 129 (0.78%)	3 / 134 (2.24%)	3 / 226 (1.33%)
occurrences (all)	1	3	3
Cerebrovascular disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Cognitive disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	1
Convulsion			
subjects affected / exposed	13 / 129 (10.08%)	11 / 134 (8.21%)	29 / 226 (12.83%)
occurrences (all)	18	15	47
Coordination abnormal			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	2 / 129 (1.55%)	5 / 134 (3.73%)	6 / 226 (2.65%)
occurrences (all)	2	5	10
Epilepsy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	1	0	2
Head titubation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	8 / 129 (6.20%)	18 / 134 (13.43%)	20 / 226 (8.85%)
occurrences (all)	14	22	26
Hypotonia			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	2 / 226 (0.88%)
occurrences (all)	1	1	2
Intention tremor			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	1	1	1
Lethargy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	1	1
Memory impairment			

subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Mental impairment			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Nystagmus			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	3 / 226 (1.33%)
occurrences (all)	0	1	3
Paraesthesia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Partial seizures with secondary generalisation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Poor quality sleep			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Postictal headache			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	1
Postictal state			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Psychomotor hyperactivity			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	1	1	1
Somnolence			
subjects affected / exposed	6 / 129 (4.65%)	15 / 134 (11.19%)	20 / 226 (8.85%)
occurrences (all)	8	16	25
Speech disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0



Status epilepticus subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Syncope subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Tremor subjects affected / exposed occurrences (all)	2 / 129 (1.55%) 2	2 / 134 (1.49%) 2	3 / 226 (1.33%) 3
Unresponsive to stimuli subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	1 / 226 (0.44%) 1
Leukopenia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	2 / 226 (0.88%) 2
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	2 / 134 (1.49%) 2	0 / 226 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Pancytopenia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Tinnitus			

subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	1
Tympanic membrane perforation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 129 (0.00%)	5 / 134 (3.73%)	5 / 226 (2.21%)
occurrences (all)	0	11	9
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Astigmatism			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Conjunctival haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Diplopia			
subjects affected / exposed	2 / 129 (1.55%)	8 / 134 (5.97%)	12 / 226 (5.31%)
occurrences (all)	2	12	14
Eye pain			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	0	0	2
Eye swelling			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Optic atrophy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	1	1

Visual impairment subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	1 / 134 (0.75%) 1	1 / 226 (0.44%) 1
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 7	3 / 134 (2.24%) 4	6 / 226 (2.65%) 8
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	4 / 134 (2.99%) 4	3 / 226 (1.33%) 4
Aphthous stomatitis subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	2 / 226 (0.88%) 2
Constipation subjects affected / exposed occurrences (all)	2 / 129 (1.55%) 2	3 / 134 (2.24%) 3	1 / 226 (0.44%) 6
Diarrhoea subjects affected / exposed occurrences (all)	3 / 129 (2.33%) 3	1 / 134 (0.75%) 1	4 / 226 (1.77%) 4
Dyspepsia subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Enteritis subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Food poisoning subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	1 / 134 (0.75%) 1	0 / 226 (0.00%) 0
Frequent bowel movements			

subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Gastroduodenitis			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	1	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	2	0	0
Irritable bowel syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Lip dry			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 129 (0.78%)	7 / 134 (5.22%)	5 / 226 (2.21%)
occurrences (all)	1	9	7
Odynophagia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Periodontitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	1
Peritonitis			

subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Rectal fissure			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Salivary hypersecretion			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	3 / 226 (1.33%)
occurrences (all)	0	1	3
Tooth disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	8 / 129 (6.20%)	8 / 134 (5.97%)	21 / 226 (9.29%)
occurrences (all)	9	11	32
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	1	0	2
Hepatic steatosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	1
Alopecia			
subjects affected / exposed	2 / 129 (1.55%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	2	0	1
Dermatitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Dermatitis acneiform			

subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Dermatitis allergic			
subjects affected / exposed	2 / 129 (1.55%)	2 / 134 (1.49%)	2 / 226 (0.88%)
occurrences (all)	3	2	2
Dermatitis atopic			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	10
Dermatitis contact			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	2 / 226 (0.88%)
occurrences (all)	0	1	2
Dermatitis diaper			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Heat rash			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Onychomadesis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Papule			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Pityriasis rosea			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	4 / 129 (3.10%)	2 / 134 (1.49%)	3 / 226 (1.33%)
occurrences (all)	5	2	3
Rash erythematous			

subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Solar dermatitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Subcutaneous abscess			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 129 (0.00%)	2 / 134 (1.49%)	0 / 226 (0.00%)
occurrences (all)	0	2	0
Haematuria			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	0	0	2
Leukocyturia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Nephropathy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Nocturia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0

Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	2 / 226 (0.88%)
occurrences (all)	0	1	2
Hypothyroidism			
subjects affected / exposed	0 / 129 (0.00%)	2 / 134 (1.49%)	2 / 226 (0.88%)
occurrences (all)	0	2	2
Precocious puberty			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	0 / 226 (0.00%)
occurrences (all)	1	2	0
Arthritis reactive			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	1	0	3
Chest wall mass			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Elbow deformity			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Groin pain			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Pain in extremity			



subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 2	1 / 134 (0.75%) 1	1 / 226 (0.44%) 1
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Acute sinusitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	2	0	0
Acute tonsillitis			
subjects affected / exposed	1 / 129 (0.78%)	1 / 134 (0.75%)	6 / 226 (2.65%)
occurrences (all)	1	2	7
Appendicitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	7 / 129 (5.43%)	5 / 134 (3.73%)	8 / 226 (3.54%)
occurrences (all)	7	5	10
Bullous impetigo			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	1	1
Conjunctivitis bacterial			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	2	0
Cystitis			
subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	0 / 226 (0.00%)
occurrences (all)	1	2	0
Ear infection			
subjects affected / exposed	3 / 129 (2.33%)	0 / 134 (0.00%)	6 / 226 (2.65%)
occurrences (all)	4	0	6
Febrile infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Fungal skin infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	0	0	2

