EU Clinical Trials Register

Clinical trial results:
A Randomized, Comparative, Double-Blind, Parallel-Group, Multicenter, Monotherapy, Study Of Pregabalin (Lyrica) And Lamotrigine(Lamicital) In Patients With Newly Diagnosed Partial Seizures

Summary

EudraCT number	2005-004023-19
Trial protocol	GB SE PT ES BE IE CZ LT DE SK IT HU FI EE BG LV
Global end of trial date	01 April 2010

Results information

Result version number	v1 (current)
This version publication date	30 May 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	A0081046

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00280059
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	08 September 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate the efficacy of pregabalin as a monotherapy treatment compared with lamotrigine, both administered twice a day (BID), in subjects with newly diagnosed partial seizures.
2. To assess the safety and tolerability of pregabalin monotherapy compared with lamotrigine.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2006
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	Norway: 3
Country: Number of subjects enrolled	Portugal: 27
Country: Number of subjects enrolled	Slovakia: 21
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Bulgaria: 29
Country: Number of subjects enrolled	Czech Republic: 41
Country: Number of subjects enrolled	Estonia: 7
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Lithuania: 81
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	China: 50

Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Hong Kong: 33
Country: Number of subjects enrolled	India: 51
Country: Number of subjects enrolled	Korea, Republic of: 82
Country: Number of subjects enrolled	Mexico: 26
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Taiwan: 34
Worldwide total number of subjects	660
EEA total number of subjects	347

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)	18
Adults (18-64 years)	609
From 65 to 84 years	32
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study was initiated on 07 August 2006 and completed on 01 April 2010. Subjects were enrolled from 28 countries.

Period 1

Period 1 title	Efficacy Assessment Phase
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
Arm title	Pregabalin- Efficacy Phase

Arm description:

Pregabalin administered orally.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Lyrica
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pregabalin 150, 300, 450 or 600 milligrams per day (mg/day) twice daily (BID); individual titration based on number of seizures experienced once Level 1 (150 mg/day) was maintained for at least 7 days, and dose reductions based on intolerable adverse events. Escalation to next dose level allowed only after completing previous dose level for at least 1 week.

Arm title	Lamotrigine- Efficacy Phase

Arm description:

Lamotrigine administered orally.

Arm type	Active comparator
Investigational medicinal product name	Lamotrigine
Investigational medicinal product code	
Other name	Lamictal
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lamotrigine 100, 200, 400, or 500 mg/day BID; individual titration based on number of seizures experienced once Level 1 (100 mg/day) was reached and maintained for 7 days, and dose reductions based on intolerable adverse events. Escalation to next dose level allowed only after completing previous dose level for at least 1 week.

Number of subjects in period 1	Pregabalin- Efficacy Phase	Lamotrigine- Efficacy Phase
Started	330	330
Completed	236	250
Not completed	94	80
Consent withdrawn by subject	26	25
Adverse Event	33	31
Death	2	-
Laboratory abnormaility	1	-
Unspecified	7	8
Lost to follow-up	6	13
Lack of efficacy	19	3

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Pregabalin- Extension Phase

Arm description:

Pregabalin administered orally.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Lyrica
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pregabalin 150, 300, 450 or 600 mg/day orally twice daily (BID); individual titration based on number of seizures experienced once Level 1 (150 mg/day) was maintained for at least 7 days, and dose reductions based on intolerable adverse events. Escalation to next dose level allowed only after completing previous dose level for at least 1 week.

Arm title	Lamotrigine- Extension Phase

Arm description:

Lamotrigine administered orally.

Arm type	Active comparator
Investigational medicinal product name	Lamotrigine
Investigational medicinal product code	
Other name	Lamictal
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lamotrigine 100, 200, 400, or 500 mg/day BID; individual titration based on number of seizures experienced once Level 1 (100 mg/day) was reached and maintained for 7 days, and dose reductions based on intolerable adverse events. Escalation to next dose level allowed only after completing previous dose level for at least 1 week.

Number of subjects in period 2[1]	Pregabalin-Extension Phase	Lamotrigine-Extension Phase
Started	194	215
Completed	145	177
Not completed	49	38
Unspecified	49	38

Notes:

[1] - 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: Since "Extension Phase" (Period 2) was an optional phase, the number of subjects who entered it was less than the number who completed the "Efficacy Assessment Phase" (Period 1).

Baseline characteristics

Reporting groups

Reporting group title	Pregabalin- Efficacy Phase
Reporting group description:	
Pregabalin administered orally.	
Reporting group title	Lamotrigine- Efficacy Phase
Reporting group description:	
Lamotrigine administered orally.	

Reporting group values	Pregabalin- Efficacy Phase	Lamotrigine- Efficacy Phase	Total
Number of subjects	330	330	660
Age categorical			
Units: Subjects			
< 18 years	9	9	18
Between 18 and 44 years	228	228	456
Between 45 and 64 years	79	74	153
>= 65 years	14	19	33
Gender categorical			
Units: Subjects			
Female	165	146	311
Male	165	184	349

End points

End points reporting groups

Reporting group title	Pregabalin- Efficacy Phase
Reporting group description:	
Pregabalin administered orally.	
Reporting group title	Lamotrigine- Efficacy Phase
Reporting group description:	
Lamotrigine administered orally.	
Reporting group title	Pregabalin- Extension Phase
Reporting group description:	
Pregabalin administered orally.	
Reporting group title	Lamotrigine- Extension Phase
Reporting group description:	
Lamotrigine administered orally.	
Subject analysis set title	Pregabalin 150 mg/Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Pregabalin 150 mg/day administered twice daily (BID).	
Subject analysis set title	Pregabalin 300 mg/Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Pregabalin 300 mg/day administered BID.	
Subject analysis set title	Pregabalin 450 mg/Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Pregabalin 450 mg/day administered BID.	
Subject analysis set title	Pregabalin 600 mg/Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Pregabalin 600 mg/day administered BID.	
Subject analysis set title	Lamotrigine 100 mg/Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Lamotrigine 100 mg/day administered BID.	
Subject analysis set title	Lamotrigine 200 mg/Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Lamotrigine 200 mg/day administered BID.	
Subject analysis set title	Lamotrigine 400 mg/Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Lamotrigine 400 mg/day administered BID.	
Subject analysis set title	Lamotrigine 500 mg/Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Lamotrigine 500 mg/day administered BID.	

