Clinical trial results:
A Double-blind, Randomized, Placebo-controlled 5 Parallel Groups, Confirmatory Trial on the Efficacy and Safety of Levetiracetam used as add-on Therapy at doses of 0.5 to 3 g/day in Patients From 16 to 65 Years With Epilepsy With Partial Onset Seizures Under Treatment With 1 to 3 Anti-epileptic Drug(s)

Summary

EudraCT number	2014-004333-57
Trial protocol	Outside EU/EEA
Global end of trial date	07 November 2007

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	01 July 2015

Trial information

Trial identification

Sponsor protocol code	N01221

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00280696
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Japan Co., Ltd.
Sponsor organisation address	2-2 Kanda-Surugadai, Tokyo, Japan, 101-0062
Public contact	CTRRD, UCB Biosciences GmbH, +49 2173481515, clinicaltrials@ucb.com
Scientific contact	CTRRD, UCB Biosciences GmbH, +49 2173481515, 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	14 December 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 November 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of levetiracetam (LEV) at doses of 1 and 3 g/day in reducing seizure frequency in patients with partial epilepsy not fully controlled despite treatment with 1 to 3 concomitant Anti-epileptic drugs (AED(s)), and to evaluate the efficacy of LEV at doses of 0.5 and 2 g/day compared to Placebo (PBO).

Protection of trial subjects:

Not applicable

Background therapy:

One to three anti-epileptic drug(s)

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 November 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	54 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 351
Worldwide total number of subjects	351
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)	0
Adolescents (12-17 years)	26
Adults (18-64 years)	325
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in November 2005 in Japan.

Pre-assignment

Screening details:

Out of 401 screened subjects, 352 subjects were randomized and 351 subjects are included in the Full Analysis Set (FAS) and Safety Set.
Subject Disposition refers to the FAS, defined as the set of randomized subjects excluding those who fall under specific pre-defined criteria, like GCP Violation, etc.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Carer, Assessor, Subject

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo tablets as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	PBO
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

- Active Substance: Placebo
- Pharmaceutical Form: Film-coated tablet
- Concentration: 250 mg and 500 mg
- Route of Administration: Oral Use

Arm title	Lev 0.5 g

Arm description:

Levetiracetam 0.5 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Arm type	Experimental
Investigational medicinal product name	Levetiracetam 250 mg
Investigational medicinal product code	
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

- Active Substance: Levetiracetam
- Pharmaceutical Form: Film-coated tablet
- Concentration: 250 mg
- Route of Administration: Oral Use

Arm title	Lev 1 g

Arm description:

Levetiracetam 1 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Arm type	Experimental
Investigational medicinal product name	Levetiracetam 250 mg
Investigational medicinal product code	
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

- Active Substance: Levetiracetam
- Pharmaceutical Form: Film-coated tablet
- Concentration: 250 mg
- Route of Administration: Oral Use

Investigational medicinal product name	Levetiracetam 500 mg
Investigational medicinal product code	
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

- Active Substance: Levetiracetam
- Pharmaceutical Form: Film-coated tablet
- Concentration: 500 mg
- Route of Administration: Oral Use

Arm title	Lev 2 g

Arm description:

Levetiracetam 2 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Arm type	Experimental
Investigational medicinal product name	Levetiracetam 250 mg
Investigational medicinal product code	
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

- Active Substance: Levetiracetam
- Pharmaceutical Form: Film-coated tablet
- Concentration: 250 mg
- Route of Administration: Oral Use

Investigational medicinal product name	Levetiracetam 500 mg
Investigational medicinal product code	
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

- Active Substance: Levetiracetam

• Pharmaceutical Form: Film-coated tablet
• Concentration: 500 mg
• Route of Administration: Oral Use

Arm title	Lev 3 g

Arm description:

Levetiracetam 3 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Arm type	Experimental
Investigational medicinal product name	Levetiracetam 250 mg
Investigational medicinal product code	
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Active Substance: Levetiracetam
• Pharmaceutical Form: Film-coated tablet
• Concentration: 250 mg
• Route of Administration: Oral Use

Investigational medicinal product name	Levetiracetam 500 mg
Investigational medicinal product code	
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Active Substance: Levetiracetam
• Pharmaceutical Form: Film-coated tablet
• Concentration: 500 mg
• Route of Administration: Oral Use

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: Roles blinded: Subject, Caregiver and Outcomes Assessor.

Number of subjects in period 1	Placebo	Lev 0.5 g	Lev 1 g
Started	70	71	70
Completed	67	62	64
Not completed	3	9	6
SAE, non-fatal + AE, non-serious non-fatal	-	-	-
Protocol deviation	1	5	2
Lack of efficacy	-	-	2
Other reason	-	1	-
SAE, non-fatal	1	1	1
AE, serious fatal	-	-	-
AE, non-serious non-fatal	-	1	-
Consent withdrawn by subject	1	1	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Lev 2 g	Lev 3 g
Started	70	70
Completed	63	60
Not completed	7	10
SAE, non-fatal + AE, non-serious non-fatal	1	-
Protocol deviation	1	3
Lack of efficacy	1	1
Other reason	-	-
SAE, non-fatal	-	2
AE, serious fatal	-	1
AE, non-serious non-fatal	3	3
Consent withdrawn by subject	-	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	
Reporting group title	Lev 0.5 g
Reporting group description:	
Levetiracetam 0.5 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	
Reporting group title	Lev 1 g
Reporting group description:	
Levetiracetam 1 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	
Reporting group title	Lev 2 g
Reporting group description:	
Levetiracetam 2 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	
Reporting group title	Lev 3 g
Reporting group description:	
Levetiracetam 3 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	

Reporting group values	Placebo	Lev 0.5 g	Lev 1 g
Number of subjects	70	71	70
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	3	5	6
Adults (18-64 years)	67	66	64
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.89	33.21	32.8
standard deviation	± 12.56	± 10.64	± 10.9
Gender categorical Units: Subjects			
Female	35	36	41
Male	35	35	29
Hospital Stay Units: Subjects			
Inpatient	1	2	3
Outpatient	69	69	67

Reporting group values	Lev 2 g	Lev 3 g	Total
Number of subjects	70	70	351
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	8	4	26
Adults (18-64 years)	62	66	325
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	30.44	33.09	
standard deviation	± 10.06	± 11.72	-
Gender categorical Units: Subjects			
Female	35	33	180
Male	35	37	171
Hospital Stay Units: Subjects			
Inpatient	2	6	14
Outpatient	68	64	337

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo tablets as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	
Reporting group title	Lev 0.5 g
Reporting group description:	
Levetiracetam 0.5 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	
Reporting group title	Lev 1 g
Reporting group description:	
Levetiracetam 1 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	
Reporting group title	Lev 2 g
Reporting group description:	
Levetiracetam 2 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	
Reporting group title	Lev 3 g
Reporting group description:	
Levetiracetam 3 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).	

Primary: Percent reduction from Baseline in partial (Type I) seizure frequency per week over the Evaluation Period

End point title	Percent reduction from Baseline in partial (Type I) seizure frequency per week over the Evaluation Period
End point description:	
The percentage reduction from Baseline in partial seizure frequency per week was calculated with the partial seizure frequency per week over the Evaluation Period (E) and the frequency over the Baseline Period (B) in the following equation: Reduction from Baseline in partial seizure frequency over the Evaluation Period as (%) = (B−E)/B×100	
End point type	Primary
End point timeframe:	
From Baseline to the 12-week Evaluation Period	

End point values	Placebo	Lev 0.5 g	Lev 1 g	Lev 2 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	68	68	68
Units: Percent Reduction				
median (inter-quartile range (Q1-Q3))	12.5 (-5.81 to 31.25)	12.92 (-13.56 to 41.89)	18 (-12.25 to 39.91)	11.11 (-19.64 to 39.09)

End point values	Lev 3 g			

Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percent Reduction				
median (inter-quartile range (Q1-Q3))	31.67 (0 to 52.07)			

Statistical analyses

Statistical analysis title	LEV 1 g vs LEV 3 g vs Placebo

Statistical analysis description:

Primary analysis related to the confirmation of the efficacy of the LEV doses 1 g and 3 g (doses used in the previous study N165) used a closed-testing procedure.
First step: Placebo, LEV 1 g and LEV 3 g were first compared using the Kruskal-Wallis test at 5 % 2-sided significance level.
If the comparison was statistically significant, the second step was performed. If p-value was > 5 %, no further inferential Analysis was conducted.

Comparison groups	Lev 1 g v Lev 3 g v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067
Method	Kruskal-wallis

Statistical analysis title	LEV 1 g versus Placebo

Statistical analysis description:

Primary analysis related to the confirmation of the efficacy of the LEV doses 1 g and 3 g (doses used in the previous study N165) used a closed-testing procedure.
Second step: Placebo and Lev 1 g were compared using the Wilcoxon Rank-Sum Test at 5 % 2-sided significance level. If the comparison was statistically significant, the last step was performed. If p-value was > 5 %, no further inferential Analysis was conducted.

Comparison groups	Placebo v Lev 1 g
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Wilcoxon Rank-Sum Test
Parameter estimate	Median difference (final values)
Point estimate	2.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.23
upper limit	14.44

Statistical analysis title	LEV 3 g versus Placebo

Statistical analysis description:

Primary analysis related to the confirmation of the efficacy of the LEV doses 1 g and 3 g (doses used in

the previous study N165) used a closed-testing procedure.
Last step: Placebo and Lev 3 g were compared using the Wilcoxon Rank Sum Test at 5 % 2-sided significance level.

Comparison groups	Placebo v Lev 3 g
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Wilcoxon Rank-Sum Test
Parameter estimate	Median difference (final values)
Point estimate	14.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.98
upper limit	27.64

Secondary: Partial (Type I) seizure frequency per week over the Evaluation Period

End point title	Partial (Type I) seizure frequency per week over the Evaluation Period

End point description:

Partial (Type I) 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:

12-week Evaluation Period

End point values	Placebo	Lev 0.5 g	Lev 1 g	Lev 2 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	68	68	68
Units: Seizure frequency				
median (inter-quartile range (Q1-Q3))	2.45 (1.17 to 5.25)	2.13 (1.13 to 5.21)	2.33 (1.04 to 4.04)	2.6 (1.13 to 6.5)

End point values	Lev 3 g			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Seizure frequency				
median (inter-quartile range (Q1-Q3))	2 (0.92 to 4.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial (Type I) seizure responder rates (50 %, 75 %) over the Evaluation Period

End point title	Partial (Type I) seizure responder rates (50 %, 75 %) over the Evaluation Period

End point description:

The percentage of subjects with 50 % or more reduction or with 75 % or more reduction from Baseline in the frequency of partial epileptic seizures during the Evaluation Period is presented below.

End point type	Secondary

End point timeframe:

From Baseline to the 12-week Evaluation Period

End point values	Placebo	Lev 0.5 g	Lev 1 g	Lev 2 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	68	68	68
Units: Percentage of subjects				
number (not applicable)				
>= 50 % reduction	11.6	19.1	17.6	16.2
>= 75 % reduction	4.3	5.9	5.9	7.4

End point values	Lev 3 g			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percentage of subjects				
number (not applicable)				
>= 50 % reduction	33.3			
>= 75 % reduction	10.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure freedom over the Evaluation Period

End point title	Seizure freedom over the Evaluation Period

End point description:

End point type	Secondary

End point timeframe:

12-week Evaluation Period

End point values	Placebo	Lev 0.5 g	Lev 1 g	Lev 2 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	68	68	68
Units: subjects	0	0	2	2

End point values	Lev 3 g			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Categorized percentage reduction from Baseline in partial (Type I) seizure frequency per week over the Evaluation Period

End point title	Categorized percentage reduction from Baseline in partial (Type I) seizure frequency per week over the Evaluation Period

End point description:

Percentage reduction from Baseline in partial (Type I) seizure frequency per week over the Evaluation Period was divided into 6 categories:
<-25 %
-25 % to <25 %
25 % to <50 %
50 % to <75 %
75 % to <100 %
100 %.

End point type	Secondary

End point timeframe:

From Baseline to the 12-week Evaluation Period

End point values	Placebo	Lev 0.5 g	Lev 1 g	Lev 2 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	68	68	68
Units: subjects				
<-25 %	4	13	11	16
-25 % to <25 %	43	28	30	28
25 % to <50 %	14	14	15	13
50 % to <75 %	5	9	8	6
75 % to <100 %	3	4	2	3
100 %	0	0	2	2

End point values	Lev 3 g			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: subjects				
<-25 %	10			
-25 % to <25 %	20			
25 % to <50 %	14			
50 % to <75 %	15			
75 % to <100 %	5			
100 %	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage reduction from Baseline in seizure frequency per week by seizure subtype (IA, IB, IC, IA + IB, other) over the Evaluation Period

End point title	Percentage reduction from Baseline in seizure frequency per week by seizure subtype (IA, IB, IC, IA + IB, other) over the Evaluation Period

End point description:

