Clinical trial results:
The Evaluation of Lamictal as an Add-on Treatment for Bipolar I Disorder in Children and Adolescents, 10 to 17 Years of Age

Summary

EudraCT number	2015-004872-31
Trial protocol	Outside EU/EEA
Global end of trial date	07 August 2013

Results information

Result version number	v1 (current)
This version publication date	22 January 2017
First version publication date	22 January 2017

Trial information

Trial identification

Sponsor protocol code	SCA102833

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	29 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2008
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	United States: 301
Worldwide total number of subjects	301
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	74
Adolescents (12-17 years)	227
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 301 participants were enrolled in the study, of which 298 subjects took at least one dose of lamotrigine (LTG). One hundred and seventy three participants met stabilization criteria and entered the Randomized Phase.

Pre-assignment

Screening details:

The study consisted of a 2-week Screening Phase, an 18-week Open-Label Phase, a 36-week Double-Blind Randomized Phase and a Taper and Follow-up Phase (up to 4 weeks depending on the dose the participant was taking at the last Open-Label or Randomized Phase visit), which was either open-label or double-blind depending on the phase of the study.

Period 1

Period 1 title	Open-Label Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	LTG: Open-Label Phase

Arm description:

Participants (par.) received lamotrigine (LTG) up to a maximum dose depending on their age and concomitant bipolar medication group. Participants 10 -12 years of age received LTG up to a maximum dose of: 3 milligrams/kilograms (mg/kg)/day or 100 mg/day, whichever was less; or 6 mg/kg/day or 200 mg/day whichever was less; or 12 mg/kg/day or 300 mg/day whichever was less, depending on their bipolar medication group. Participants 13-17 years of age received LTG up to a maximum dose of 150 mg/day, 300 mg/day, or 400 mg/day depending on their bipolar medication group. Participants took LTG for a duration of up to 18 weeks.

Arm type	Experimental
Investigational medicinal product name	Lamictal (Lamotrigine) 5, 25, 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants 10 -12 years of age received LTG up to a maximum dose of: 3 milligrams/kilograms (mg/kg)/day or 100 mg/day, whichever was less; or 6 mg/kg/day or 200 mg/day whichever was less; or 12 mg/kg/day or 300 mg/day whichever was less, depending on their bipolar medication group. Participants 13-17 years of age received LTG up to a maximum dose of 150 mg/day, 300 mg/day, or 400 mg/day depending on their bipolar medication group. Participants took LTG for a duration of up to 18 weeks

Number of subjects in period 1	LTG: Open-Label Phase
Started	298
Completed	173
Not completed	125
Physician decision	2
Consent withdrawn by subject	37

Adverse event, non-fatal	26
Lost to follow-up	7
Lack of efficacy	18
Protocol deviation	35

Period 2

Period 2 title	Randomized Phase
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received matching placebo in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received matching placebo in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks.

Arm title	Lamotrigine

Arm description:

Participants received LTG equivalent to the dose established in the Open-Label Phase. Participants received LTG tablets in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks.

Arm type	Experimental
Investigational medicinal product name	Lamotrigine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received LTG equivalent to the dose established in the Open-Label Phase . Participants received LTG

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Participants (par.) received lamotrigine (LTG) up to a maximum dose depending on their age and concomitant bipolar medication group. Participants 10 -12 years of age received LTG up to a maximum dose of: 3 milligrams/kilograms (mg/kg)/day or 100 mg/day, whichever was less; or 6 mg/kg/day or 200 mg/day whichever was less; or 12 mg/kg/day or 300 mg/day whichever was less,

depending on their bipolar medication group. Participants 13-17 years of age received LTG up to a maximum dose of 150 mg/day.

Number of subjects in period 2[2]	Placebo	Lamotrigine
Started	86	87
Completed	21	20
Not completed	65	67
Physician decision	3	1
Consent withdrawn by subject	14	22
Adverse event, non-fatal	26	17
Lost to follow-up	2	3
Lack of efficacy	11	11
Protocol deviation	9	13

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 301 participants were enrolled in the study, of which 298 subjects took at least one dose of lamotrigine (LTG). One hundred and seventy three participants met stabilization criteria and entered the Randomized Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks.	
Reporting group title	Lamotrigine
Reporting group description:	
Participants received LTG equivalent to the dose established in the Open-Label Phase. Participants received LTG tablets in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks.	

Reporting group values	Placebo	Lamotrigine	Total
Number of subjects	86	87	173
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	13.5	13.4	
standard deviation	± 2.22	± 2.33	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	39	33	72
Male	47	54	101
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	9	9	18
American Indian or Alaska Native	0	1	1
Asian - East Asian Heritage	1	0	1
White - Arabic/North African Heritage	1	0	1
White - White/Caucasian/European Heritage	71	71	142
Mixed Race	4	6	10

End points

End points reporting groups

Reporting group title	LTG: Open-Label Phase

Reporting group description:

Participants (par.) received lamotrigine (LTG) up to a maximum dose depending on their age and concomitant bipolar medication group. Participants 10 -12 years of age received LTG up to a maximum dose of: 3 milligrams/kilograms (mg/kg)/day or 100 mg/day, whichever was less; or 6 mg/kg/day or 200 mg/day whichever was less; or 12 mg/kg/day or 300 mg/day whichever was less, depending on their bipolar medication group. Participants 13-17 years of age received LTG up to a maximum dose of 150 mg/day, 300 mg/day, or 400 mg/day depending on their bipolar medication group. Participants took LTG for a duration of up to 18 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks.

