Clinical trial results:
A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Lacosamide as Adjunctive Therapy in Japanese and Chinese Adults With Uncontrolled Partial-Onset Seizures With or Without Secondary Generalization

Summary

EudraCT number	2014-003622-41
Trial protocol	Outside EU/EEA
Global end of trial date	06 August 2014

Results information

Result version number	v1
This version publication date	28 June 2016
First version publication date	07 February 2015

Trial information

Trial identification

Sponsor protocol code	EP0008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01710657
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC: JapicCTI-121988

Notes:

Sponsors

Sponsor organisation name	UCB Pharma SA
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, B-1070
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173481515, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, 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	01 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of Lacosamide (LCM) administered concomitantly with 1 to 3 Antiepileptic Drugs (AEDs) in Japanese and Chinese subjects with or without additional vagus nerve stimulation (VNS) who currently have uncontrolled partial-onset seizures with or without secondary generalization.

Protection of trial subjects:

The use of benzodiazepines, which have the indication for epilepsy for the control of uncountable seizures due to clustering, is restricted to rescue therapy where there is no alternative for 1-time rescue (ie, 3 doses over a 24-hour period) during the Titration Period and 1-time rescue during the Maintenance Period. Benzodiazepines are not allowed during the Baseline Period but may be used during the Transition or Taper Periods to control seizures at the discretion of the investigator.

Background therapy:

Subject must be on a stable dose regimen of at least 1, but no more than 3 Antiepileptic Drugs (AEDs). Only oral administration and daily use are permitted.

Evidence for comparator:

Not applicable

Actual start date of recruitment	28 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 142
Country: Number of subjects enrolled	China: 405
Worldwide total number of subjects	547
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	35
Adults (18-64 years)	509
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 676 subjects with uncontrolled partial-onset seizures (of the 676 subjects, the number of Chinese subjects and Japanese subjects was planned to be 507 and 169, respectively) was planned to be screened and 540 subjects were planned to be enrolled in all regions of Japan and China.

Pre-assignment

Screening details:

Overall, 692 subjects were screened and 548 subjects were enrolled. The Participant Flow refers to the Safety Set (SS) which was defined as all enrolled subjects who took at least 1 dose of Lacosamide. Reasons for discontinuation were only calculated for the SS. 547 subjects were included in the Safety Set.

Period 1

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

Blinding implementation details:

Lacosamide and matching placebo and their accompanying packaging were identical in appearance (size and color), so that neither the investigator nor the subject was able to tell whether the subject was receiving LCM or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching Placebo for 16 weeks.

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

Dosage and administration details:

Matching oral Placebo tablets twice daily for 16 weeks.

Arm title	Lacosamide 200 mg / day

Arm description:

Lacosamide Treatment with dosing of 200 mg / day for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Lacosamide 50 mg
Investigational medicinal product code	SPM927
Other name	Vimpat
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to LCM 200 mg / day will receive LCM 100 mg / day for the first week and LCM 200 mg / day for the remaining 3 weeks of the Titration Period.

Frequency: twice daily
Duration: Subjects who complete the Titration Period will enter a 12-Week Maintenance Period. Subjects will be maintained on the dose achieved during the Titration Period.

Investigational medicinal product name	Lacosamide 100 mg
Investigational medicinal product code	SPM927
Other name	Vimpat
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet Dosage: Subjects randomized to LCM 200 mg / day will receive LCM 100 mg / day for the first week and LCM 200 mg / day for the remaining 3 weeks of the Titration Period.

Frequency: twice daily
Duration: Subjects who complete the Titration Period will enter a 12-Week Maintenance Period. Subjects will be maintained on the dose achieved during the Titration Period.

Arm title	Lacosamide 400 mg / day

Arm description:

Lacosamide Treatment with dosing of 400 mg / day for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Lacosamide 50 mg
Investigational medicinal product code	SPM927
Other name	Vimpat
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage: Subjects randomized to LCM 400 mg / day will start at a dose of 100 mg / day during the first week of the Titration Period. The dose will then be increased by LCM 100 mg / day each week until the 400 mg / day dose is reached at the beginning of Week 4.

Frequency: twice daily
Duration: Subjects who complete the Titration Period will enter a 12-Week Maintenance Period. Subjects will be maintained on the dose achieved during the Titration Period.

Investigational medicinal product name	Lacosamide 100 mg
Investigational medicinal product code	SPM927
Other name	Vimpat
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage: Subjects randomized to LCM 400 mg / day will start at a dose of 100 mg / day during the first week of the Titration Period. The dose will then be increased by LCM 100 mg / day each week until the 400 mg / day dose is reached at the beginning of Week 4.

Frequency: twice daily
Duration: Subjects who complete the Titration Period will enter a 12-Week Maintenance Period. Subjects will be maintained on the dose achieved during the Titration Period.

Number of subjects in period 1	Placebo	Lacosamide 200 mg / day	Lacosamide 400 mg / day
Started	184	183	180
Completed	166	171	148
Not completed	18	12	32
Consent withdrawn by subject	-	1	2

AE, non-serious non-fatal	14	7	25
Lost to follow-up	2	-	1
SAE, non-fatal	-	1	3
Protocol deviation	2	2	-
Lack of efficacy	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo for 16 weeks.	
Reporting group title	Lacosamide 200 mg / day
Reporting group description:	
Lacosamide Treatment with dosing of 200 mg / day for 16 weeks.	
Reporting group title	Lacosamide 400 mg / day
Reporting group description:	
Lacosamide Treatment with dosing of 400 mg / day for 16 weeks.	

Reporting group values	Placebo	Lacosamide 200 mg / day	Lacosamide 400 mg / day
Number of subjects	184	183	180
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)	12	11	12
Adults (18-64 years)	172	170	167
From 65-84 years	0	2	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	31.8	33.2	32.3
standard deviation	± 12	± 12.2	± 11.9
Gender categorical			
Units: Subjects			
Female	82	89	76
Male	102	94	104
Racial group			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	184	183	180
African or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	0	0	0
Other/Mixed	0	0	0
Racial Subgroup			
Units: Subjects			
Chinese	136	136	133
Japanese	48	47	47

Reporting group values	Total		
Number of subjects	547		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	35		
Adults (18-64 years)	509		
From 65-84 years	3		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	247		
Male	300		
Racial group Units: Subjects			
American Indian or Alaska Native	0		
Asian	547		
African or African American	0		
Native Hawaiian or other Pacific Islander	0		
White	0		
Other/Mixed	0		
Racial Subgroup Units: Subjects			
Chinese	405		
Japanese	142		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Matching Placebo for 16 weeks.	
Reporting group title	Lacosamide 200 mg / day
Reporting group description: Lacosamide Treatment with dosing of 200 mg / day for 16 weeks.	
Reporting group title	Lacosamide 400 mg / day
Reporting group description: Lacosamide Treatment with dosing of 400 mg / day for 16 weeks.	
Subject analysis set title	Full Analysis Set - Placebo
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set consists of all subjects who were randomized, received at least 1 dose of study drug, and had at least 1 post-baseline efficacy assessment.	
Subject analysis set title	Full Analysis Set - Lacosamide 200 mg / day
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set consists of all subjects who were randomized, received at least 1 dose of study drug, and had at least 1 post-baseline efficacy assessment.	
Subject analysis set title	Full Analysis Set - Lacosamide 400 mg / day
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set consists of all subjects who were randomized, received at least 1 dose of study drug, and had at least 1 post-baseline efficacy assessment.	

Primary: Change in Partial-Onset Seizure frequency per 28 days from Baseline to the Maintenance Period

End point title	Change in Partial-Onset Seizure frequency per 28 days from Baseline to the Maintenance Period

End point description:

Partial-onset seizure (POS) frequency per 28 days was calculated as:
POS frequency = (Number of POS over the specified time interval) / (Number of days in the interval with available diary data) x 28.
A negative value in Change in Partial-onset seizure frequency indicates a reduction of Partial-onset seizure frequency from Baseline to the Maintenance Period.

End point type	Primary

End point timeframe:

8-week Baseline Period (Visit 1 to 3) and 12-week Maintenance Period (Visit 5 to 8)

End point values	Full Analysis Set - Placebo	Full Analysis Set - Lacosamide 200 mg / day	Full Analysis Set - Lacosamide 400 mg / day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	183	182	179	
Units: Seizure frequency				
median (full range (min-max))	-1.22 (-93 to	-3.33 (-754.3	-4.5 (-97.5 to	

39.8)	to 165.2)	28.2)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Full Analysis Set - Placebo v Full Analysis Set - Lacosamide 400 mg / day
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	ANCOVA
Parameter estimate	% Reduction over Placebo
Point estimate	39.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.5
upper limit	47.6

Notes:

[1] - To avoid inflation of Type I error, hypothesis testing followed predefined hierarchical procedure starting LCM 400 mg/day treatment group versus the placebo group.
If the test was not statistically significant, the procedure stopped and no Groups were declared different from placebo. If the test was statistically significant, the treatment group was considered different from placebo and the procedure continued with the LCM 200 mg/day treatment group.
[2] - Significant at the 0.05 level.
This testing procedure is considered a closed testing procedure and no adjustment of the significance level was necessary.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Full Analysis Set - Placebo v Full Analysis Set - Lacosamide 200 mg / day
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	ANCOVA
Parameter estimate	% Reduction over Placebo
Point estimate	29.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.7
upper limit	38.7

Notes:

[3] - To avoid inflation of Type I error, hypothesis testing followed predefined hierarchical procedure starting LCM 400 mg/day treatment group versus the placebo group.
If the test was not statistically significant, the procedure stopped and no Groups were declared different from placebo. If the test was statistically significant, the treatment group was considered different from placebo and the procedure continued with the LCM 200 mg/day treatment group.

[4] - Significant at the 0.05 level.
This testing procedure is considered a closed testing procedure and no adjustment of the significance level was necessary.

Secondary: The proportion of individual patients who experience a 50 % or greater reduction in Partial-Onset Seizure frequency from Baseline to the Maintenance Period (50 % responder rate)

End point title	The proportion of individual patients who experience a 50 % or greater reduction in Partial-Onset Seizure frequency from Baseline to the Maintenance Period (50 % responder rate)

End point description:

End point type	Secondary

End point timeframe:

8-week Baseline Period (Visit1 to 3) to the 12-week Maintenance Period (Visit 5 to 8)

End point values	Full Analysis Set - Placebo	Full Analysis Set - Lacosamide 200 mg / day	Full Analysis Set - Lacosamide 400 mg / day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	183	182	179	
Units: Participants	36	70	88	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Partial-Onset Seizure Frequency Per 28 Days From Baseline to the Maintenance Period

End point title	Percent Change in Partial-Onset Seizure Frequency Per 28 Days From Baseline to the Maintenance Period

End point description:

Calculates as 28-day seizure frequency during the Maintenance Period - 28-day seizure frequency during the Baseline Period, divided by the 28-day seizure frequency during the Baseline Period with this quantity multiplied by 100. A negative value in percent change from Baseline indicates a decrease in Partial-Onset Seizure frequency from Baseline to the Maintenance Period.

End point type	Secondary

End point timeframe:

8-week Baseline Period (Visit 1 to 3) to the 12-week Maintenance Period (Visit 5 to 8)

End point values	Full Analysis Set - Placebo	Full Analysis Set - Lacosamide 200 mg / day	Full Analysis Set - Lacosamide 400 mg / day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	183	182	179	
Units: percent				
median (full range (min-max))	-10.1 (-97.6 to 233.5)	-36.75 (-100 to 185.5)	-48.78 (-100 to 346.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Partial-Onset Seizure frequency per 28 days from Baseline to the Treatment Period (i.e., Titration + Maintenance Period)

End point title	Change in Partial-Onset Seizure frequency per 28 days from Baseline to the Treatment Period (i.e., Titration + Maintenance Period)

End point description:

Partial-onset seizure (POS) frequency per 28 days was calculated as:
POS frequency = (Number of POS over the specified time interval) / (Number of days in the interval with available diary data) x 28.
A negative value in Change in Partial-onset seizure frequency indicates a reduction of Partial-onset seizure frequency from Baseline to the Treatment Period.

End point type	Secondary

End point timeframe:

8-week Baseline Period (Visit 1 to 3) to the 16-week Treatment Period (Visit 3 to 8)

End point values	Full Analysis Set - Placebo	Full Analysis Set - Lacosamide 200 mg / day	Full Analysis Set - Lacosamide 400 mg / day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	183	182	179	
Units: Seizure frequency				
median (full range (min-max))	-1.1 (-102.4 to 102.5)	-3.39 (-670 to 138.9)	-4 (-92.4 to 34.2)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events (AEs) were collected from Baseline to the end of the study (up to Week 19).	
Adverse event reporting additional description:	
Treatment Emergent Adverse Events (TEAEs) refer to the Safety Set (SS). The SS includes all randomized subjects who took at least 1 dose of study drug.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo for 16 weeks.	
Reporting group title	Lacosamide 200 mg / day
Reporting group description:	
Lacosamide Treatment with dosing of 200 mg / day for 16 weeks.	
Reporting group title	Lacosamide 400 mg / day
Reporting group description:	
Lacosamide Treatment with dosing of 400 mg / day for 16 weeks.	

Serious adverse events	Placebo	Lacosamide 200 mg / day	Lacosamide 400 mg / day
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 184 (2.17%)	2 / 183 (1.09%)	9 / 180 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 180 (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
Injury, poisoning and procedural complications			
Comminuted fracture			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			

subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
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			
Abortion induced			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
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			
Dizziness			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 180 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Epileptic psychosis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 180 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
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	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 180 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 180 (0.56%)
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: 5 %

Non-serious adverse events	Placebo	Lacosamide 200 mg / day	Lacosamide 400 mg / day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 184 (41.85%)	87 / 183 (47.54%)	112 / 180 (62.22%)
Investigations			
White blood cell count decreased			
subjects affected / exposed	2 / 184 (1.09%)	8 / 183 (4.37%)	10 / 180 (5.56%)
occurrences (all)	2	14	12
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 184 (13.04%)	33 / 183 (18.03%)	63 / 180 (35.00%)
occurrences (all)	32	57	118
Somnolence			
subjects affected / exposed	9 / 184 (4.89%)	18 / 183 (9.84%)	19 / 180 (10.56%)
occurrences (all)	10	26	21
Headache			
subjects affected / exposed	11 / 184 (5.98%)	16 / 183 (8.74%)	19 / 180 (10.56%)
occurrences (all)	21	18	32
Eye disorders			
Diplopia			
subjects affected / exposed	4 / 184 (2.17%)	4 / 183 (2.19%)	13 / 180 (7.22%)
occurrences (all)	5	8	15
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 184 (2.17%)	5 / 183 (2.73%)	14 / 180 (7.78%)
occurrences (all)	4	6	18
Nausea			
subjects affected / exposed	9 / 184 (4.89%)	7 / 183 (3.83%)	10 / 180 (5.56%)
occurrences (all)	10	8	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 184 (13.04%)	28 / 183 (15.30%)	29 / 180 (16.11%)
occurrences (all)	41	40	36
Upper respiratory tract infection			
subjects affected / exposed	22 / 184 (11.96%)	10 / 183 (5.46%)	19 / 180 (10.56%)
occurrences (all)	31	14	28

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/23859801