Percentage reduction from Baseline in seizure frequency per week over the Evaluation Period is presented by the following seizure subtypes:
- simple partial seizures (Type IA)
- complex partial seizures (Type IB)
- secondarily generalized seizures (Type IC)
- simple and complex partial seizures (Types IA + IB)
- other seizures (all except partial seizures)

End point type	Secondary

End point timeframe:

From Baseline to the 12-week Evaluation Period

End point values	Placebo	Lev 0.5 g	Lev 1 g	Lev 2 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70[1]	71[2]	70[3]	70[4]
Units: Percentage reduction				
median (inter-quartile range (Q1-Q3))				
simple partial seizures (Type IA)	27.92 (-33.33 to 25)	50 (-25 to 83.33)	22.25 (-23.08 to 80.95)	29.73 (-8.31 to 69.19)
complex partial seizures (Type IB)	13.77 (-8.9 to 73.86)	10.1 (-13.55 to 42.65)	19.38 (-8.78 to 41.52)	0 (-32.14 to 45.45)
secondarily generalized seizures (Type IC)	37.13 (-9.88 to 38.37)	42.11 (-27.27 to 81.25)	85 (16.8 to 100)	86.84 (45.45 to 100)
simple & complex partial seizures (Types IA + IB)	5.97 (0 to 100)	13.33 (-13.58 to 42.98)	17.16 (-13.04 to 41.38)	4.86 (-25.71 to 26.81)

other seizures (all except partial seizures)	1.16 (-9.88 to 30)	0 (0 to 0)	49.11 (-1.79 to 100)	100 (100 to 100)

Notes:

[1] - Type IA: n=36, Type IB: n=63, Type IC: n=18, Type IA+IB: n=67, Other types: n=3

[2] - Type IA: n=33, Type IB: n=62, Type IC: n=21, Type IA+IB: n=67, Other types: n=1

[3] - Type IA: n=38, Type IB: n=60, Type IC: n=20, Type IA+IB: n=66, Other types: n=2

[4] - Type IA: n=41, Type IB: n=63, Type IC: n=14, Type IA+IB: n=68, Other types: n=1

End point values	Lev 3 g			
Subject group type	Reporting group			
Number of subjects analysed	70[5]			
Units: Percentage reduction				
median (inter-quartile range (Q1-Q3))				
simple partial seizures (Type IA)	42.86 (-14 to 88.89)			
complex partial seizures (Type IB)	30 (-13.07 to 63.33)			
secondarily generalized seizures (Type IC)	82.35 (2.63 to 100)			
simple & complex partial seizures (Types IA + IB)	29.44 (-11.11 to 54.55)			
other seizures (all except partial seizures)	100 (100 to 100)			

Notes:

[5] - Type IA: n=41, Type IB: n=61, Type IC: n=21, Type IA+IB: n=66, Other types: n=1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected over a 4-week Up-Titration, 12-week Evaluation (fixed dosage), and 4-week Down-Titration or Transition Period.

Adverse event reporting additional description:

Adverse Events refer to the Safety Set, which is identical to the Full Analysis Set in this study. Full Analysis Set is defined as the set of randomized subjects excluding those who fall under specific pre-defined criteria, like GCP Violation, etc.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo tablets as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Reporting group title	Lev 0.5 g

Reporting group description:

Levetiracetam 0.5 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Reporting group title	Lev 1 g

Reporting group description:

Levetiracetam 1 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Reporting group title	Lev 2 g

Reporting group description:

Levetiracetam 2 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Reporting group title	Lev 3 g

Reporting group description:

Levetiracetam 3 g/day as add-on therapy to ongoing treatment with 1 to 3 AED(s) administered orally twice daily (in the morning and evening).

Serious adverse events	Placebo	Lev 0.5 g	Lev 1 g
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 70 (4.29%)	4 / 71 (5.63%)	2 / 70 (2.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Brain contusion			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	0 / 70 (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
Injury			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	0 / 70 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	0 / 70 (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
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 70 (0.00%)	2 / 71 (2.82%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	0 / 70 (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
Epilepsy			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental impairment			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	0 / 70 (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
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 71 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyoderma			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	0 / 70 (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

Serious adverse events	Lev 2 g	Lev 3 g	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 70 (1.43%)	5 / 70 (7.14%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 70 (0.00%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 70 (0.00%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 70 (0.00%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Ventricular tachycardia			

subjects affected / exposed	0 / 70 (0.00%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 70 (0.00%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 70 (0.00%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental impairment			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 70 (0.00%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Insomnia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyoderma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Lev 0.5 g	Lev 1 g
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 70 (67.14%)	51 / 71 (71.83%)	43 / 70 (61.43%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 70 (5.71%)	3 / 71 (4.23%)	3 / 70 (4.29%)
occurrences (all)	4	3	5
Excoriation			
subjects affected / exposed	0 / 70 (0.00%)	4 / 71 (5.63%)	3 / 70 (4.29%)
occurrences (all)	0	6	3
Investigations			
Neutrophil count decreased			
subjects affected / exposed	3 / 70 (4.29%)	6 / 71 (8.45%)	3 / 70 (4.29%)
occurrences (all)	3	6	3
White blood cell count increased			
subjects affected / exposed	4 / 70 (5.71%)	0 / 71 (0.00%)	0 / 70 (0.00%)
occurrences (all)	4	0	0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	3 / 70 (4.29%)	3 / 71 (4.23%)	2 / 70 (2.86%)
occurrences (all)	6	3	2
Pharyngolaryngeal pain			
subjects affected / exposed	2 / 70 (2.86%)	4 / 71 (5.63%)	4 / 70 (5.71%)
occurrences (all)	2	4	5

Nervous system disorders			
Somnolence			
subjects affected / exposed	7 / 70 (10.00%)	8 / 71 (11.27%)	8 / 70 (11.43%)
occurrences (all)	7	8	9
Headache			
subjects affected / exposed	9 / 70 (12.86%)	6 / 71 (8.45%)	3 / 70 (4.29%)
occurrences (all)	11	7	4
Dizziness			
subjects affected / exposed	3 / 70 (4.29%)	8 / 71 (11.27%)	1 / 70 (1.43%)
occurrences (all)	3	8	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 70 (5.71%)	8 / 71 (11.27%)	4 / 70 (5.71%)
occurrences (all)	6	13	6
Constipation			
subjects affected / exposed	1 / 70 (1.43%)	2 / 71 (2.82%)	2 / 70 (2.86%)
occurrences (all)	1	2	2
Abdominal pain			
subjects affected / exposed	5 / 70 (7.14%)	4 / 71 (5.63%)	0 / 70 (0.00%)
occurrences (all)	5	10	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 70 (34.29%)	24 / 71 (33.80%)	26 / 70 (37.14%)
occurrences (all)	34	36	35
Gastroenteritis			
subjects affected / exposed	2 / 70 (2.86%)	4 / 71 (5.63%)	1 / 70 (1.43%)
occurrences (all)	2	4	1
Dental caries			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	4 / 70 (5.71%)
occurrences (all)	1	0	4

Non-serious adverse events	Lev 2 g	Lev 3 g	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 70 (67.14%)	49 / 70 (70.00%)	

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 70 (10.00%)	6 / 70 (8.57%)	
occurrences (all)	13	7	
Excoriation			
subjects affected / exposed	0 / 70 (0.00%)	3 / 70 (4.29%)	
occurrences (all)	0	3	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 70 (1.43%)	6 / 70 (8.57%)	
occurrences (all)	2	7	
White blood cell count increased			
subjects affected / exposed	1 / 70 (1.43%)	3 / 70 (4.29%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	4 / 70 (5.71%)	4 / 70 (5.71%)	
occurrences (all)	4	6	
Pharyngolaryngeal pain			
subjects affected / exposed	3 / 70 (4.29%)	0 / 70 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Somnolence			
subjects affected / exposed	12 / 70 (17.14%)	12 / 70 (17.14%)	
occurrences (all)	14	12	
Headache			
subjects affected / exposed	4 / 70 (5.71%)	7 / 70 (10.00%)	
occurrences (all)	11	7	
Dizziness			
subjects affected / exposed	5 / 70 (7.14%)	4 / 70 (5.71%)	
occurrences (all)	9	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 70 (2.86%)	1 / 70 (1.43%)	
occurrences (all)	2	1	
Constipation			
subjects affected / exposed	1 / 70 (1.43%)	4 / 70 (5.71%)	

occurrences (all)	1	4	
Abdominal pain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	25 / 70 (35.71%)	28 / 70 (40.00%)	
occurrences (all)	46	45	
Gastroenteritis			
subjects affected / exposed	2 / 70 (2.86%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Dental caries			
subjects affected / exposed	1 / 70 (1.43%)	1 / 70 (1.43%)	
occurrences (all)	1	1	

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