Reporting group title	Lamotrigine

Reporting group description:

Participants received LTG equivalent to the dose established in the Open-Label Phase. Participants received LTG tablets in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks.

Primary: Time from randomization to the occurrence of a bipolar event (TOBE)

End point title	Time from randomization to the occurrence of a bipolar event (TOBE)

End point description:

TOBE is defined as the first prescription of any additional pharmacotherapy to treat bipolar symptoms, increasing the dose(s) of the participants conventional bipolar medication(s), treatment with electroconvulsive therapy, or moving the participant to a more restricted environment for observation, safety, or treatment; or participant withdrawal from the study due to a bipolar-related adverse event (AE) or serious adverse event (SAE); or participants withdrawal from the study due to lack of efficacy as defined by rating scale threshold scores. TOBE is calculated using a log rank test with stratification for index mood state (depression, mania/hypomania, mixed mood). Randomized Intent-to-Treat (ITT) Population: all participants who were randomized to LTG or placebo and received at least one dose of investigational product.

End point type	Primary

End point timeframe:

From randomization until Week 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[1]	87[2]		
Units: Days				
arithmetic mean (standard error)				
Stratum: Depression, n=22,21	50 (± 3.8)	155 (± 14.7)		
Stratum: Mania/Hypomania, n=36, 37	120 (± 12.2)	163 (± 12.2)		
Stratum: Mixed Mood, n=28, 29	107 (± 13.8)	136 (± 15.4)		

Notes:

[1] - Randomized Intent-to-Treat (ITT) Population

[2] - Randomized Intent-to-Treat (ITT) Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Lamotrigine
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0717
Method	Logrank
Confidence interval	
level	95 %

Secondary: Time from randomization to withdrawal from the study for any cause (TTW)

End point title	Time from randomization to withdrawal from the study for any cause (TTW)

End point description:

The time from randomization to the withdrawal from study was analyzed. TTW was calculated using the log rank test with stratification for index mood state (depression, mania/hypomania, mixed mood).

End point type	Secondary

End point timeframe:

From randomization until withdrawal from the study for any cause (up to Week 36)

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[3]	87[4]		
Units: Days				
arithmetic mean (standard error)				
Stratum: Depression, n=22, 21	113 (± 21.4)	141 (± 20)		
Stratum: Mania/Hypomania, n=36, 37	138 (± 17.3)	144 (± 15.6)		
Stratum: Mixed Mood, n=28, 29	101 (± 15.7)	106 (± 16.3)		

Notes:

[3] - Randomized ITT Population.

[4] - Randomized ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Time from randomization to intervention for a mood episode (TIME)

End point title	Time from randomization to intervention for a mood episode (TIME)

End point description:

The time from randomization to the intervention for a mood episode (depression, mania/hypomania or mixed mood) was analyzed. TIME was calculated using the log rank test with stratification for index mood state (depression, mania/hypomania, mixed mood).

End point type	Secondary

End point timeframe:

From randomization until intervention administered for a mood episode (up to Week 36)

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[5]	87[6]		
Units: Days				
arithmetic mean (standard error)				
Stratum: Depression, n=22, 21	62 (± 5.2)	164 (± 12.7)		
Stratum: Mania/Hypomania, n=36, 37	129 (± 11.7)	179 (± 10.8)		
Stratum: Mixed Mood, n=28, 29	120 (± 13.7)	127 (± 12)		

Notes:

[5] - Randomized ITT Population.

[6] - Randomized ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Time from randomization to intervention for depression (TIDep), mania/hypomania (TIMan), or a mixed episode (TIMix)

End point title	Time from randomization to intervention for depression (TIDep), mania/hypomania (TIMan), or a mixed episode (TIMix)

End point description:

The time from randomization to intervention for depression (TIDep), mania/hypomania (TIMan), or a mixed episode (TIMix) was analyzed. TIDep, TIMan, and TIMix were calculated using the log rank test with stratification for index mood state (depression, mania/hypomania, mixed mood). A value of 99999 indicates that the arithmetic mean is not available.

End point type	Secondary

End point timeframe:

From randomization until intervention administered for depression, mania/hypomania or a mixed episode (up to Week 36)

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[7]	87[8]		
Units: Days				
arithmetic mean (standard error)				
TIDep: Depression, n=22, 21	61 (± 1.5)	46 (± 1.5)		
TIDep: Mania/Hypomania, n=36, 37	99999 (± 99999)	99999 (± 99999)		

TIDep: Mixed Mood, n=28, 29	59 (± 2.6)	159 (± 99999)		
TIMan: Depression, n=22, 21	74 (± 3.9)	182 (± 99999)		
TIMan: Mania/Hypomania, n=36, 37	139 (± 11.5)	61 (± 2.1)		
TIMan: Mixed Mood, n=28, 29	105 (± 7.3)	148 (± 8.5)		
TIMix: Depression, n=22, 21	37 (± 1.3)	158 (± 99999)		
TIMix: Mania/Hypomania, n=36, 37	135 (± 6.3)	194 (± 7.5)		
TIMix: Mixed Mood, n=28, 29	160 (± 10.7)	57 (± 2.5)		

Notes:

[7] - Randomized ITT Population.

[8] - Randomized ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants experiencing a relapse/recurrence to depression, mania/hypomania, or mixed mood state

End point title	Number of participants experiencing a relapse/recurrence to depression, mania/hypomania, or mixed mood state

End point description:

The number of participants requiring intervention to treat either the emergence of or a change in bipolar symptoms that is, experiencing a relapse/recurrence to depression, mania/hypomania, or mixed mood state were analyzed. Randomized ITT Population. Only those participants requiring intervention to treat either the emergence of, or a change, in bipolar symptoms were analyzed.

End point type	Secondary

End point timeframe:

From randomization until a relapse/recurrence to depression, mania/hypomania, or mixed mood state (up to Week 36)

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[9]	18[10]		
Units: Participants				
Depression	5	3		
Mania/hypomania	16	6		
Mixed episode state	10	9		

Notes:

[9] - Randomized ITT Population

[10] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants experiencing a relapse/recurrence within the first 30, 90, and 180 days in the Randomized Phase

End point title	Number of participants experiencing a relapse/recurrence within the first 30, 90, and 180 days in the Randomized Phase

End point description:

The proportion of participants (par.) requiring intervention to treat either the emergence of or a change in bipolar symptoms, that is, experiencing a relapse/recurrence to depression, mania/hypomania, or mixed mood state at any time within the first 30, 90, and 180 days in the Randomized Phase were

analyzed. Randomized ITT Population. Only those participants requiring intervention to treat either the emergence of, or a change, in bipolar symptoms were analyzed.

End point type	Secondary

End point timeframe:

From randomization up to Week 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[11]	18[12]		
Units: Participants				
Mania/hypomania, 30 days, n=16, 6	9	2		
Mania/hypomania, 90 days, n=16, 6	12	4		
Mania/hypomania, 180 days, n=16, 6	16	5		
Depression, 30 days, n=5, 3	1	1		
Depression, 90 days, n=5, 3	5	2		
Depression, 180 days, n=5, 3	5	3		
Mixed mood state, 30 days, n= 10, 9	3	2		
Mixed mood state, 90 days, n= 10, 9	7	6		
Mixed mood state, 180 days, n= 10, 9	10	8		

Notes:

[11] - Randomized ITT Population

[12] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Quick Inventory of Depressive Symptomatology – Clinician interview, semi-structured, adolescent version (QIDS-A17-C) at each visit in the Open-Label Phase

End point title	Change from Baseline in the Quick Inventory of Depressive Symptomatology – Clinician interview, semi-structured, adolescent version (QIDS- A17-C) at each visit in the Open-Label Phase

End point description:

The QIDS-A17-C is a 17-item scale used to assess depression severity in adolescents according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) diagnostic criteria for a major depressive episode; it is a modified version of the Quick Inventory of Depressive Symptomatology (QIDS) used for adults. Each item is scored on a 0-3 scale, yielding 9 domain scores. The range of scores is 0 (best possible outcome) to 27 (worst possible outcome). Analysis was performed using mixed model repeated measures. Open-Label ITT population: all participants who entered the Open-Label Phase and received at least one dose of LTG.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18

End point values	LTG: Open-Label Phase			
Subject group type	Reporting group			
Number of subjects analysed	298[13]			
Units: Scores on a Scale				
least squares mean (standard error)				
Week 1	-2.1 (± 0.22)			
Week 2	-2.9 (± 0.28)			
Week 3	-3.7 (± 0.28)			
Week 4	-3.8 (± 0.3)			
Week 5	-4.3 (± 0.3)			
Week 6	-4.7 (± 0.3)			
Week 7	-5.1 (± 0.3)			
Week 8	-4.9 (± 0.31)			
Week 9	-5.6 (± 0.3)			
Week 10	-6.1 (± 0.29)			
Week 11	-6.4 (± 0.3)			
Week 12	-6.6 (± 0.32)			
Week 13	-6.7 (± 0.32)			
Week 14	-6.8 (± 0.34)			
Week 15	-6.8 (± 0.4)			
Week 16	-6.8 (± 0.41)			
Week 17	-6.5 (± 0.53)			
Week 18	-6.5 (± 0.7)			

Notes:

[13] - Open-Label ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization in the Quick Inventory of Depressive Symptomatology – Clinician interview, semi-structured, adolescent version (QIDS-A17-C) at each visit in the Randomized Phase

End point title	Change from Randomization in the Quick Inventory of Depressive Symptomatology – Clinician interview, semi-structured, adolescent version (QIDS- A17-C) at each visit in the Randomized Phase

End point description:

The QIDS-A17-C is a 17-item scale used to assess depression severity in adolescents according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) diagnostic criteria for a major depressive episode; it is a modified version of the Quick Inventory of Depressive Symptomatology (QIDS) used for adults. Each item is scored on a 0-3 scale, yielding 9 domain scores. The range of scores is 0 (best possible outcome) to 27 (worst possible outcome). Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Randomization and Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, and 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[14]	87[15]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 1	0.8 (± 0.3)	0.5 (± 0.31)		
Week 2	1.5 (± 0.37)	1.1 (± 0.37)		
Week 3	1.3 (± 0.36)	0.6 (± 0.36)		
Week 4	1.2 (± 0.39)	1 (± 0.39)		
Week 6	1.9 (± 0.49)	1.5 (± 0.47)		
Week 8	1.9 (± 0.47)	1.7 (± 0.45)		
Week 10	1.4 (± 0.44)	1.5 (± 0.41)		
Week 12	1.4 (± 0.4)	1.2 (± 0.39)		
Week 16	2.2 (± 0.48)	1.8 (± 0.47)		
Week 20	1.5 (± 0.5)	2.5 (± 0.46)		
Week 24	1.7 (± 0.53)	1.8 (± 0.51)		
Week 28	1.6 (± 0.61)	2.3 (± 0.57)		
Week 32	1 (± 0.72)	1.9 (± 0.72)		
Week 36	2 (± 0.63)	1.9 (± 0.63)		

Notes:

[14] - Randomized ITT Population

[15] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Quick Inventory of Depressive Symptomatology – self-report adolescent version (QIDS-A17-SR) at each visit in the Open-Label Phase

End point title	Change from Baseline in the Quick Inventory of Depressive Symptomatology – self-report adolescent version (QIDS-A17-SR) at each visit in the Open-Label Phase

End point description:

The QIDS-A17-SR is a 17-item scale used to assess depression severity in adolescents according to the DSM-IV-TR diagnostic criteria for a major depressive episode; it is a modified version of the Quick Inventory of Depressive Symptomatology (QIDS) used for adults. Each item is scored on a 0-3 scale, yielding 9 domain scores. The range of scores is 0 (best possible outcome) to 27 (worst possible outcome). The scale is completed by the participant. Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, 16, and 18

End point values	LTG: Open-Label Phase			
Subject group type	Reporting group			
Number of subjects analysed	298[16]			
Units: Scores on a scale				
least squares mean (standard error)				
Week 4	-2.7 (± 0.25)			

Week 8	-3.3 (± 0.27)			
Week 12	-4.3 (± 0.28)			
Week 16	-4.5 (± 0.33)			
Week 18	-5 (± 0.52)			

Notes:

[16] - Open-Label ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization in the Quick Inventory of Depressive Symptomatology – self-report adolescent version (QIDS-A17-SR) at each visit in the Randomized Phase

End point title	Change from Randomization in the Quick Inventory of Depressive Symptomatology – self-report adolescent version (QIDS-A17-SR) at each visit in the Randomized Phase

End point description:

The QIDS-A17-SR is a 17-item scale used to assess depression severity in adolescents according to the DSM-IV-TR diagnostic criteria for a major depressive episode; it is a modified version of the Quick Inventory of Depressive Symptomatology (QIDS) used for adults. Each item is scored on a 0-3 scale, yielding 9 domain scores. The range of scores is 0 (best possible outcome) to 27 (worst possible outcome). The scale is completed by the participant. Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Randomization and Weeks 8, 16, 24, 32, and 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[17]	87[18]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8	1.6 (± 0.47)	1.2 (± 0.48)		
Week 16	1.6 (± 0.6)	1.4 (± 0.58)		
Week 24	1 (± 0.6)	1.5 (± 0.56)		
Week 32	0.6 (± 0.66)	0.2 (± 0.63)		
Week 36	0.9 (± 0.66)	0.8 (± 0.68)		

Notes:

[17] - Randomized ITT Population

[18] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Clinical Global Impressions – Bipolar, Severity of Illness (CGI-BP[S]) at each visit in the Open-Label Phase

End point title	Change from Baseline in the Clinical Global Impressions – Bipolar, Severity of Illness (CGI-BP[S]) at each visit in the Open-Label Phase

End point description:

Severity of the bipolar illness was based on the CGI-BP(S) score which had a range from 1 (normal, not ill) to 7 (very severely ill). Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18

End point values	LTG: Open-Label Phase			
Subject group type	Reporting group			
Number of subjects analysed	298[19]			
Units: Scores on a scale				
least squares mean (standard error)				
Week 1	-0.4 (± 0.05)			
Week 2	-0.6 (± 0.05)			
Week 3	-0.9 (± 0.06)			
Week 4	-1 (± 0.06)			
Week 5	-1.2 (± 0.06)			
Week 6	-1.3 (± 0.06)			
Week 7	-1.4 (± 0.07)			
Week 8	-1.5 (± 0.07)			
Week 9	-1.6 (± 0.07)			
Week 10	-1.8 (± 0.07)			
Week 11	-1.9 (± 0.07)			
Week 12	-2.1 (± 0.07)			
Week 13	-2.1 (± 0.07)			
Week 14	-2.1 (± 0.07)			
Week 15	-2.1 (± 0.08)			
Week 16	-2.1 (± 0.1)			
Week 17	-2 (± 0.12)			
Week 18	-2.1 (± 0.15)			

Notes:

[19] - Open-Label ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization in the Clinical Global Impressions – Bipolar, Severity of Illness (CGI-BP[S]) at each visit in the Randomized Phase

End point title	Change from Randomization in the Clinical Global Impressions – Bipolar, Severity of Illness (CGI-BP[S]) at each visit in the Randomized Phase

End point description:

Severity of the bipolar illness was based on the CGI-BP(S) score which had a range from 1 (normal, not ill) to 7 (very severely ill). Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Randomization and Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, and 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[20]	87[21]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 1	0.2 (± 0.09)	0 (± 0.09)		
Week 2	0.4 (± 0.12)	0.2 (± 0.12)		
Week 3	0.4 (± 0.12)	0.2 (± 0.12)		
Week 4	0.6 (± 0.13)	0.3 (± 0.13)		
Week 6	0.8 (± 0.15)	0.4 (± 0.15)		
Week 8	0.7 (± 0.15)	0.4 (± 0.14)		
Week 10	0.4 (± 0.13)	0.6 (± 0.13)		
Week 12	0.5 (± 0.14)	0.4 (± 0.14)		
Week 16	0.6 (± 0.17)	0.6 (± 0.15)		
Week 20	0.5 (± 0.17)	0.8 (± 0.16)		
Week 24	0.4 (± 0.17)	0.6 (± 0.16)		
Week 28	0.3 (± 0.17)	0.5 (± 0.16)		
Week 32	0.2 (± 0.19)	0.5 (± 0.2)		
Week 36	0.4 (± 0.19)	0.3 (± 0.21)		

Notes:

[20] - Randomized ITT Population

[21] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Clinical Global Impressions – Bipolar – Improvement of Illness (CGI-BP [I]) Scores during Open-label Phase

End point title	Summary of Clinical Global Impressions – Bipolar – Improvement of Illness (CGI-BP [I]) Scores during Open-label Phase

End point description:

Improvement of bipolar illness was based on the CGI-BP (I) score which ranged from 1 (very much improved) to 7 (very much worse). Analysis was performed using mixed model repeated measures. Open-Label ITT Population. Only those par. available at the specified time points were analyzed (represented by n=X). Different par. may have been analyzed at different time points, so the overall number of par. analyzed reflects everyone in the Open-Label Population.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18

End point values	LTG: Open-Label Phase			
Subject group type	Reporting group			
Number of subjects analysed	298[22]			
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 1, n=290	3.6 (± 0.8)			
Week 2, n=278	3.3 (± 0.9)			
Week 3, n=270	3.1 (± 0.96)			
Week 4, n=265	3 (± 1.03)			
Week 5, n=258	2.8 (± 1.01)			
Week 6, n=243	2.7 (± 1.05)			
Week 7, n=246	2.5 (± 1.07)			
Week 8, n=236	2.5 (± 1.09)			
Week 9, n=227	2.3 (± 1.05)			
Week 10, n=205	2.2 (± 1.09)			
Week 11, n=181	2.2 (± 0.92)			
Week 12, n=168	2 (± 0.87)			
Week 13, n=141	1.9 (± 0.85)			
Week 14, n=118	1.9 (± 0.69)			
Week 15, n=93	1.8 (± 0.71)			
Week 16, n=72	2 (± 0.89)			
Week 17, n=42	2 (± 0.7)			
Week 18, n=28	2 (± 0.88)			

Notes:

[22] - Open-Label ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Clinical Global Impressions – Bipolar – Improvement of Illness (CGI-BP [I]) Scores during Randomized Phase

End point title	Summary of Clinical Global Impressions – Bipolar – Improvement of Illness (CGI-BP [I]) Scores during Randomized Phase

End point description:

Improvement of bipolar illness was based on the CGI-BP(I) score which ranged from 1 (very much improved) to 7 (very much worse). Analysis was performed using mixed model repeated measures. Randomized ITT Population. Only those par. available at the specified time points were analyzed (represented by n=X). Different par. may have been analyzed at different time points, so the overall number of par. analyzed reflects everyone in the Randomized ITT Population.

End point type	Secondary

End point timeframe:

Randomization weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32 and 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[23]	87[24]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 1, n=84, 85	3.3 (± 1.4)	3.3 (± 1.37)		
Week 2, n=82, 81	3.7 (± 1.48)	3.6 (± 1.38)		
Week 3, n=74, 75	3.6 (± 1.39)	3.6 (± 1.34)		
Week 4, n=65, 70	3.6 (± 1.51)	3.6 (± 1.35)		
Week 6, n=58, 64	3.8 (± 1.64)	3.4 (± 1.49)		
Week 8, n=51, 60	3.5 (± 1.72)	3.6 (± 1.47)		
Week 10, n=45, 55	3.3 (± 1.64)	3.8 (± 1.19)		
Week 12, n=45, 49	3.3 (± 1.52)	3.4 (± 1.29)		
Week 16, n=43, 50	3.4 (± 1.73)	3.5 (± 1.37)		
Week 20, n=37, 43	3 (± 1.48)	3.8 (± 1.36)		
Week 24, n=34, 36	3 (± 1.59)	3.4 (± 1.44)		
Week 28, n=29, 32	2.7 (± 1.56)	3.5 (± 1.44)		
Week 32, n=28, 27	3 (± 1.63)	3.5 (± 1.28)		
Week 36, n=27, 24	3 (± 1.68)	3.6 (± 1.1)		

Notes:

[23] - Randomized ITT Population

[24] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants considered much improved or very much improved [defined as a Clinical Global Impression-Bipolar Version, Improvement of Illness (CGI-BP[I]), score of 1 or 2] at each visit compared to Baseline in the Open-Label Phase

End point title	Number of participants considered much improved or very much improved [defined as a Clinical Global Impression-Bipolar Version, Improvement of Illness (CGI-BP[I]), score of 1 or 2] at each visit compared to Baseline in the Open-Label Phase

End point description:

The CGI-BP(I) asks the following question: "Compared to the Baseline assessment in this trial, how much has the participant changed?". Scores on the CGI-I range from 1 (very much improved) to 7 (very much worse). The investigator or their designee rated improvement regardless of whether the improvement to be due to drug treatment. Improvement defined as CGI-BP(I)=1 (improved) or 2 (very much improved). Missing data imputed using last-observation carried forward (LOCF). Open-Label ITT Population. Only those par. available at the specified time points were analyzed (represented by n=X). Different par. may have been analyzed at different time points, so the overall number of par. analyzed reflects everyone in the Open-Label Population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18

End point values	LTG: Open-Label Phase			
Subject group type	Reporting group			
Number of subjects analysed	298[25]			
Units: Participants				
Week 1, n=297	27			
Week 2, n=297	46			
Week 3, n=297	72			
Week 4, n=297	86			
Week 5, n=297	113			
Week 6, n=297	124			
Week 7, n=297	138			
Week 8, n=297	140			
Week 9, n=297	159			
Week 10, n=297	176			
Week 11, n=297	182			
Week 12, n=297	195			
Week 13, n=297	205			
Week 14, n=297	211			
Week 15, n=297	210			
Week 16, n=297	209			
Week 17, n=297	208			
Week 18, n=297	206			

Notes:

[25] - Open-Label ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants considered much improved or very much improved [defined as a Clinical Global Impression-Bipolar Version, Improvement of Illness (CGI-BP[I]), score of 1 or 2] at each visit compared to Randomization in the Randomized Phase

End point title	Number of participants considered much improved or very much improved [defined as a Clinical Global Impression-Bipolar Version, Improvement of Illness (CGI-BP[I]), score of 1 or 2] at each visit compared to Randomization in the Randomized Phase

End point description:

The CGI-BP(I) asks the following question: "Compared to the Randomization assessment in this trial, how much has the participant changed?". Scores on the CGI-I range from 1 (very much improved) to 7 (very much worse). The investigator or their designee rated improvement regardless of whether the improvement to be due to drug treatment. Improvement defined as CGI-BP(I)=1 (improved) or 2 (very much improved). Missing data imputed using last-observation carried forward (LOCF).

End point type	Secondary

End point timeframe:

Randomization and Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, and 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[26]	87[27]		
Units: Participants				
Week 1	31	31		
Week 2	25	22		
Week 3	24	21		
Week 4	22	19		
Week 6	20	23		
Week 8	22	19		
Week 10	22	12		
Week 12	21	17		
Week 16	21	16		
Week 20	21	14		
Week 24	21	15		
Week 28	22	15		
Week 32	19	15		
Week 36	20	13		

Notes:

[26] - Randomized ITT Population

[27] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Young Mania Rating Scale (YMRS) at each visit in the Open-Label Phase

End point title	Change from Baseline in the Young Mania Rating Scale (YMRS) at each visit in the Open-Label Phase

End point description:

The YMRS consists of 11 items and is based on the participant's report of their mania symptoms. It is clinician rated. Four items (irritability, speech, thought content, and disruptive/aggressive behavior) are rated on a scale of 0 to 8, while the other seven items (elevated mood, increased motor activity-energy, sexual interest, sleep, language, appearance, and insight) are rated on a scale of 0 to 4. The range of scores for the YMRS is 0 (best possible outcome) to 60 (worst possible outcome). The YMRS was completed by the investigator or their qualified designee. Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18

End point values	LTG: Open-Label Phase			
Subject group type	Reporting group			
Number of subjects analysed	298[28]			
Units: Scores on a scale				
least squares mean (standard error)				
Week 1	-3.2 (± 0.39)			
Week 2	-4.8 (± 0.42)			
Week 3	-6.4 (± 0.45)			

Week 4	-6.5 (± 0.46)			
Week 5	-7.5 (± 0.5)			
Week 6	-8.4 (± 0.5)			
Week 7	-9.1 (± 0.51)			
Week 8	-8.8 (± 0.48)			
Week 9	-9.6 (± 0.48)			
Week 10	-10.3 (± 0.49)			
Week 11	-11.1 (± 0.48)			
Week 12	-11.6 (± 0.53)			
Week 13	-12 (± 0.58)			
Week 14	-12 (± 0.59)			
Week 15	-12.4 (± 0.63)			
Week 16	-12.3 (± 0.78)			
Week 17	-12.2 (± 0.88)			
Week 18	-12.1 (± 1.43)			

Notes:

[28] - Open-Label ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization in the Young Mania Rating Scale (YMRS) at each visit in the Randomized Phase

End point title	Change from Randomization in the Young Mania Rating Scale (YMRS) at each visit in the Randomized Phase

End point description:

The YMRS consists of 11 items and is based on the participant's report of their mania symptoms. It is clinician rated. Four items (irritability, speech, thought content, and disruptive/aggressive behavior) are rated on a scale of 0 to 8, while the other seven items (elevated mood, increased motor activity-energy, sexual interest, sleep, language, appearance, and insight) are rated on a scale of 0 to 4. The range of scores for the YMRS is 0 (best possible outcome) to 60 (worst possible outcome). The YMRS was completed by the investigator or their qualified designee. Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Randomization and Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, and 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[29]	87[30]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 1	1.3 (± 0.57)	0.4 (± 0.59)		
Week 2	2.6 (± 0.72)	2.1 (± 0.72)		
Week 3	2.6 (± 0.69)	1.3 (± 0.71)		
Week 4	3.7 (± 0.85)	2 (± 0.84)		
Week 6	4.9 (± 0.96)	2.3 (± 0.93)		
Week 8	4.3 (± 0.98)	3.5 (± 0.93)		
Week 10	3.5 (± 0.87)	2.9 (± 0.82)		

Week 12	3.2 (± 0.84)	1.6 (± 0.81)		
Week 16	4.7 (± 0.93)	3 (± 0.89)		
Week 20	4.8 (± 0.99)	4.5 (± 0.92)		
Week 24	4.2 (± 1.06)	2.9 (± 1.02)		
Week 28	4.4 (± 1.04)	3.7 (± 1.01)		
Week 32	4.5 (± 1.1)	2.6 (± 1.14)		
Week 36	3.5 (± 0.92)	1.2 (± 0.95)		

Notes:

[29] - Randomized ITT Population

[30] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Parent Version of the Young Mania Rating Scale (P-YMRS) at each visit in the Open-Label Phase

End point title	Change from Baseline in the Parent Version of the Young Mania Rating Scale (P-YMRS) at each visit in the Open-Label Phase

End point description:

The P-YMRS was adapted from the YMRS for completion by parents of the pediatric participants with bipolar disorder in order to assess the severity of the manic symptoms. The P-YMRS consisted of 11 items and had a total score range of 0 (best possible outcome) to 60 (worst possible outcome). The P-YMRS was completed by the participant's custodial parent or legal guardian. Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, 16, and 18

End point values	LTG: Open-Label Phase			
Subject group type	Reporting group			
Number of subjects analysed	298[31]			
Units: Scores on a scale				
least squares mean (standard error)				
Week 4	-4.7 (± 0.57)			
Week 8	-6 (± 0.62)			
Week 12	-7.4 (± 0.62)			
Week 16	-8.2 (± 0.72)			
Week 18	-9.3 (± 1.29)			

Notes:

[31] - Open-Label ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization in the Parent Version of the Young Mania Rating Scale (P-YMRS) at each visit in the Randomized Phase

End point title	Change from Randomization in the Parent Version of the Young Mania Rating Scale (P-YMRS) at each visit in the Randomized

	Phase

End point description:

The P-YMRS was adapted from the YMRS for completion by parents of the pediatric participants with bipolar disorder in order to assess the severity of the manic symptoms. The P-YMRS consisted of 11 items and had a total score range of 0 (best possible outcome) to 60 (worst possible outcome). The P-YMRS was completed by the participant's custodial parent or legal guardian. Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Randomization and Weeks 8, 16, 24, 32, and 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[32]	87[33]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8	4.9 (± 0.93)	4.3 (± 0.95)		
Week 16	2.7 (± 1.13)	2.6 (± 1.09)		
Week 24	5.3 (± 1.35)	5.7 (± 1.29)		
Week 32	5.1 (± 1.33)	6 (± 1.32)		
Week 36	5.3 (± 1.33)	4.5 (± 1.6)		

Notes:

[32] - Randomized ITT Population

[33] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Conners' Global Index – Parent Version (CGI-P) at each visit in the Open-Label Phase

End point title	Change from Baseline in the Conners' Global Index – Parent Version (CGI-P) at each visit in the Open-Label Phase

End point description:

The CGI-P is a 10-item scale used to assess attention deficit hyperactivity disorder (ADHD) symptoms in children and adolescents aged 3-17 years of age. The scale is composed of two factors: restless-impulsive behavior and emotional lability. Each item was scored on a 0-3 scale. The range of scores for the CGI-P is 0 (best possible outcome) to 30 (worst possible outcome). The CGI-P was completed by the participant's custodial parent or legal guardian. Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, 16, and 18

End point values	LTG: Open-Label Phase			
Subject group type	Reporting group			
Number of subjects analysed	298[34]			
Units: Scores on a scale				
least squares mean (standard error)				
Week 4	-4 (± 0.36)			
Week 8	-5.7 (± 0.43)			
Week 12	-6.7 (± 0.47)			
Week 16	-7.1 (± 0.56)			
Week 18	-8.2 (± 1.07)			

Notes:

[34] - Open-Label ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization in the Conners' Global Index – Parent Version (CGI-P) at each visit in the Randomized Phase.

End point title	Change from Randomization in the Conners' Global Index – Parent Version (CGI-P) at each visit in the Randomized Phase.

End point description:

The CGI-P is a 10-item scale used to assess attention deficit hyperactivity disorder (ADHD) symptoms in children and adolescents aged 3-17 years of age. The scale is composed of two factors: restless-impulsive behavior and emotional lability. Each item was scored on a 0-3 scale. The range of scores for the CGI-P is 0 (best possible outcome) to 30 (worst possible outcome). The CGI-P was completed by the participant's custodial parent or legal guardian. Analysis was performed using mixed model repeated measures.

End point type	Secondary

End point timeframe:

Randomization and Weeks 8, 16, 24, 32, and 36

End point values	Placebo	Lamotrigine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[35]	87[36]		
Units: Scores on a scale				
least squares mean (standard error)				
Week 8	3.1 (± 0.75)	2.1 (± 0.77)		
Week 16	3.4 (± 0.92)	1.2 (± 0.9)		
Week 24	2.4 (± 1.12)	3.1 (± 1.05)		
Week 32	2.7 (± 1.1)	2.6 (± 1.08)		
Week 36	1.5 (± 1)	0.5 (± 1.03)		

Notes:

[35] - Randomized ITT Population

[36] - Randomized ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the first dose of investigational product until the last visit of the Open-Label or Double-Blind Taper and Follow-up Phase (up to Taper Week 4).

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs, were reported for ITT population (Open-Label and Randomized Phase), comprised of all participants who were randomized to LTG or placebo (only for Randomized Phase) and received at least one dose of the investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Open-Label and Open-Label Taper Phases: LTG

Reporting group description:

Participants (par.) received lamotrigine (LTG) up to a maximum dose depending on their age and concomitant bipolar medication group. Participants 10 -12 years of age received LTG up to a maximum dose of : 3 milligrams/kilograms (mg/kg)/day or 100 mg/day, whichever was less; or 6 mg/kg/day or 200 mg/day whichever was less; or 12 mg/kg/day or 300 mg/day whichever was less, depending on their bipolar medication group. Participants 13-17 years of age received LTG up to a maximum dose of 150 mg/day, 300 mg/day, or 400 mg/day depending on their bipolar medication group. Participants took LTG for a duration of up to 18 weeks. Participants discontinuing from the study during the Open-Label Phase entered an open Taper and Follow-up Phase.The Taper and Follow-up Phase may last up to 4 weeks, dependent on the dose of LTG the participant received during the Open-Label Phase.

Reporting group title	Randomized and Double-blind Taper Phases: Placebo

Reporting group description:

Participants received matching placebo in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks. Participants completing the Randomized Phase entered Double-Blind Taper and Follow-up Phase. The Taper and Follow-up Phase may last up to 4 weeks. The participant received Placebo during this Phase.

Reporting group title	Randomized and Double-blind Taper Phases: LTG

Reporting group description:

Participants received LTG equivalent to the dose established in the Open-Label Phase. Participants received LTG tablets in the evening for participants taking one dose and for participants taking two divided doses, one dose in the morning and one dose in the evening, for a duration of up to 36 weeks. Participants completing the Randomized Phase entered Double-Blind Taper and Follow-up Phase. The Taper and Follow-up Phase may last up to 4 weeks, dependent on the dose of LTG the participant received during the Randomized Phase.

Serious adverse events	Open-Label and Open-Label Taper Phases: LTG	Randomized and Double-blind Taper Phases: Placebo	Randomized and Double-blind Taper Phases: LTG
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 298 (6.38%)	5 / 86 (5.81%)	1 / 87 (1.15%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Neoplasm			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 298 (0.00%)	1 / 86 (1.16%)	0 / 87 (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
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	2 / 298 (0.67%)	0 / 86 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	5 / 298 (1.68%)	1 / 86 (1.16%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	3 / 298 (1.01%)	0 / 86 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			

subjects affected / exposed	3 / 298 (1.01%)	1 / 86 (1.16%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (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
Bipolar I disorder			
subjects affected / exposed	1 / 298 (0.34%)	1 / 86 (1.16%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (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
Impulsive behaviour			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (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
Intentional self-injury			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (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
Pressure of speech			
subjects affected / exposed	1 / 298 (0.34%)	0 / 86 (0.00%)	0 / 87 (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
Emotional disorder			

subjects affected / exposed	0 / 298 (0.00%)	0 / 86 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infectious mononucleosis			
subjects affected / exposed	0 / 298 (0.00%)	1 / 86 (1.16%)	0 / 87 (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
Urinary tract infection			
subjects affected / exposed	0 / 298 (0.00%)	1 / 86 (1.16%)	0 / 87 (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

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

Non-serious adverse events	Open-Label and Open-Label Taper Phases: LTG	Randomized and Double-blind Taper Phases: Placebo	Randomized and Double-blind Taper Phases: LTG
Total subjects affected by non-serious adverse events			
subjects affected / exposed	177 / 298 (59.40%)	41 / 86 (47.67%)	45 / 87 (51.72%)
Nervous system disorders			
Headache			
subjects affected / exposed	106 / 298 (35.57%)	18 / 86 (20.93%)	18 / 87 (20.69%)
occurrences (all)	201	38	26
Dizziness			
subjects affected / exposed	24 / 298 (8.05%)	4 / 86 (4.65%)	3 / 87 (3.45%)
occurrences (all)	31	7	3
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	16 / 298 (5.37%)	14 / 86 (16.28%)	7 / 87 (8.05%)
occurrences (all)	19	16	7
Fatigue			
subjects affected / exposed	17 / 298 (5.70%)	2 / 86 (2.33%)	1 / 87 (1.15%)
occurrences (all)	19	4	1
Pyrexia			

subjects affected / exposed	14 / 298 (4.70%)	5 / 86 (5.81%)	2 / 87 (2.30%)
occurrences (all)	19	5	3
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	47 / 298 (15.77%)	3 / 86 (3.49%)	5 / 87 (5.75%)
occurrences (all)	64	6	7
Nausea			
subjects affected / exposed	39 / 298 (13.09%)	3 / 86 (3.49%)	2 / 87 (2.30%)
occurrences (all)	47	4	2
Diarrhoea			
subjects affected / exposed	23 / 298 (7.72%)	1 / 86 (1.16%)	2 / 87 (2.30%)
occurrences (all)	29	1	2
Vomiting			
subjects affected / exposed	25 / 298 (8.39%)	3 / 86 (3.49%)	5 / 87 (5.75%)
occurrences (all)	30	5	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 298 (7.05%)	4 / 86 (4.65%)	7 / 87 (8.05%)
occurrences (all)	22	4	9
Oropharyngeal pain			
subjects affected / exposed	30 / 298 (10.07%)	2 / 86 (2.33%)	7 / 87 (8.05%)
occurrences (all)	35	3	13
Nasal congestion			
subjects affected / exposed	10 / 298 (3.36%)	6 / 86 (6.98%)	6 / 87 (6.90%)
occurrences (all)	11	7	11
Psychiatric disorders			
Insomnia			
subjects affected / exposed	23 / 298 (7.72%)	5 / 86 (5.81%)	6 / 87 (6.90%)
occurrences (all)	35	7	6
Suicidal ideation			
subjects affected / exposed	16 / 298 (5.37%)	1 / 86 (1.16%)	4 / 87 (4.60%)
occurrences (all)	18	2	5
Agitation			
subjects affected / exposed	11 / 298 (3.69%)	1 / 86 (1.16%)	5 / 87 (5.75%)
occurrences (all)	11	1	5
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	25 / 298 (8.39%)	5 / 86 (5.81%)	7 / 87 (8.05%)
occurrences (all)	31	5	7
Influenza			
subjects affected / exposed	14 / 298 (4.70%)	2 / 86 (2.33%)	7 / 87 (8.05%)
occurrences (all)	14	2	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2008	To 1) comply with the FDA's advice to increase the lower weight limit for the 10-12 year old subjects receiving valproate; 2) clarify the mg/kg/day dosing for the 10-12 year-old subjects; 3) add and clarify the laboratory analytes; and 4) specify the availability of laboratory and ECG results prior to randomization
08 March 2009	To 1) Comply with FDA's recommendation to add the Simpson-Angus scale to assess extrapyramidal symptoms; 2) add paliperidone to the list of acceptable bipolar medications; and, 3) to make other minor clarifications throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported