Clinical trial results:
An Open Label, Single-Arm, Multi-Center Study on the Efficacy, Safety and Pharmacokinetics of Levetiracetam in Pediatric Patients (4 to 16 Years) With Partial Seizures Despite Treatment With 1 or 2 Anti-Epileptic Drugs

Summary

EudraCT number	2014-004335-39
Trial protocol	Outside EU/EEA
Global end of trial date	24 October 2013

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	25 April 2015

Trial information

Trial identification

Sponsor protocol code	N01223

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01063764
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Japan Co. Ltd.
Sponsor organisation address	8-17-1 Nishi-Shinjuku, Tokyo, Japan, 160-0023
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 4815 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, 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	10 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

First Period:
The primary objective was to evaluate the efficacy of Levetiracetam (LEV) dry syrup at doses up to a maximum of 60 mg/kg/day or 3000 mg/day used as an adjunctive therapy in Japanese pediatric subjects aged ≥4 to <16 years and with uncontrolled partial seizures despite treatment with 1 or 2 anti-epileptic drugs (AEDs).

Second Period:
To provide LEV treatment to subjects who were judged by the investigators to benefit from long-term treatment and who are willing to continuously receive this drug and to continuously evaluate the safety of long-term administration of LEV at doses ranging from 20 mg/kg/day or 1000 mg/day to 60 mg/kg/day or 3000 mg/day in subjects who completed the First Period of this study.

Protection of trial subjects:

Not applicable

Background therapy:

One or two anti-epileptic drug(s)

Evidence for comparator:

Not applicable

Actual start date of recruitment	29 January 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 73
Worldwide total number of subjects	73
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	44
Adolescents (12-17 years)	29
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Full Analysis Set (FAS) includes all subjects taking at least one dose of study medication. Per-Protocol Set (PPS) is a subset of the FAS, consisting of subjects without major protocol violations affecting the primary efficacy variable.

Pre-assignment

Screening details:

Participant Flow refers to the Full Analysis Set.
First Period started after Baseline (Week 0 to Week 8).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Levetiracetam

Arm description:

•First Period (4 weeks Up-titration and 10 weeks Evaluation): Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.
•Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.
•Withdrawal Period (6 weeks): Patients on the dose at 60 mg/kg/day or 3000 mg/day will be decreased to 40 mg/kg/day or 2000 mg/day for first 2 weeks and then to 20 mg/kg/day or 1000 mg/day for 2 additional weeks. For patients on the dose at 40 mg/kg/day or 2000 mg/day, the dosage will be decreased to 20 mg/kg/day or 1000 mg/day for 2 weeks and then the treatment with LEV will be stopped.

Arm type	Experimental
Investigational medicinal product name	Levetiracetam tablet
Investigational medicinal product code	ucb L059
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

First Period: Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.
Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.

Investigational medicinal product name	Levetiracetam dry syrup
Investigational medicinal product code	ucb L059
Other name	EKeppra
Pharmaceutical forms	Powder for syrup
Routes of administration	Oral use

Dosage and administration details:

First Period: Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.
Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.

Number of subjects in period 1	Levetiracetam
Started	73
Completed	35
Not completed	38
AE, serious fatal	1
Consent withdrawn by subject	10
AE, non-serious non-fatal	5
SAE, non-fatal	1
Lack of efficacy	20
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Levetiracetam
Reporting group description:	
•First Period (4 weeks Up-titration and 10 weeks Evaluation): Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks. •Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted. •Withdrawal Period (6 weeks): Patients on the dose at 60 mg/kg/day or 3000 mg/day will be decreased to 40 mg/kg/day or 2000 mg/day for first 2 weeks and then to 20 mg/kg/day or 1000 mg/day for 2 additional weeks. For patients on the dose at 40 mg/kg/day or 2000 mg/day, the dosage will be decreased to 20 mg/kg/day or 1000 mg/day for 2 weeks and then the treatment with LEV will be stopped.	

Reporting group values	Levetiracetam	Total	
Number of subjects	73	73	
Age Categorical Units: Subjects			
>=4 - <8 years	22	22	
>=8 - <12 years	22	22	
>=12 - <16 years	29	29	
Age Continuous Units: years			
arithmetic mean	10.1		
standard deviation	± 3.4	-	
Gender Categorical Units: Subjects			
Female	32	32	
Male	41	41	
Region of Enrollment Units: Subjects			
Japan	73	73	
Hospitalization Status Units: Subjects			
Yes	0	0	
No	73	73	
Body Weight Units: kilogram (kg)			
arithmetic mean	32.43		
standard deviation	± 13.2	-	
Height Units: centimeter (cm)			
arithmetic mean	134.55		
standard deviation	± 20.69	-	
Body Mass Index (BMI) Units: kilogram / meter^2 (kg/m^2)			
arithmetic mean	17.15		
standard deviation	± 2.99	-	

End points

End points reporting groups

Reporting group title	Levetiracetam

Reporting group description:

•First Period (4 weeks Up-titration and 10 weeks Evaluation): Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.
•Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.
•Withdrawal Period (6 weeks): Patients on the dose at 60 mg/kg/day or 3000 mg/day will be decreased to 40 mg/kg/day or 2000 mg/day for first 2 weeks and then to 20 mg/kg/day or 1000 mg/day for 2 additional weeks. For patients on the dose at 40 mg/kg/day or 2000 mg/day, the dosage will be decreased to 20 mg/kg/day or 1000 mg/day for 2 weeks and then the treatment with LEV will be stopped.

Primary: Change from Baseline in partial seizure frequency per week over the 14-weeks Treatment Period

End point title	Change from Baseline in partial seizure frequency per week over the 14-weeks Treatment Period[1]

End point description:

The change in partial seizure frequency from Baseline (B) over the Treatment Period (T) is given as a percentage reduction computed as:
(B values- T values) / B values x 100.

Positive values in percent reduction mean that the value decreased from Baseline during the first 14-week Period.
Frequency per week of partial seizures = (Total number of partial seizures in a certain Period/number of observation days in the Period) x 7.
Partial seizures can be classified into:
- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

End point type	Primary

End point timeframe:

From Baseline (Week 0-8) to the 14-weeks Treatment Period (First Period: 4 weeks Up-titration (Week 8-12) and 10 weeks Evaluation (Week 12-22)); Week 0-22

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: The efficacy of LEV in this study was considered positive if the lower limit of the 2-sided 95 % CI of the median percentage reduction in the partial seizure frequency per week was greater than 16.3 %. This was based on the median percentage reduction of the seizure frequency per week in the placebo in N159. Furthermore, a percentage reduction greater than 16.3 % was considered clinically relevant.
Descriptive statistics with 95 % CI of the median percentage reduction were presented.

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Percent reduction				
median (confidence interval 95%)				
median (95 % confidence interval)	43.21 (26.19 to 52.14)			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Treatment-Emergent Adverse Events (TEAEs) during the Second Period (up to three years until the time of approval granted)

End point title	Incidence of Treatment-Emergent Adverse Events (TEAEs) during the Second Period (up to three years until the time of approval granted)[2]

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with the pharmaceutical product. Incidence of treatment-emergent AEs is reported by the percentage of subjects with at least one treatment-emergent AE.

End point type	Primary

End point timeframe:

During the second Period from Visit 8 (Week 22) to the end of the Follow-up Period (up to three years until the time of approval granted)

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: There was no statistical analysis for this endpoint in this open-label study.

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: percentage of participants				
number (not applicable)				
percentage of participants	98.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in partial seizure frequency per week over the 10-week Evaluation Period

End point title	Change from Baseline in partial seizure frequency per week over the 10-week Evaluation Period

End point description:

The change in partial seizure frequency from Baseline (B) over the Evaluation Period (E) is given as a percentage reduction computed as:
(B values- E values) / B values x 100.
Positive values in percent reduction mean that the value decreased from Baseline to the 10-week Evaluation Period.
Frequency per week of partial seizures = (Total number of partial seizures in a certain Period/number of observation days in the Period) x 7.
Partial seizures can be classified into:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

End point type	Secondary

End point timeframe:

From Baseline (Week 0-8) to the 10-weeks Evaluation Period (Part of the first Period: Week 12 to Week 22)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Percent reduction				
median (confidence interval 95%)				
median (95 % confidence interval)	39.02 (26.67 to 52.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial seizure frequency per week over the 14-weeks Treatment Period

End point title	Partial seizure frequency per week over the 14-weeks Treatment Period

End point description:

The seizure frequency per week was calculated as:
Frequency per week of partial seizures = (Total number of partial seizures in the Treatment Period/number of days for observation in the Treatment Period) x 7.
Partial seizures can be classified into one of the following three groups:
- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

End point type	Secondary

End point timeframe:

14-weeks Treatment Period (First Period: 4 weeks Up-titration (Week 8-12) and 10 weeks Evaluation (Week 12-22))

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Seizures per week				
median (inter-quartile range (Q1-Q3))				
median (95 % confidence interval)	3.92 (0.93 to 17.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial seizure frequency per week over the 10-weeks Evaluation Period

End point title	Partial seizure frequency per week over the 10-weeks Evaluation Period

End point description:

The seizure frequency per week was calculated as:
Frequency per week of partial seizures = (Total number of partial seizures in the Evaluation Period/number of days for observation in the Evaluation Period) x 7.
Partial seizures can be classified into one of the following three groups:
- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

End point type	Secondary

End point timeframe:

10-weeks Evaluation Period (Part of the first Period: Week 12 to Week 22)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Seizures per week				
median (inter-quartile range (Q1-Q3))				
median (95 % confidence interval)	3.9 (0.86 to 17.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of partial seizures 50 % responders over the 14-weeks Treatment Period

End point title	Percentage of partial seizures 50 % responders over the 14-weeks Treatment Period

End point description:

50 % responders are those subjects which have a 50 % or more reduction in the frequency of partial seizures from Baseline to the Treatment Period. The results show the percentage of participants that are 50 % responders.
Partial seizures can be classified into one of the following three groups:
- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

End point type	Secondary

End point timeframe:

14-weeks Treatment Period (First Period: 4 weeks Up-titration (Week 8-12) and 10 weeks Evaluation (Week 12-22))

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
number (confidence interval 95%)				
number (95% confidence interval)	38.4 (27.2 to 50.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of partial seizures 50 % responders over the 10-weeks Evaluation Period

End point title	Percentage of partial seizures 50 % responders over the 10-weeks Evaluation Period

End point description:

50 % responders are those subjects which have a 50 % or more reduction in the frequency of partial seizures from Baseline to the Evaluation Period. The results show the percentage of participants that are 50 % responders.

Partial seizures can be classified into one of the following three groups:
- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

End point type	Secondary

End point timeframe:

10-weeks Evaluation Period (Part of the first Period: Week 12 to Week 22)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: percentage of participants				
number (confidence interval 95%)				
number (95% confidence interval)	38.2 (26.7 to 50.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seizure-free subjects over the 14-weeks Treatment Period

End point title	Number of seizure-free subjects over the 14-weeks Treatment Period

End point description:

Seizure-free means not having a seizure of type I (Partial seizure).
Partial seizures can be classified into one of the following three groups:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

End point type	Secondary

End point timeframe:

14-weeks Treatment Period (First Period: 4 weeks Up-titration (Week 8-12) and 10 weeks Evaluation (Week 12-22))

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: participants				
participants	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seizure-free subjects over the 10-weeks Evaluation Period

End point title	Number of seizure-free subjects over the 10-weeks Evaluation Period

End point description:

Seizure-free means not having a seizure of type I (Partial seizure).
Partial seizures can be classified into one of the following three groups:
- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

End point type	Secondary

End point timeframe:

10-weeks Evaluation Period (Part of the first Period: Week 12 to Week 22)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: participants				
participants	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment-emergent Adverse Drug Reactions (ADRs) during the Second Period (up to three years until the time of approval granted)

End point title	Incidence of treatment-emergent Adverse Drug Reactions (ADRs) during the Second Period (up to three years until the time of approval granted)

End point description:

An Adverse Drug Reaction (ADR) is an Adverse Event for which a causal relationship between the product and the occurrence is suspected. Incidence of ADRs is reported by the number of subjects with at least one ADR.

End point type	Secondary

End point timeframe:

During the second Period from Visit 8 (Week 22) to the end of the Follow-up Period (up to three years until the time of approval granted)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: participants				
participants	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in partial seizure frequency per week for the Second Period (up to three years from informed consent until the time of approval granted)

End point title	Change from Baseline in partial seizure frequency per week for the Second Period (up to three years from informed consent until the time of approval granted)

End point description:

The outcome was also calculated for each 3-month Period but here only the result for the total Second Evaluation Period (Second Period without following 6-weeks Withdrawal Period for withdrawers) is presented.
Change in partial seizure frequency from Baseline (B) over Second Evaluation Period (E) is given as a percentage reduction computed as:
(B values- E values) / B values x 100.
Positive values in percent reduction show a decrease from Baseline.
Frequency per week of partial seizures = (Total number of partial seizures in a certain Period/number of observation days in the Period) x 7.

End point type	Secondary

End point timeframe:

From Baseline (Week 0-8) until the time of approval granted (up to three years from date of informed consent (Week 0); without 6-weeks Withdrawal Period)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Percent reduction				
median (inter-quartile range (Q1-Q3))				
median (inter-quartile range)	41.32 (15.37 to 82.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected over the whole study from Baseline (Visit 2) over the complete First Period (14 weeks plus up to 6-week Down-titration and Follow-up) and the Second Period (Week 22 to the end of study).

Adverse event reporting additional description:

AEs refer to the Full Analysis Set (FAS). FAS includes all subjects which received at least one dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Levetiracetam

Reporting group description:

•First Period (4 weeks Up-titration and 10 weeks Evaluation): Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.
•Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.
•Withdrawal Period (6 weeks): Patients on the dose at 60 mg/kg/day or 3000 mg/day will be decreased to 40 mg/kg/day or 2000 mg/day for first 2 weeks and then to 20 mg/kg/day or 1000 mg/day for 2 additional weeks. For patients on the dose at 40 mg/kg/day or 2000 mg/day, the dosage will be decreased to 20 mg/kg/day or 1000 mg/day for 2 weeks and then the treatment with LEV will be stopped.

Serious adverse events	Levetiracetam		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 73 (10.96%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Near drowning			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Strabismus			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acetonaemic vomiting			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Dental caries			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Conversion disorder			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	1 / 73 (1.37%)		
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	Levetiracetam		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 73 (90.41%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	11		
Excoriation			
subjects affected / exposed	6 / 73 (8.22%)		
occurrences (all)	8		
Wound			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	10		
Arthropod bite			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	21		
Nervous system disorders			
Somnolence			
subjects affected / exposed	34 / 73 (46.58%)		
occurrences (all)	48		
Headache			
subjects affected / exposed	10 / 73 (13.70%)		
occurrences (all)	20		
Convulsion			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	8		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all)	17 / 73 (23.29%) 32 4 / 73 (5.48%) 4		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	 4 / 73 (5.48%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal Pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Dental Caries subjects affected / exposed occurrences (all)	 9 / 73 (12.33%) 16 5 / 73 (6.85%) 5 5 / 73 (6.85%) 7 6 / 73 (8.22%) 7 5 / 73 (6.85%) 11		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Rhinitis allergic	 6 / 73 (8.22%) 8 5 / 73 (6.85%) 10 4 / 73 (5.48%) 5		

subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 73 (8.22%)		
occurrences (all)	6		
Heat rash			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Eczema			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	5		
Pruritus			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	6		
Urticaria			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Psychiatric disorders			
Agitation			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	54 / 73 (73.97%)		
occurrences (all)	205		
Influenza			
subjects affected / exposed	20 / 73 (27.40%)		
occurrences (all)	24		
Upper respiratory tract infection			
subjects affected / exposed	12 / 73 (16.44%)		
occurrences (all)	37		
Gastroenteritis			

subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	13		
Impetigo			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Pharyngitis			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24018745