Gastroenteritis			
subjects affected / exposed	1 / 129 (0.78%)	3 / 134 (2.24%)	8 / 226 (3.54%)
occurrences (all)	1	4	9
Gastroenteritis viral			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	2 / 226 (0.88%)
occurrences (all)	0	1	2
Gastrointestinal viral infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Helicobacter infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Herpes simplex			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Impetigo			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	0	0	2
Infected bites			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 129 (0.78%)	4 / 134 (2.99%)	6 / 226 (2.65%)
occurrences (all)	2	9	14
Laryngitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	2 / 226 (0.88%)
occurrences (all)	0	0	2
Lower respiratory tract infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	15 / 129 (11.63%)	15 / 134 (11.19%)	31 / 226 (13.72%)
occurrences (all)	23	22	43

Onychomycosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 129 (0.00%)	2 / 134 (1.49%)	1 / 226 (0.44%)
occurrences (all)	0	2	1
Otitis externa			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	2 / 226 (0.88%)
occurrences (all)	1	2	2
Otitis media acute			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Parasitic gastroenteritis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	9 / 129 (6.98%)	9 / 134 (6.72%)	10 / 226 (4.42%)
occurrences (all)	9	10	14
Pharyngotonsillitis			
subjects affected / exposed	1 / 129 (0.78%)	2 / 134 (1.49%)	3 / 226 (1.33%)
occurrences (all)	1	2	3
Pneumonia			
subjects affected / exposed	2 / 129 (1.55%)	1 / 134 (0.75%)	2 / 226 (0.88%)
occurrences (all)	2	1	2
Pulmonary tuberculosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Pulpitis dental			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	7 / 129 (5.43%)	7 / 134 (5.22%)	13 / 226 (5.75%)
occurrences (all)	7	10	28

Respiratory tract infection viral subjects affected / exposed occurrences (all)	3 / 129 (2.33%) 3	2 / 134 (1.49%) 3	6 / 226 (2.65%) 14
Rhinitis subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 7	4 / 134 (2.99%) 5	5 / 226 (2.21%) 7
Sinusitis subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Tinea infection subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Tonsillitis subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 4	2 / 134 (1.49%) 2	4 / 226 (1.77%) 5
Tracheitis subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Tracheobronchitis subjects affected / exposed occurrences (all)	0 / 129 (0.00%) 0	0 / 134 (0.00%) 0	1 / 226 (0.44%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 129 (3.88%) 8	6 / 134 (4.48%) 8	10 / 226 (4.42%) 18
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	4 / 226 (1.77%) 4
Urinary tract infection bacterial subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	0 / 134 (0.00%) 0	0 / 226 (0.00%) 0
Varicella subjects affected / exposed occurrences (all)	2 / 129 (1.55%) 2	2 / 134 (1.49%) 2	2 / 226 (0.88%) 2
Viral infection subjects affected / exposed occurrences (all)	6 / 129 (4.65%) 7	5 / 134 (3.73%) 5	12 / 226 (5.31%) 13

Viral pharyngitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Viral rash			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 129 (2.33%)	5 / 134 (3.73%)	7 / 226 (3.10%)
occurrences (all)	6	6	9
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 129 (0.00%)	2 / 134 (1.49%)	0 / 226 (0.00%)
occurrences (all)	0	2	0
Decreased appetite			
subjects affected / exposed	1 / 129 (0.78%)	6 / 134 (4.48%)	2 / 226 (0.88%)
occurrences (all)	1	8	2
Dehydration			
subjects affected / exposed	1 / 129 (0.78%)	0 / 134 (0.00%)	0 / 226 (0.00%)
occurrences (all)	1	0	0
Feeding disorder			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Hyperphagia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	1	1
Increased appetite			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	1 / 226 (0.44%)
occurrences (all)	0	1	1
Iron deficiency			
subjects affected / exposed	0 / 129 (0.00%)	1 / 134 (0.75%)	0 / 226 (0.00%)
occurrences (all)	0	1	0
Obesity			
subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1
Weight gain poor			

subjects affected / exposed	0 / 129 (0.00%)	0 / 134 (0.00%)	1 / 226 (0.44%)
occurrences (all)	0	0	1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2007	Global Amendment#1 The reason for this study global protocol amendment is to harmonized the requests from different Ethics Committees and/or Regulatory Authorities
29 April 2009	Global Amendment#2 The reason is to define a study extension (Part III) in order to allow patients who participated in study SCO/BIA-2093-305 to continue receiving the study medication
17 May 2010	Global Amendment#3 The reason is to define a study extension (Part IV) in order to allow patients who participated in study SCO/BIA-2093-305 to continue receiving the study medication
07 June 2010	Global Amendment#4 The reason is the recall of the oral suspension formulation of the investigational medicinal product (50 mg/mL) used in the age group of 2-6 years children for Part I and Part II.
16 September 2010	Global Amendment#4 The reason is the recall of the oral suspension formulation of the investigational medicinal product (50 mg/mL) used in the age group of 2-6 years children for Part I and Part II.
12 May 2011	Global Amendment#3 The reason is to define a study extension (Part V) in order to allow patients who participated in study SCO/BIA-2093-305 to continue receiving the study medication

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported