



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 (TIDep), or a mixed episode (TIMix)

| | |
|---|---|
| End point title | Time from randomization to intervention for depression (TIDep), mania/hypomania (TIDep), or a mixed episode (TIMix) |
| End point description: The time from randomization to intervention for depression (TIDep), mania/hypomania (TIDep), or a mixed episode (TIMix) was analyzed. TIDep, TIDep, 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 (\pm 0.27) | | | |
| Week 12 | -4.3 (\pm 0.28) | | | |
| Week 16 | -4.5 (\pm 0.33) | | | |
| Week 18 | -5 (\pm 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 (\pm 0.47) | 1.2 (\pm 0.48) | | |
| Week 16 | 1.6 (\pm 0.6) | 1.4 (\pm 0.58) | | |
| Week 24 | 1 (\pm 0.6) | 1.5 (\pm 0.56) | | |
| Week 32 | 0.6 (\pm 0.66) | 0.2 (\pm 0.63) | | |
| Week 36 | 0.9 (\pm 0.66) | 0.8 (\pm 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 occurrences (all) | 14 / 298 (4.70%) 19 | 5 / 86 (5.81%) 5 | 2 / 87 (2.30%) 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