Primary: Percentage of Seizure-free Subjects (Responders) During Efficacy Assessment Phase

End point title	Percentage of Seizure-free Subjects (Responders) During Efficacy Assessment Phase

End point description:

Responders equal to (=) subjects who achieved any 6 consecutive months (greater than [>] 182 days) of seizure-freedom (absence of partial seizures, generalized seizures and unclassified epileptic seizures) during the 52 week efficacy assessment phase. Full analysis set (FAS) (intent to treat population): randomized subjects who took at least 1 dose of study medication. Analysis excludes subjects who did not enter maintenance phase of study.

End point type	Primary

End point timeframe:

Week 5 up to Week 56

End point values	Pregabalin- Efficacy Phase	Lamotrigine- Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314[1]	308[2]		
Units: percentage of subjects				
number (not applicable)	51.6	67.9		

Notes:

[1] - N = number of subjects who had at least 1 dose of study treatment and seizure efficacy data.

[2] - N = number of subjects who had at least 1 dose of study treatment and seizure efficacy data.

Statistical analyses

Statistical analysis title	Analysis of Percentage (%) of Responders

Statistical analysis description:

Analysis of binary response variable for 6 consecutive months seizure freedom analyzed by comparing proportions of favorable responders between the 2 treatment groups after stratifying by clusters and correcting for skewness(Gart and Nam,1990). Percentage obtained by multiplying proportion by 100. 95% confidence interval(CI) for true difference in proportions, as well as 1-sided test at α=0.025;CI adjusted for centers clustered within a geographical region with upper and lower confidence limits.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	Gart and Nam: correction of skewness
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	-0.09

Notes:

[3] - Non-inferiority margin for the proportion of seizure free subjects set at 10%; non-inferiority declared if the lower bound of the 95% confidence interval (CI) of the difference in seizure-free proportion between pregabalin and lamotrigine was no more than 10% in favor of lamotrigine, but 0 was contained within the lower bound of the CI. Interpretation of superiority required lower bound of CI did not contain 0 in favor of pregabalin.

Secondary: Time to 6 Consecutive Months of Seizure-freedom After 4-week Dose

Escalation Phase: All Seizures

End point title	Time to 6 Consecutive Months of Seizure-freedom After 4-week Dose Escalation Phase: All Seizures

End point description:

Time in days, from first day of study medication to the first 6 months of seizure freedom after Day 28. Subjects who did not achieve 6 months seizure freedom after Day 28 were censored from analysis. FAS. N = number of subjects who entered maintenance phase of study and had seizure efficacy data.

End point type	Secondary

End point timeframe:

Week 4 up to Week 56

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	308		
Units: days				
median (confidence interval 95%)	254 (199 to 295)	183 (183 to 209)		

Statistical analyses

Statistical analysis title	Analysis of Time to 6 Months of Seizure-freedom

Statistical analysis description:

Risk ratio=hazard ratio estimated from the Cox proportional hazards model for assessing a treatment difference, risk ratio > 1 is in favor of pregabalin. The 95% confidence interval is for the true risk ratio.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034 [4]
Method	Regression, Cox
Parameter estimate	Risk ratio (RR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.9

Notes:

[4] - Nominal value for 2-sided test calculated using Cox proportional hazards model, adjusted for geographic regions.

Secondary: Exit Due to Adverse Events During the Double-blind Treatment Phase (Including Dose Escalation Phase)

End point title	Exit Due to Adverse Events During the Double-blind Treatment Phase (Including Dose Escalation Phase)

End point description:

Number of subjects who exited the study due to adverse events during the double-blind treatment period. Time in days, from first day of study treatment to day of exit from the study due to an adverse

event (that is [ie], last day on study medication) during the double blind treatment period (including dose escalation phase) was inestimable. Observations with other reasons for exiting or subjects who did not exit the study were right censored as of the last day on study medication. FAS. Time to exit due to adverse events was inestimable as survival estimate at end of maintenance phase was below 0.500.

End point type	Secondary
End point timeframe:	

Week 0 to Week 56

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330[5]	330[6]		
Units: subjects	33	31		

Notes:

[5] - N = number of subjects who entered maintenance phase of study and had seizure efficacy data.

[6] - N = number of subjects who entered maintenance phase of study and had seizure efficacy data.

Statistical analyses

Statistical analysis title	Analysis of Exit due to Adverse Events

Statistical analysis description:

Risk ratio=hazard ratio estimated from the Cox proportional hazards model for assessing a treatment difference, risk ratio less than (<) 1 is in favor of pregabalin. The 95% confidence interval is for the true risk ratio.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8047 [7]
Method	Cox proportional hazards model
Parameter estimate	Risk ratio (RR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.74

Notes:

[7] - Nominal value for 2-sided test calculated using Cox proportional hazards model adjusted for geographical cluster.

Secondary: Exit for Any Reason During the Double-blind Treatment Phase (Including Dose Escalation Phase)

End point title	Exit for Any Reason During the Double-blind Treatment Phase (Including Dose Escalation Phase)

End point description:

Number of subjects who exited the study for any reason during the double blind treatment phase. Time in days, from first day of study treatment to day of exit from the study due to any reason (ie, last day on study medication) was inestimable. Subjects who did not exit the study were right censored as of the last day on study medication. FAS. Time to exit for any reason during the double-blind treatment phase was inestimable as the survival estimate at the end of the maintenance phase was below 0.500.

End point type	Secondary

End point timeframe:

Week 0 to Week 56

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330[8]	330[9]		
Units: subjects	94	80		

Notes:

[8] - N = number of subjects who had at least 1 dose of study treatment and seizure efficacy data.

[9] - N = number of subjects who had at least 1 dose of study treatment and seizure efficacy data.

Statistical analyses

Statistical analysis title	Analysis of Exit for any Reason

Statistical analysis description:

Risk ratio=hazard ratio estimated from the Cox proportional hazards model for assessing a treatment difference, risk ratio < 1 is in favor of pregabalin. The 95% confidence interval is for the true risk ratio.

Comparison groups	Lamotrigine- Efficacy Phase v Pregabalin- Efficacy Phase
Number of subjects included in analysis	660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2537 [10]
Method	Cox proportional hazards model
Parameter estimate	Risk ratio (RR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.6

Notes:

[10] - Nominal value for 2-sided test calculated using Cox proportional hazards model adjusted for geographical cluster.

Secondary: Exit Due to Lack of Efficacy After 4-week Dose Escalation Phase

End point title	Exit Due to Lack of Efficacy After 4-week Dose Escalation Phase

End point description:

Number of subjects who exited the study due to lack of efficacy after the 4-week dose escalation phase. Time in days, from first day of study treatment to day of exit due to lack of efficacy after Day 28 of the escalation phase (ie, last day on study medication) was inestimable. Subjects who did not exit or exited for a different reason were right censored as of the last day on study medication. FAS.Time to exit due to lack of efficacy after 4-week dose escalation phase was inestimable as survival estimate at end of maintenance phase was below 0.500.

End point type	Secondary

End point timeframe:

Week 4 up to Week 56

End point values	Pregabalin- Efficacy Phase	Lamotrigine- Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[11]	330		
Units: subjects	78	58		

Notes:

[11] - N = number of subjects who entered maintenance phase of study and had seizure efficacy data.

Statistical analyses

Statistical analysis title	Analysis of Exit due to Efficacy

Statistical analysis description:

Risk ratio=hazard ratio estimated from the Cox proportional hazards model for assessing a treatment difference, risk ratio < 1 is in favor of pregabalin. The 95% confidence interval is for the true risk ratio.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0025 [12]
Method	Cox proportional hazards model
Parameter estimate	Risk ratio (RR)
Point estimate	6.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.93
upper limit	22.04

Notes:

[12] - Nominal value for 2-sided test calculated using Cox proportional hazards model adjusted for geographical cluster.

Secondary: Exit Due to Any Reason After 4-week Dose Escalation Phase

End point title	Exit Due to Any Reason After 4-week Dose Escalation Phase

End point description:

Number of subjects who exited the study due to any reason after the 4-week dose escalation phase. Time in days, from first day of study treatment to day of exit after Day 28 of the study due to any reason (ie, last day on study medication) was inestimable. Subjects who did not exit or did not reach this phase were right censored as of the last day on study medication. FAS. Time to exit for any reason after the 4-week dose escalation phase was inestimable as the survival estimate at the end of the maintenance phase was below 0.500.

End point type	Secondary

End point timeframe:

Week 4 up to Week 56

End point values	Pregabalin- Efficacy Phase	Lamotrigine- Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[13]	300[14]		
Units: subjects	78	58		

Notes:

[13] - N = number of subjects who entered maintenance phase of study and had seizure efficacy data.

[14] - N = number of subjects who entered maintenance phase of study and had seizure efficacy data.

Statistical analyses

Statistical analysis title	Exit After 4-week Dose Escalation Phase
Statistical analysis description:	
Risk ratio=hazard ratio estimated from the Cox proportional hazards model for assessing a treatment difference, risk ratio < 1 is in favor of pregabalin. The 95% confidence interval is for the true risk ratio.	
Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0744 [15]
Method	Cox proportional hazards model
Parameter estimate	Risk ratio (RR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.91

Notes:

[15] - Nominal value for 2-sided test calculated using Cox proportional hazards model adjusted for geographical cluster.

Secondary: Time to First Seizure After the 4-Week Dose Escalation Phase

End point title	Time to First Seizure After the 4-Week Dose Escalation Phase
End point description:	
Time in days, from first day of study treatment to the day of first seizure after Day 28 of the escalation phase (ie, last day on study medication). Subjects who did not reach this phase or who did not have a seizure after Day 28 were right censored from the analysis as of the last day on study medication. FAS.	
End point type	Secondary
End point timeframe:	
Week 4 up to Week 56	

End point values	Pregabalin- Efficacy Phase	Lamotrigine- Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[16]	300[17]		
Units: days				
median (confidence interval 95%)	85 (59 to 120)	211 (145 to 342)		

Notes:

[16] - N = number of subjects who entered maintenance phase of study and had seizure efficacy data.

[17] - N = number of subjects who entered maintenance phase of study and had seizure efficacy data.

Statistical analyses

Statistical analysis title	Analysis of Time to First Seizure
Statistical analysis description:	
Risk ratio=hazard ratio estimated from the Cox proportional hazards model for assessing a treatment difference, risk ratio < 1 is in favor of pregabalin. The 95% confidence interval is for the true risk ratio.	
Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [18]
Method	Cox proportional hazards model
Parameter estimate	Risk ratio (RR)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.8

Notes:

[18] - Nominal value for 2-sided test calculated using Cox proportional hazards model adjusted for geographical cluster.

Secondary: Median Monthy Seizure Frequency: All Partial Seizures

End point title	Median Monthy Seizure Frequency: All Partial Seizures
End point description:	
All partial seizures include complex partial seizures, simple partial seizures, and partial seizures evolving to secondarily generalized seizures. Seizure frequency based on 28-day seizure rate: number (#) of seizures in period (month) divided by # days in period minus # of missing diary days in period * 28. Month of time = number of months after Week 4 (Dose Escalation). FAS.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 60	

End point values	Pregabalin- Efficacy Phase	Lamotrigine- Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[19]	330		
Units: seizures/28 days				
median (standard deviation)				
Dose-escalation phase (Weeks 1 - 4) (n=329, 330)	0 (± 9.348)	0 (± 27.118)		
Month 1 (n=314, 308)	0 (± 6.139)	0 (± 31.453)		
Month 2 (n=300, 295)	0 (± 3.382)	0 (± 28.839)		
Month 3 (n=287, 288)	0 (± 2.568)	0 (± 32.783)		
Month 4 (n=279, 278)	0 (± 2.313)	0 (± 16.046)		
Month 5 (n=274, 276)	0 (± 2.27)	0 (± 15.254)		
Month 6 (n=266, 272)	0 (± 2.702)	0 (± 15.126)		
Month 7 (n=260, 270)	0 (± 2.839)	0 (± 16.855)		
Month 8 (n=256, 266)	0 (± 3.247)	0 (± 19.111)		
Month 9 (n=253, 262)	0 (± 2.538)	0 (± 17.204)		

Month 10 (n=250, 257)	0 (± 4.935)	0 (± 16.905)	
Month 11 (n=242, 254)	0 (± 3.082)	0 (± 19.268)	
Month 12 (n=238, 252)	0 (± 7.018)	0 (± 19.59)	
Month 13 (n=210, 227)	0 (± 3.247)	0 (± 19.462)	
Taper (Week 57 to Week 60) (n=71, 45)	0 (± 6.418)	0 (± 97.196)	

Notes:

[19] - N = number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Monthy Seizure Frequency: All Partial Seizures

End point title	Mean Monthy Seizure Frequency: All Partial Seizures

End point description:

All partial seizures include complex partial seizures, simple partial seizures, and partial seizures evolving to secondarily generalized seizures. Seizure frequency based on 28-day seizure rate: number (#) of seizures in period (month) divided by # days in period minus # of missing diary days in period * 28. Month of time = number of months after Week 4 (Dose Escalation). FAS.n = number of subjects with analyzable data at observation.

End point type	Secondary

End point timeframe:

Baseline up to Week 60

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[20]	330		
Units: seizures/28 days				
arithmetic mean (standard deviation)				
Dose escalation phase (n=329, 330)	2.56 (± 9.348)	5.08 (± 27.118)		
Month 1 (n=314, 308)	2.23 (± 6.139)	4.21 (± 31.453)		
Month 2 (n=300, 295)	1.18 (± 3.382)	3.21 (± 28.839)		
Month 3 (n=287, 288)	0.94 (± 2.568)	3.54 (± 32.783)		
Month 4 (n=279, 278)	0.89 (± 2.313)	1.67 (± 16.046)		
Month 5 (n=274, 276)	0.78 (± 2.27)	1.58 (± 15.254)		
Month 6 (n=266, 272)	0.82 (± 2.702)	1.41 (± 15.126)		
Month 7 (n=260, 270)	0.78 (± 2.839)	1.5 (± 16.855)		
Month 8 (n=256, 266)	0.77 (± 3.247)	1.36 (± 19.111)		
Month 9 (n=253, 262)	0.71 (± 2.538)	1.38 (± 17.204)		
Month 10 (n=250, 257)	1.05 (± 4.935)	1.33 (± 16.905)		
Month 11 (n=242, 254)	0.79 (± 3.082)	1.41 (± 19.268)		

Month 12 (n=238, 252)	0.94 (± 7.018)	1.67 (± 19.59)	
Month 13 (n=210, 227)	0.65 (± 3.247)	2.11 (± 19.462)	
Taper (n=71, 45)	2.13 (± 6.418)	19.97 (± 97.196)	

Notes:

[20] - N = number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Monthy Seizure Frequency: All Seizures

End point title	Median Monthy Seizure Frequency: All Seizures

End point description:

Seizure frequency based on 28-day seizure rate: number (#) of seizures in period (month) divided by # days in period minus # of missing diary days in period * 28. Month of time = number of months after Week 4 (Dose Escalation). FAS. n = number of subjects with analyzable data at observation.

End point type	Secondary

End point timeframe:

Baseline up to Week 60

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[21]	330		
Units: seizures/28 days				
median (standard deviation)				
Dose-escalation phase (Weeks 1 - 4)(n=329, 330)	0 (± 9.819)	0 (± 27.128)		
Month 1 (n=314, 308)	0 (± 6.164)	0 (± 31.452)		
Month 2 (n=300, 295)	0 (± 5.498)	0 (± 28.838)		
Month 3 (n=287, 288)	0 (± 2.702)	0 (± 32.782)		
Month 4 (n=279, 278)	0 (± 3.223)	0 (± 16.046)		
Month 5 (n=274, 276)	0 (± 2.458)	0 (± 15.254)		
Month 6 (n=266, 272)	0 (± 2.853)	0 (± 15.126)		
Month 7 (n=260, 270)	0 (± 2.898)	0 (± 16.855)		
Month 8 (n=256, 266)	0 (± 3.304)	0 (± 19.11)		
Month 9 (n=253, 262)	0 (± 2.636)	0 (± 17.204)		
Month 10 (n=250, 257)	0 (± 4.934)	0 (± 16.905)		
Month 11 (n=242, 254)	0 (± 3.224)	0 (± 19.268)		
Month 12 (n=238, 252)	0 (± 7.019)	0 (± 19.59)		
Month 13 (n=210, 227)	0 (± 3.247)	0 (± 19.462)		
Taper (Week 57 to Week 60) (n=71, 45)	0 (± 6.418)	0 (± 97.196)		

Notes:

[21] - N = number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Monthy Seizure Frequency: All Seizures

End point title	Mean Monthy Seizure Frequency: All Seizures

End point description:

Seizure frequency based on 28-day seizure rate: number (#) of seizures in period (month) divided by # days in period minus # of missing diary days in period * 28. Month of time = number of months after Week 4 (Dose Escalation). FAS. n = number of subjects with analyzable data at observation.

End point type	Secondary

End point timeframe:

Baseline up to Week 60

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[22]	330		
Units: seizures/28 days				
arithmetic mean (standard deviation)				
Dose-escalation phase (n=329, 330)	2.74 (± 9.819)	5.1 (± 27.128)		
Month 1 (n=314, 308)	2.31 (± 6.164)	4.24 (± 31.452)		
Month 2 (n=300, 295)	1.53 (± 5.498)	3.22 (± 28.838)		
Month 3 (n=287, 288)	1.02 (± 2.702)	3.57 (± 32.782)		
Month 4 (n=279, 278)	1.06 (± 3.223)	1.68 (± 16.046)		
Month 5 (n=274, 276)	0.87 (± 2.458)	1.59 (± 15.254)		
Month 6 (n=266, 272)	0.89 (± 2.853)	1.41 (± 15.126)		
Month 7 (n=260, 270)	0.83 (± 2.898)	1.5 (± 16.855)		
Month 8 (n=256, 266)	0.82 (± 3.304)	1.37 (± 19.11)		
Month 9 (n=253, 262)	0.78 (± 2.636)	1.38 (± 17.204)		
Month 10 (n=250, 257)	1.06 (± 4.934)	1.33 (± 16.905)		
Month 11 (n=242, 254)	0.81 (± 3.224)	1.41 (± 19.268)		
Month 12 (n=238, 252)	0.96 (± 7.019)	1.67 (± 19.59)		
Month 13 (n=210, 227)	0.65 (± 3.247)	2.12 (± 19.462)		
Taper (n=71, 45)	2.13 (± 6.418)	19.97 (± 97.196)		

Notes:

[22] - N = number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Monthy Seizure Frequency of Responders for the Months After

Achieving 6 Consecutive Months of Seizure Freedom: All Partial Seizures

End point title	Median Monthy Seizure Frequency of Responders for the Months After Achieving 6 Consecutive Months of Seizure Freedom: All Partial Seizures

End point description:

All partial seizures include complex partial seizures, simple partial seizures, and partial seizures evolving to secondarily generalized seizures. Seizure frequency based on 28-day seizure rate: number (#) of seizures in period (month) divided by # days in period minus # of missing diary days in period * 28. Responder = subject who achieved at least 6 months of seizure freedom after Week 4 and up to Week 56. Monthly seizure frequency measured from day of achievement of 6 months of seizure freedom. FAS. n = number of responders with analyzable data at observation. Here "99999" in the standard deviation (SD) and median signifies not available (NA). SD was not calculated as either no subject (n=0) or 1 subject (n=1) was evaluated at these time points. Median was not calculated at month 9 for 'Pregabalin' arm as no responders with analyzable data were found.

End point type	Secondary

End point timeframe:

Month 1 through Month 9 (after 6 months seizure freedom achieved)

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[23]	208[24]		
Units: seizures/28 days				
median (standard deviation)				
Month 1 (n=162, 208)	0 (± 1)	0 (± 0.226)		
Month 2 (n=155, 194)	0 (± 1.783)	0 (± 0.226)		
Month 3 (n=147, 184)	0 (± 0.384)	0 (± 0.439)		
Month 4 (n=139, 173)	0 (± 0.329)	0 (± 0.211)		
Month 5 (n=127, 158)	0 (± 0.926)	0 (± 0.823)		
Month 6 (n=122, 152)	0 (± 0.156)	0 (± 0.213)		
Month 7 (n=105, 136)	0 (± 0)	0 (± 2.843)		
Month 8 (n=1, 5)	0 (± 99999)	0 (± 0)		
Month 9 (n=0, 1)	99999 (± 99999)	6 (± 99999)		

Notes:

[23] - N = number of responders.

[24] - N = number of responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Monthy Seizure Frequency of Responders for the Months After Achieving 6 Consecutive Months of Seizure Freedom: All Partial Seizures

End point title	Mean Monthy Seizure Frequency of Responders for the Months After Achieving 6 Consecutive Months of Seizure Freedom: All Partial Seizures

End point description:

All partial seizures include complex partial seizures, simple partial seizures, and partial seizures evolving to secondarily generalized seizures. Seizure frequency based on 28-day seizure rate: number (#) of seizures in period (month) divided by # days in period minus # of missing diary days in period * 28. Responder = subject who achieved at least 6 months of seizure freedom after Week 4 and up to Week 56. Monthly seizure frequency measured from day of achievement of 6 months of seizure freedom. FAS. n = number of responders with analyzable data at observation. Here "99999" in SD and arithmetic mean signifies not available (NA). SD was not calculated as either no subject (n=0) or only 1 subject (n=1)

was evaluated at these time points. Mean was not calculated at month 9 for 'Pregabalin' arm as no responders with analyzable data were found.

End point type	Secondary

End point timeframe:

Month 1 through Month 9 (after 6 months seizure freedom achieved)

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[25]	208[26]		
Units: 28-day seizure rate				
arithmetic mean (standard deviation)				
Month 1 (n=162, 208)	0.19 (± 1)	0.04 (± 0.226)		
Month 2 (n=155, 194)	0.28 (± 1.783)	0.03 (± 0.226)		
Month 3 (n=147, 184)	0.05 (± 0.384)	0.07 (± 0.439)		
Month 4 (n=139, 173)	0.09 (± 0.329)	0.05 (± 0.211)		
Month 5 (n=127, 158)	0.15 (± 0.926)	0.1 (± 0.823)		
Month 6 (n=122, 152)	0.02 (± 0.156)	0.03 (± 0.213)		
Month 7 (n=105, 136)	0 (± 0)	0.28 (± 2.843)		
Month 8 (n=1, 5)	0 (± 99999)	0 (± 0)		
Month 9 (n=0, 1)	99999 (± 99999)	6 (± 99999)		

Notes:

[25] - N = number of responders.

[26] - N = number of responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Monthy Seizure Frequency of Responders for the Months After Achieving 6 Consecutive Months of Seizure Freedom: All Seizures

End point title	Median Monthy Seizure Frequency of Responders for the Months After Achieving 6 Consecutive Months of Seizure Freedom: All Seizures

End point description:

Seizure frequency based on 28-day seizure rate: number (#) of seizures in period (month) divided by # days in period minus # of missing diary days in period * 28. Responder = subject who achieved at least 6 months of seizure freedom after Week 4 and up to Week 56. Monthly seizure frequency measured from day of achievement of 6 months of seizure freedom. FAS. n = number of responders with analyzable data at observation. Here "99999" in the SD and median signifies not available (NA). SD was not calculated as either no subject (n=0) or only 1 subject (n=1) was evaluated at these time points. Median was not calculated at month 9 for 'Pregabalin' arm as no responders with analyzable data were found.

End point type	Secondary

End point timeframe:

Month 1 through Month 9 (after 6 months seizure freedom achieved)

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[27]	208[28]		
Units: seizures/28 days				
median (standard deviation)				
Month 1 (n=162, 208)	0 (± 1)	0 (± 0.236)		
Month 2 (n=155, 194)	0 (± 1.783)	0 (± 0.226)		
Month 3 (n=147, 184)	0 (± 0.4)	0 (± 0.439)		
Month 4 (n=139, 173)	0 (± 0.359)	0 (± 0.211)		
Month 5 (n=127, 158)	0 (± 0.971)	0 (± 0.823)		
Month 6 (n=122, 152)	0 (± 0.156)	0 (± 0.213)		
Month 7 (n=105, 136)	0 (± 0)	0 (± 2.844)		
Month 8 (n=1, 5)	0 (± 99999)	0 (± 0)		
Month 9 (n=0, 1)	99999 (± 99999)	6 (± 99999)		

Notes:

[27] - N = number of responders.

[28] - N = number of responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Monthy Seizure Frequency of Responders for the Months After Achieving 6 Consecutive Months of Seizure Freedom: All Seizures

End point title	Mean Monthy Seizure Frequency of Responders for the Months After Achieving 6 Consecutive Months of Seizure Freedom: All Seizures

End point description:

Seizure frequency based on 28-day seizure rate: number (#) of seizures in period (month) divided by # days in period minus # of missing diary days in period * 28. Responder = subject who achieved at least 6 months of seizure freedom after Week 4 and up to Week 56. Monthly seizure frequency measured from day of achievement of 6 months of seizure freedom. FAS. n = number of responders with analyzable data at observation. Here "99999" in the (SD) and arithmetic mean signifies not available (NA). SD was not calculated as either no subject (n=0) or only 1 subject (n=1) was evaluated at these time points. Mean was not calculated at month 9 for 'Pregabalin' arm as no responders with analyzable data were found.

End point type	Secondary

End point timeframe:

Month 1 through Month 9 (after 6 months seizure freedom achieved)

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[29]	208[30]		
Units: 28-day seizure rate				
arithmetic mean (standard deviation)				
Month 1 (n=162, 208)	0.19 (± 1)	0.05 (± 0.236)		
Month 2 (n=155, 194)	0.28 (± 1.783)	0.03 (± 0.226)		
Month 3 (n=147, 184)	0.07 (± 0.4)	0.07 (± 0.439)		
Month 4 (n=139, 173)	0.09 (± 0.359)	0.05 (± 0.211)		
Month 5 (n=127, 158)	0.18 (± 0.971)	0.1 (± 0.823)		

Month 6 (n=122, 152)	0.02 (± 0.156)	0.03 (± 0.213)		
Month 7 (n=105, 136)	0 (± 0)	0.29 (± 2.844)		
Month 8 (n=1, 5)	0 (± 99999)	0 (± 0)		
Month 9 (n=0, 1)	99999 (± 99999)	6 (± 99999)		

Notes:

[29] - N = number of responders.

[30] - N = number of responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved at Least 6 Consecutive Months of Seizure Freedom (Responders) by Final Dosage Levels and Treatment Group

End point title	Percentage of Subjects Who Achieved at Least 6 Consecutive Months of Seizure Freedom (Responders) by Final Dosage Levels and Treatment Group

End point description:

Responder = subject who achieved at least 6-months of seizure freedom (all seizures) after Week 4, and up to Week 56. Dose Level defined as last total-daily-dose received after Week 4, and up to Week 56. FAS.

End point type	Secondary

End point timeframe:

Week 5 up to Week 56

End point values	Pregabalin 150 mg/Day	Pregabalin 300 mg/Day	Pregabalin 450 mg/Day	Pregabalin 600 mg/Day
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[31]	67[32]	49[33]	46[34]
Units: percentage of subjects				
number (not applicable)	70.5	59.7	20.4	13

Notes:

[31] - N = number of subjects with analyzable data.

[32] - N = number of subjects with analyzable data.

[33] - N = number of subjects with analyzable data.

[34] - N = number of subjects with analyzable data.

End point values	Lamotrigine 100 mg/Day	Lamotrigine 200 mg/Day	Lamotrigine 400 mg/Day	Lamotrigine 500 mg/Day
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	164[35]	84[36]	34[37]	18[38]
Units: percentage of subjects				
number (not applicable)	80.5	67.9	38.2	16.7

Notes:

[35] - N = number of subjects with analyzable data.

[36] - N = number of subjects with analyzable data.

[37] - N = number of subjects with analyzable data.

[38] - N = number of subjects with analyzable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 56 in Hospital Anxiety and Depression Scale (HADS)

End point title	Change From Baseline to Week 56 in Hospital Anxiety and Depression Scale (HADS)

End point description:

Subject rated questionnaire with 2 subscales. HADS-A assesses state of generalized anxiety (anxious mood, restlessness, anxious thoughts, panic attacks); HADS-D assesses state of lost interest and diminished pleasure response (lowering of hedonic tone). Each subscale comprised of 7 items; range: 0 (no presence of anxiety or depression) to 3 (severe feeling of anxiety or depression). Total score 0 to 21 for each subscale; higher score indicates greater severity of symptoms. Scores relative to start of randomized treatment. FAS.

End point type	Secondary

End point timeframe:

Baseline to Week 56

End point values	Pregabalin-Efficacy Phase	Lamotrigine-Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237[39]	238[40]		
Units: scores on scale				
least squares mean (standard error)				
Anxiety	-0.3 (± 0.25)	-1.1 (± 0.25)		
Depression	-0.1 (± 0.23)	-0.7 (± 0.23)		

Notes:

[39] - N = number of subjects with a HADS measurement at baseline and Week 56.

[40] - N = number of subjects with a HADS measurement at baseline and Week 56.

Statistical analyses

Statistical analysis title	Analysis of Change in Anxiety: HADS

Statistical analysis description:

Anxiety; model includes treatment and geographical cluster as fixed effects and respective baseline scores as a continuous covariate.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0025
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.4

Statistical analysis title	Analysis of Change in Depression: HADS

Statistical analysis description:

Depression; model includes treatment and geographical cluster as fixed effects and respective baseline scores as a continuous covariate.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0186
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.1

Secondary: Medical Outcomes Study Sleep Scale (MOS-SS): Optimal Sleep Subscale

End point title	Medical Outcomes Study Sleep Scale (MOS-SS): Optimal Sleep Subscale

End point description:

MOS-SS: subject-rated instrument used to assess the key constructs of sleep over the past week; assesses sleep quantity and quality and is comprised 12 items yielding 7 subscale scores and 2 composite index scores. Optimal Sleep subscale is derived from sleep quantity average hours of sleep each night during the past week. Number of subjects with response Optimal if sleep quantity was 7 or 8 hours of sleep per night, and Non-optimal if average sleep was less than or greater than 7 to 8 hours per night. Analysis assesses the MOS-Sleep scale relative to the start of randomized treatment. FAS.

End point type	Secondary

End point timeframe:

Week 8, Week 32, and Week 56

End point values	Pregabalin- Efficacy Phase	Lamotrigine- Efficacy Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	330		
Units: subjects				
Week 8: Optimal sleep	195	173		
Week 8: Non-optimal sleep	103	126		
Week 32: Optimal sleep	167	155		

Week 32: Non-optimal sleep	97	103		
Week 56: Optimal sleep	152	145		
Week 56: Non-optimal sleep	82	90		

Statistical analyses

Statistical analysis title	Analysis of MOS-SS at Week 8

Statistical analysis description:

Week 8: dichotomized sleep assessment analyzed using a logistic regression model for repeated measures with fixed effects for treatment, geographical region, the average hours per night of sleep at baseline as a continuous covariate, time, and treatment-by-time interaction. The within subject covariance structure assumes an auto-regressive of order one covariance structure.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0683
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.93

Statistical analysis title	Analysis of MOS-SS at Week 32

Statistical analysis description:

Week 32: dichotomized sleep assessment analyzed using a logistic regression model for repeated measures with fixed effects for treatment, geographical region, the average hours per night of sleep at baseline as a continuous covariate, time, and treatment-by-time interaction. The within subject covariance structure assumes an auto-regressive of order one covariance structure.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5096
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit:	0.78
upper limit	1.66

Statistical analysis title	Analysis of MOS-SS at Week 56

Statistical analysis description:

Week 56 (termination): dichotomized sleep assessment analyzed using a logistic regression model for repeated measures with fixed effects for treatment, geographical region, the average hours per night of sleep at baseline as a continuous covariate, time, and treatment-by-time interaction. The within subject covariance structure assumes an auto-regressive of order one covariance structure.

Comparison groups	Pregabalin- Efficacy Phase v Lamotrigine- Efficacy Phase
Number of subjects included in analysis	660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6804
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.63

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from Day 0 (randomization visit) to End of Week 56 (termination visit).

Adverse event reporting additional description:

Same event may appear as both AE,SAE. However,what is presented are distinct events.An event may be categorized as serious in 1 subject and as nonserious in another,or 1 subject may experience both serious,nonserious event. EU BR specific AE tables were generated separately as per EU format. Latest coding dictionary has been used for EU BR tables.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Lamotrigine

Reporting group description:

Lamotrigine 100, 200, 400, or 500 mg/day orally BID; individual titration based on number of seizures experienced once Level 1 (100 mg/day) was reached and maintained for 7 days, and dose reductions based on intolerable adverse events. Escalation to next dose level allowed only after completing previous dose level for at least 1 week.

Reporting group title	Pregabalin

Reporting group description:

Pregabalin 150, 300, 450 or 600 mg/day orally twice daily (BID); individual titration based on number of seizures experienced once Level 1 (150 mg/day) was maintained for at least 7 days, and dose reductions based on intolerable adverse events. Escalation to next dose level allowed only after completing previous dose level for at least 1 week.

Serious adverse events	Lamotrigine	Pregabalin	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 330 (9.70%)	44 / 330 (13.33%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Medullary thyroid cancer			
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Thyroid cancer		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine leiomyoma		
subjects affected / exposed	1 / 330 (0.30%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Waldenstrom's macroglobulinaemia		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal neoplasm		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Brain neoplasm		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Vascular disorders		
Vasculitis		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haematoma		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Surgical and medical procedures		

Carpal tunnel decompression		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ostectomy		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hip arthroplasty		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Splenectomy		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
General disorders and administration site conditions		
Chest pain		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
General physical health deterioration		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyrexia		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Drowning		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1

Sudden unexplained death in epilepsy				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Reproductive system and breast disorders				
Vulval oedema				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 330 (0.30%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Asthma				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vocal cord cyst				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Psychiatric disorders				
Anxiety				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Delirium tremens				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Depression				

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Psychogenic seizure				
subjects affected / exposed	1 / 330 (0.30%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Psychotic disorder				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Injury, poisoning and procedural complications				
Cartilage injury				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Concussion				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Fall				
subjects affected / exposed	4 / 330 (1.21%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	1 / 4	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Foot fracture				
subjects affected / exposed	3 / 330 (0.91%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hand fracture				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Head injury				

subjects affected / exposed	2 / 330 (0.61%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	1 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ligament rupture				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Joint dislocation				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ligament sprain				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Limb injury				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Meniscus injury				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pelvic fracture				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Thermal burn				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Road traffic accident				

subjects affected / exposed	0 / 330 (0.00%)	2 / 330 (0.61%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Skin abrasion				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Congenital, familial and genetic disorders				
Multiple endocrine neoplasia Type 2				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac disorders				
Myocardial ischaemia				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nervous system disorders				
Brain oedema				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cerebrovascular accident				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dizziness				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dementia				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Drug withdrawal convulsions				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Generalised tonic-clonic seizure				
subjects affected / exposed	0 / 330 (0.00%)	2 / 330 (0.61%)		
occurrences causally related to treatment / all	0 / 0	1 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Epilepsy				
subjects affected / exposed	4 / 330 (1.21%)	5 / 330 (1.52%)		
occurrences causally related to treatment / all	0 / 6	0 / 7		
deaths causally related to treatment / all	0 / 0	0 / 0		
Headache				
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hemiparesis				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Partial seizures				
subjects affected / exposed	0 / 330 (0.00%)	2 / 330 (0.61%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Partial seizures with secondary generalisation				
subjects affected / exposed	0 / 330 (0.00%)	2 / 330 (0.61%)		
occurrences causally related to treatment / all	0 / 0	1 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Postictal headache				
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Seizure				

subjects affected / exposed	1 / 330 (0.30%)	10 / 330 (3.03%)
occurrences causally related to treatment / all	0 / 1	2 / 13
deaths causally related to treatment / all	0 / 0	0 / 0

Spinal cord disorder

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Status epilepticus

subjects affected / exposed	1 / 330 (0.30%)	4 / 330 (1.21%)
occurrences causally related to treatment / all	0 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0

Transient ischaemic attack

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Wernicke's encephalopathy

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Blood and lymphatic system disorders

Splenomegaly

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Pancytopenia

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Eye disorders

Entropion

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Trichiasis

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Gastrointestinal disorders

Dyspepsia

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Gastritis

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Vomiting

subjects affected / exposed	0 / 330 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Hepatobiliary disorders

Cholecystitis acute

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Hepatic function abnormal

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Skin and subcutaneous tissue disorders

Rash

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Stevens-Johnson syndrome

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Toxic epidermal necrolysis		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal and urinary disorders		
Calculus ureteric		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary retention		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Endocrine disorders		
Parathyroid gland enlargement		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders		
Arthropathy		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Back pain		
subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal pain		
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle haemorrhage		

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Trigger finger

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Infections and infestations

Diverticulitis

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Hepatitis B

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Pneumonia

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Sinusitis

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Vulvovaginitis

subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Upper respiratory tract infection

subjects affected / exposed	0 / 330 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Tuberculosis

	Lamotrigine	Pregabalin	
subjects affected / exposed	1 / 330 (0.30%)	0 / 330 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Lamotrigine	Pregabalin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	173 / 330 (52.42%)	186 / 330 (56.36%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 330 (2.12%)	4 / 330 (1.21%)	
occurrences (all)	7	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 330 (5.76%)	30 / 330 (9.09%)	
occurrences (all)	22	37	
Pyrexia			
subjects affected / exposed	14 / 330 (4.24%)	6 / 330 (1.82%)	
occurrences (all)	15	9	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed[1]	3 / 146 (2.05%)	0 / 165 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	10 / 330 (3.03%)	2 / 330 (0.61%)	
occurrences (all)	12	2	
Cough			
subjects affected / exposed	9 / 330 (2.73%)	2 / 330 (0.61%)	
occurrences (all)	13	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 330 (3.03%)	5 / 330 (1.52%)	
occurrences (all)	14	7	
Depression			

	subjects affected / exposed	14 / 330 (4.24%)	10 / 330 (3.03%)	
	occurrences (all)	16	11	
Insomnia				
	subjects affected / exposed	19 / 330 (5.76%)	15 / 330 (4.55%)	
	occurrences (all)	21	20	
Sleep disorder				
	subjects affected / exposed	7 / 330 (2.12%)	2 / 330 (0.61%)	
	occurrences (all)	14	3	
Investigations				
Weight increased				
	subjects affected / exposed	7 / 330 (2.12%)	22 / 330 (6.67%)	
	occurrences (all)	7	23	
Nervous system disorders				
Disturbance in attention				
	subjects affected / exposed	6 / 330 (1.82%)	7 / 330 (2.12%)	
	occurrences (all)	6	9	
Dizziness				
	subjects affected / exposed	47 / 330 (14.24%)	57 / 330 (17.27%)	
	occurrences (all)	102	114	
Headache				
	subjects affected / exposed	73 / 330 (22.12%)	74 / 330 (22.42%)	
	occurrences (all)	180	166	
Memory impairment				
	subjects affected / exposed	13 / 330 (3.94%)	8 / 330 (2.42%)	
	occurrences (all)	15	8	
Somnolence				
	subjects affected / exposed	16 / 330 (4.85%)	29 / 330 (8.79%)	
	occurrences (all)	20	36	
Eye disorders				
Vision blurred				
	subjects affected / exposed	2 / 330 (0.61%)	7 / 330 (2.12%)	
	occurrences (all)	6	8	
Gastrointestinal disorders				
Abdominal pain upper				
	subjects affected / exposed	17 / 330 (5.15%)	12 / 330 (3.64%)	
	occurrences (all)	19	15	
Abdominal pain				

subjects affected / exposed	9 / 330 (2.73%)	4 / 330 (1.21%)
occurrences (all)	14	4
Nausea		
subjects affected / exposed	11 / 330 (3.33%)	14 / 330 (4.24%)
occurrences (all)	12	15
Dyspepsia		
subjects affected / exposed	12 / 330 (3.64%)	8 / 330 (2.42%)
occurrences (all)	14	10
Diarrhoea		
subjects affected / exposed	13 / 330 (3.94%)	10 / 330 (3.03%)
occurrences (all)	16	10
Constipation		
subjects affected / exposed	5 / 330 (1.52%)	9 / 330 (2.73%)
occurrences (all)	5	9
Toothache		
subjects affected / exposed	4 / 330 (1.21%)	9 / 330 (2.73%)
occurrences (all)	4	9
Vomiting		
subjects affected / exposed	8 / 330 (2.42%)	7 / 330 (2.12%)
occurrences (all)	10	7
Skin and subcutaneous tissue disorders		
Pruritus		
subjects affected / exposed	9 / 330 (2.73%)	4 / 330 (1.21%)
occurrences (all)	12	4
Rash		
subjects affected / exposed	18 / 330 (5.45%)	12 / 330 (3.64%)
occurrences (all)	23	15
Musculoskeletal and connective tissue disorders		
Myalgia		
subjects affected / exposed	6 / 330 (1.82%)	7 / 330 (2.12%)
occurrences (all)	6	8
Back pain		
subjects affected / exposed	10 / 330 (3.03%)	9 / 330 (2.73%)
occurrences (all)	10	10
Infections and infestations		

Influenza			
subjects affected / exposed	12 / 330 (3.64%)	13 / 330 (3.94%)	
occurrences (all)	15	14	
Nasopharyngitis			
subjects affected / exposed	21 / 330 (6.36%)	15 / 330 (4.55%)	
occurrences (all)	33	17	
Pharyngitis			
subjects affected / exposed	4 / 330 (1.21%)	7 / 330 (2.12%)	
occurrences (all)	4	8	
Upper respiratory tract infection			
subjects affected / exposed	23 / 330 (6.97%)	20 / 330 (6.06%)	
occurrences (all)	38	30	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 330 (2.12%)	2 / 330 (0.61%)	
occurrences (all)	7	2	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Since menorrhagia is a gender specific event, only female population (146) is considered to be exposed to this adverse event which is less than the total number of subjects exposed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2006	1. Addition of a blinded extension for completers of the double-blind efficacy phase who wished to continue on study medication. Subjects who continued on study medication in the blinded extension did not not enter the taper period. The blinded extension continued until the entire study was unblinded. A subject who withdrew from the blinded extension before the study was completed also entered the 4-week taper phase. 2. Subjects who received a single dose of a benzodiazepine as emergency treatment were allowed to enroll. 3. During the blinded extension visits concurrent medications and adverse events were documented. A urine pregnancy test was performed on women of childbearing potential. 4. Assessments of sensation (upper and lower), reflexes, cranial nerves, and muscle strength and tone were added to neurological examination. 5. Instead of a 12-lead Electrocardiogram (ECG) "with a 2-minute rhythm strip", just a 12-lead ECG was performed at Screening.
15 August 2006	1. Exposure in Utero definition was amended to include paternal exposure. 2. Follow-up was conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Cox proportional hazards model for time to event (TTE) analyses; three summary statistics were not generated as median TTE will not exist if survival function (Kaplan-Meier product limit estimates) does not fall below 0.5 (post-hoc analysis).

Notes: