Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FLEXIBLE-DOSE, PARALLEL-GROUP STUDY OF LURASIDONE ADJUNCTIVE TO LITHIUM OR DIVALPROEX FOR THE PREVENTION OF RECURRENCE IN SUBJECTS WITH BIPOLAR I DISORDER

Summary

EudraCT number	2011-000986-10
Trial protocol	HU SK CZ PL
Global end of trial date	04 April 2015

Results information

Result version number	v1 (current)
This version publication date	22 June 2016
First version publication date	22 June 2016

Trial information

Trial identification

Sponsor protocol code	D1050296

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01358357
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sunovion Pharmaceuticals Inc.
Sponsor organisation address	One Bridge Plaza Suite 510, Fort Lee, New Jersey, United States, NJ 07024
Public contact	Rob Goldman, Sunovion Pharmaceuticals Inc., +1 201-228-8319, Robert.Goldman@sunovion.com
Scientific contact	Rob Goldman, Sunovion Pharmaceuticals Inc., +1 201-228-8319, Robert.Goldman@sunovion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2015
Global end of trial reached?	Yes
Global end of trial date	04 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of lurasidone (in combination with lithium or divalproex) for the maintenance treatment of bipolar I disorder in subjects with or without rapid cycling and/or psychotic features.

Protection of trial subjects:

The study was conducted according to the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), ICH guidelines, and the ethical principles that have their origin in the Declaration of Helsinki. The study was conducted in accordance with applicable local law(s) and regulation(s).
Use of nonprescription pain medications (eg, aspirin) was allowed during all phases of the study provided these medications did not have a propensity for psychotropic effects and did not interfere with the evaluation of study medication

Background therapy:

Prior therapies/ drugs:
- Ongoing psychotherapy treatment for at least 12 weeks prior to screening was permitted during the study
- Lorazepam, temazepam, eszopiclone, zaleplon, zolpidem, and zolpidem CR permitted
Concomitant Non-psychotropic drugs:
To treat mild, chronic medical conditions if the dose and regimen were stable (± 25%) for at least 30 days prior to screening:
- β-adrenergic antagonists to treat stable hypertension could be continued during the study
- Nonprescription pain medications (eg, aspirin) weres allowed during the study provided these medications did not have a propensity for psychotropic effects and did not interfere with the evaluation of study drug
- Short-term treatment of a medical condition (no more than 14 days) was allowed provided that the drug were not cytochrome P450 3A4 (CYP3A4) inhibitors/inducers and did not consistently prolong the QTc interval
Concomitant Psychotropic drugs:
- Benztropine (up to 6 mg/day) permitted as needed for movement disorders. When it was not available or an inadequate response or intolerability to benztropine treatment occurred, biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day) were used to treat acute EPS. Treatment with propranolol (up to 120 mg/day) was permitted as needed for akathisia. Medications used to treat movement disorders were not given prophylactically
- When anticholinergic agents or sedative/hypnotic agents (or any agents that may cause sedation) were administered, these were taken at the same time each day and were not taken within 8 hours of scheduled assessments. Similar drugs at equivalent dosages were substituted
- Lorazepam, temazepam, eszopiclone, zaleplon, zolpidem, and zolpidem CR permitted with some restricctions
- Anxiolytics, sedatives, or hypnotics were not administered within 8 hours prior to any psychiatric assessments. Opiates rarely used

If above not available, similars used as per Op. Manual/Med.Monitor

Evidence for comparator:

Bipolar disorder is a chronic and often disabling condition with a lifetime prevalence of approximately 4.4%. The episodic nature of bipolar disorder means that the majority of subjects can expect a lifelong course of recurrent acute episodes, in addition to residual symptoms in the intervening years.Despite therapeutic intervention, relapse rates for subjects who are receiving treatment range from 40% to 60%, even after a first life-time episode with as many as one-half of subjects experiencing a 2nd mood episode within a year of recovery: the goal of effective maintenance treatment is to prevent relapse,

reduce subsyndromal symptoms, decrease hospitalizations, decrease morbidity and mortality, and improve functioning and quality of life
At present, the following atypical antipsychotics have demonstrated the ability to maintain efficacy in bipolar I disorder in previously stabilized subjects either as monotherapy or in combination with lithium or divalproex: olanzapine, aripiprazole, quetiapine, and ziprasidone.
Lurasidone is an atypical antipsychotic agent with a unique chemical structure. Lurasidone has high affinity for dopamine D2, serotonin 5-HT2A and serotonin 5-HT7 receptors where it has antagonist effects. In addition, lurasidone is a partial agonist at the serotonin 5-HT1A receptor.
More than 2,500 lurasidone-treated subjects have participated in over 40 clinical studies, including five 6-week, double-blind, placebo-controlled studies involving hospitalized subjects with schizophrenia. Clinical trials demonstrated that lurasidone was efficacious in the treatment of schizophrenia and generally well tolerated
The current randomized, placebo-controlled, flexible-dose, parallel-group study was designed to evaluate the efficacy of lurasidone compared with placebo in preventing recurrence of affective symptoms in subjects with bipolar I disorder who demonstrated a stable response to acute treatment with lurasidone in combination with lithium or divalproex.

Actual start date of recruitment	06 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Slovakia: 9
Country: Number of subjects enrolled	Bulgaria: 53
Country: Number of subjects enrolled	Czech Republic: 62
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Hungary: 51
Country: Number of subjects enrolled	United States: 471
Country: Number of subjects enrolled	Argentina: 51
Country: Number of subjects enrolled	Chile: 25
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Japan: 25
Country: Number of subjects enrolled	Russian Federation: 81
Country: Number of subjects enrolled	Serbia: 54
Worldwide total number of subjects	965
EEA total number of subjects	256

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	935
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1412 patients were evaluated for eligibility during a screening/wash-out period of 3-14 days (28 days for subjects on fluoxetine): other than lithium or divalproex, subjects were tapered off selected psychotropic drugs according to labeling recommendations and usual medical practice.
Screen Failures: 447.
965 patients entered Open-Label Phase

Period 1

Period 1 title	Open-label Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lurasidone + lithium / divalproex

Arm description:

Upon meeting entry criteria, subjects began open-label treatment with lurasidone (20-80 mg/day) and either lithium or divalproex (if not currently taking one of these mood stabilizers) on the evening of Visit 2 (open-label phase baseline).
For subjects previously not on either lithium or divalproex, Investigators determined which mood stabilizer was most appropriate to initiate: lithium and divalproex were dosed to achieve serum trough concentrations of 0.4-1.2 mEq/L and 50-125 µg/mL, respectively. All country-approved formulations of lithium or divalproex (including extended-release and controlled-release formulations) were permitted (with the exception of lithium orotate and magnesium valproate).
Subjects remained in the open-label phase for a maximum of 20 weeks until they achieved and maintained consistent clinical stability.

Arm type	Experimental
Investigational medicinal product name	Lurasidone Hydrochloride
Investigational medicinal product code	SM-13496
Other name	CAS Number: 367514-88-3, EV Substance code: SUB34204
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lurasidone was dosed as follows: 20 mg/day on Days 1-3; 40 mg/day on Days 4-7; and flexibly (20-80 mg/day) thereafter. Beginning on Day 8, if dose adjustments were necessary, they were to occur at weekly intervals and in increments/decrements of 1 dose level (ie, 20 mg/day), based on Investigator judgment in order to optimize efficacy and tolerability. However, dose reductions for tolerability purposes were permitted to occur more frequently than at weekly intervals and more than 1 dose level at a time (maximum of 2 dose levels at a time).

Number of subjects in period 1	Lurasidone + lithium / divalproex
Started	965
Completed	503
Not completed	462
Consent withdrawn by subject	112
Did not meet criteria for double-blind phase	16

Study terminated by Sponsor	5
Adverse event, non-fatal	59
Mood episode	42
Lost to follow-up	76
Protocol deviation	45
Lack of efficacy	107

Period 2

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

Blinding implementation details:

Stratified randomization was performed at double-blind phase baseline using an Interactive Voice Response System (IVRS) to ensure balance across the 2 groups relative to mood stabilizer treatment (lithium or divalproex).

Arms

Are arms mutually exclusive?	Yes
Arm title	Lurasidone + lithium / divalproex

Arm description:

Lurasidone in combination with either lithium or divalproex for up to 28 weeks: the last open-label dose level was maintained entering the double-blind phase (Visit 13). Subsequent dose adjustments, if necessary, were to occur at weekly intervals and in increments/decrements of 1 dose level, based on Investigator judgment.

Arm type	Experimental
Investigational medicinal product name	Lurasidone Hydrochloride
Investigational medicinal product code	SM-13496
Other name	CAS Number: 367514-88-3, EV Substance code: SUB34204
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The last open-label dose level was maintained entering the double-blind phase (Visit 13)

Arm title	Placebo + lithium / divalproex

Arm description:

Placebo in combination with either lithium or divalproex) for up to 28 weeks. Subjects randomized to matching placebo, the lurasidone dose taken during the open-label phase was discontinued. Subsequent dose adjustments, if necessary, were to occur at weekly intervals and in increments/decrements of 1 dose level, based on Investigator judgment.
Subjects who completed the double-blind phase of the study or experienced a protocol-specified recurrence of any mood event during the double-blind phase were eligible to participate in a separate 3-month, open-label lurasidone extension study (D1050308).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For subjects randomized to matching placebo, the lurasidone dose was discontinued. Subsequent dose adjustments, if necessary, were to occur at weekly intervals and in increments/decrements of 1 dose level, based on Investigator judgment.

Number of subjects in period 2[1]	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex
Started	246	250
Completed	166	150
Not completed	80	100
Consent withdrawn by subject	16	12
Adverse event, non-fatal: no mood event recurrence	8	5
Administrative	-	1
Lost to follow-up	5	7
Recurrence of mood event	48	64
Study terminated by the Sponsor	2	-
Protocol deviation	1	11

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Of the 503 subjects who completed the open-label phase, 7 subjects were not randomized to the double-blind phase (3 subjects due to a mood episode, 3 subjects due to not meeting the criteria for the double blind phase, and 1 subject due to an insufficient clinical response), thus only 496 subjects were randomized to the double blind phase.

Baseline characteristics

Reporting groups	
Reporting group title	Open-label Phase
Reporting group description:	
'OL/DB baseline' values in the following table represent Open-Label (OL) Baseline	

Reporting group values	Open-label Phase	Total	
Number of subjects	965	965	
Age categorical			
Units: Subjects			
85 years and over	0	0	
<55	771	771	
>=55	194	194	
Age continuous			
Units: years			
arithmetic mean	42.5		
standard deviation	± 12.6	-	
Gender categorical			
Units: Subjects			
Female	568	568	
Male	397	397	
Region			
Units: Subjects			
North America	471	471	
Asia	25	25	
Europe	393	393	
South America	76	76	
Race			
Units: Subjects			
White	782	782	
Black or African American	123	123	
Asian	33	33	
American Indian or Alaska native	7	7	
Native Hawaiian or Other Pacific Islander	2	2	
Other	18	18	
OL/DB baseline YMRS total score			
Units: rating scales			
arithmetic mean	12.9		
standard deviation	± 9.23	-	
OL/DB baseline MADRS total score			
Units: rating scales			
arithmetic mean	21.3		
standard deviation	± 10.35	-	
OL/DB baseline CGI-BP-S overall score			
Units: rating scales			
arithmetic mean	4.15		
standard deviation	± 0.72	-	

Subject analysis sets	
Subject analysis set title	Intent-to treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT population included all subjects who were randomized and received at least 1 dose of study medication in the double-blind phase. Each subject was assigned to the randomized treatment.
'OL/DB baseline' values in the following table represent Double-blind (DB) Baseline

Subject analysis set title	Double-blind safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Double-blind Safety Population included all subjects who received at least one dose of study medication in the Double-blind phase. Each subject was assigned to the treatment they actually received.
'OL/DB baseline' values in the following table represent Double-blind (DB) Baseline

Subject analysis set title	Per-Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

PP population included all ITT subjects who received the randomized study medication, were 75% - 125% compliant over the double-blind phase, and had no major protocol deviations.
'OL/DB baseline' values in the following table represent Double-blind (DB) Baseline

Reporting group values	Intent-to treat population	Double-blind safety population	Per-Protocol Population
Number of subjects	496	496	458
Age categorical Units: Subjects			
85 years and over	0	0	0
<55	378	378	347
>=55	118	118	111
Age continuous Units: years			
arithmetic mean	44.4	44.4	44.6
standard deviation	± 12.36	± 12.36	± 12.41
Gender categorical Units: Subjects			
Female	279	279	259
Male	217	217	199
Region Units: Subjects			
North America	149	149	135
Asia	10	10	9
Europe	279	279	260
South America	58	58	54
Race Units: Subjects			
White	429	429	401
Black or African American	44	44	39
Asian	13	13	11
American Indian or Alaska native	2	2	2

Native Hawaiian or Other Pacific Islander	0	0	0
Other	8	8	5

OL/DB baseline YMRS total score			
Units: rating scales			
arithmetic mean	2.2	2.2	2.1
standard deviation	± 2.66	± 2.66	± 2.61
OL/DB baseline MADRS total score			
Units: rating scales			
arithmetic mean	4	4	4.1
standard deviation	± 3.56	± 3.56	± 3.6
OL/DB baseline CGI-BP-S overall score			
Units: rating scales			
arithmetic mean	1.67	1.67	1.66
standard deviation	± 0.694	± 0.694	± 0.7

End points

End points reporting groups

Reporting group title	Lurasidone + lithium / divalproex

Reporting group description:

Upon meeting entry criteria, subjects began open-label treatment with lurasidone (20-80 mg/day) and either lithium or divalproex (if not currently taking one of these mood stabilizers) on the evening of Visit 2 (open-label phase baseline).
For subjects previously not on either lithium or divalproex, Investigators determined which mood stabilizer was most appropriate to initiate: lithium and divalproex were dosed to achieve serum trough concentrations of 0.4-1.2 mEq/L and 50-125 µg/mL, respectively. All country-approved formulations of lithium or divalproex (including extended-release and controlled-release formulations) were permitted (with the exception of lithium orotate and magnesium valproate).
Subjects remained in the open-label phase for a maximum of 20 weeks until they achieved and maintained consistent clinical stability.

Reporting group title	Lurasidone + lithium / divalproex

Reporting group description:

Lurasidone in combination with either lithium or divalproex for up to 28 weeks: the last open-label dose level was maintained entering the double-blind phase (Visit 13). Subsequent dose adjustments, if necessary, were to occur at weekly intervals and in increments/decrements of 1 dose level, based on Investigator judgment.

Reporting group title	Placebo + lithium / divalproex

Reporting group description:

Placebo in combination with either lithium or divalproex) for up to 28 weeks. Subjects randomized to matching placebo, the lurasidone dose taken during the open-label phase was discontinued.
Subsequent dose adjustments, if necessary, were to occur at weekly intervals and in increments/decrements of 1 dose level, based on Investigator judgment.
Subjects who completed the double-blind phase of the study or experienced a protocol-specified recurrence of any mood event during the double-blind phase were eligible to participate in a separate 3-month, open-label lurasidone extension study (D1050308).

Subject analysis set title	Intent-to treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT population included all subjects who were randomized and received at least 1 dose of study medication in the double-blind phase. Each subject was assigned to the randomized treatment.
'OL/DB baseline' values in the following table represent Double-blind (DB) Baseline

Subject analysis set title	Double-blind safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Double-blind Safety Population included all subjects who received at least one dose of study medication in the Double-blind phase. Each subject was assigned to the treatment they actually received.
'OL/DB baseline' values in the following table represent Double-blind (DB) Baseline

Subject analysis set title	Per-Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

PP population included all ITT subjects who received the randomized study medication, were 75% - 125% compliant over the double-blind phase, and had no major protocol deviations.
'OL/DB baseline' values in the following table represent Double-blind (DB) Baseline

Primary: Time to recurrence of any mood event (during double-blind [DB] phase)

End point title	Time to recurrence of any mood event (during double-blind [DB] phase)

End point description:

Mood event was defined as any of the following:

• Fulfilled Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV-TR) criteria for manic, mixed manic, hypomanic, or depressive episode.
• Required treatment intervention for manic, mixed manic, hypomanic, or depressive symptoms with any antipsychotic (other than study drug), antidepressant, mood

stabilizer (other than lithium or divalproex), anxiolytic agents, benzodiazepine (beyond dosage allowed for anxiety, agitation, or insomnia).
• Psychiatric hospitalization for any bipolar mood episode.
• Young Mania Rating Scale (YMRS) or Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 18 or Clinical Global Impression-Bipolar Version, Severity of Illness (CGI-BP-S) score ≥ 4 at 2 consecutive assessments no more than 10 days apart.
• Discontinuation from the study because of a mood event (as determined by the Investigator).

End point type	Primary

End point timeframe:

28 weeks

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex	Intent-to treat population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	246	250	496	
Units: Number of Recurrence events	48	64	112	

Statistical analyses

Statistical analysis title	Analysis of time to recurrence of any mood event

Statistical analysis description:

The primary efficacy analysis for the time to recurrence of any mood event will be performed using a stratified Cox model to assess the hazard ratio of recurrence between the two treatment groups on the ITT population.

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.078 [2]
Method	stratified Cox model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.04

Notes:

[1] - It was assumed that the recurrence event rates during the double-blind phase were to be 24% and 39% for subjects treated with lurasidone and placebo, respectively. A total of 120 recurrence events were required to achieve 90% power to detect the 15% difference in subjects who had a recurrence event during the double-blind phase between the treatment groups using a log-rank test with two sided alpha level of 0.05.

[2] - A hazard ratio of time to recurrence and its corresponding 95% Wald CI were estimated for lurasidone arm vs the placebo arm, using a Cox proportional hazards model. Cox model included treatment effect as fixed effect, and stratified by pooled country

Secondary: Time to All-cause Discontinuation

End point title	Time to All-cause Discontinuation

End point description:

Time to all-cause discontinuation is defined as: ((date of discontinuation - date of randomization) + 1). For subjects who completed the study or discontinued early due to sponsor's decision to stop the study, time to discontinuation is censored at time of completion or discontinuation.

End point type	Secondary

End point timeframe:

28 weeks double-blind phase

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex	Intent-to treat population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	246	250	496	
Units: number of recurrence events	78	100	178	

Statistical analyses

Statistical analysis title	Time to all-cause discontinuation

Statistical analysis description:

Time to all-cause discontinuation is defined as: ((date of discontinuation - date of randomization) + 1). For subjects who completed the study or discontinued early due to sponsor's decision to stop the study, time to discontinuation is censored at time of completion or discontinuation

Comparison groups	Placebo + lithium / divalproex v Lurasidone + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 [3]
Method	stratified Cox model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.98

Notes:

[3] - A hazard ratio of time to discontinuation and its corresponding 95% Wald CI were estimated for lurasidone vs placebo arms, using a Cox proportional hazards model. Cox model included treatment effect as fixed effect, and stratified by pooled country

Secondary: Time to recurrence of a manic, mixed manic, hypomanic or depressed episode

End point title	Time to recurrence of a manic, mixed manic, hypomanic or depressed episode

End point description:

Recurrence is defined as any event of manic, mixed manic, hypomanic, or depressed episode. For subjects who discontinued early or completed the study without experiencing a recurrence event, time to recurrence is censored at the time of discontinuation or completion.

End point type	Secondary

End point timeframe:

28 weeks double-blind phase

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex	Intent-to treat population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	246	250	496	
Units: Number of recurrence events	41	54	95	

Statistical analyses

Statistical analysis title	Time to Recurrence of a Manic, Mxd Manic, HM or DE
Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.113 [4]
Method	stratified Cox model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.08

Notes:

[4] - A hazard ratio of time to recurrence and its corresponding 95% Wald CI were estimated for lurasidone versus placebo arms, using a Cox proportional hazards model. The Cox model included treatment as a fixed effect, stratified by pooled countries.

Secondary: Proportion of subjects with recurrence of manic, mixed manic, hypomanic or depressing episode

End point title	Proportion of subjects with recurrence of manic, mixed manic, hypomanic or depressing episode

End point description:

End point type	Secondary

End point timeframe:

28 weeks double-blind phase

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex	Intent-to treat population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	246	250	496	
Units: subjects	41	54	95	

Statistical analyses

No statistical analyses for this end point

Secondary: Global Severity: CGI-BP-S, YMRS, MADRS, QIDS-SR16, and PANSS-P

End point title	Global Severity: CGI-BP-S, YMRS, MADRS, QIDS-SR16, and PANSS-P

End point description:

CGI-BP-S is a clinical-rated assessment of th subject's current illness state (mania, depression, and overall bipolar illness), on a 7-point scale, where a higher score is associated with greater illness severity. YMRS is an 11-item instrument used to assess the severity of mania in subjects wiht a bipolar disorder. Ratings are based on patient self-reporting, combined with clinician observation (accorded greater score). YMRS total score ranges from 0-60, with higher scores indicating greater severity of mania. MADRS is a clinician-rated assessment of the subject's level of depression containing 10 items scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. QIDS-SR16 is a 16-item self-report measure of depressive symptomatology which uses a computerized assessment interface for administration. The total score ranges form 0 to 27, with higher scores indicating greater severity of depression. PANSS-P rates 7 positive symptoms of schizophrenia.

End point type	Secondary

End point timeframe:

Outcome Measure Timeframe: 28 weeks double-blind phase

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[5]	250[6]		
Units: score				
least squares mean (standard error)				
CGI-BP-S overall	0.4 (± 0.085)	0.49 (± 0.085)		
CGI-BP-S mania	0.1 (± 0.062)	0.21 (± 0.062)		
CGI-BP-S depression	0.35 (± 0.082)	0.42 (± 0.081)		
YMRS	1 (± 0.43)	1.8 (± 0.43)		
MADRS	3 (± 0.57)	3.5 (± 0.57)		
QIDS-SR16	0.9 (± 0.27)	1.1 (± 0.27)		
PANSS-P	0.2 (± 0.13)	0.3 (± 0.13)		

Notes:

[5] - No. subjects analysed for the below questionnaires:
CGI, YMRS, MADRS: 244
QIDS: 239
PANSS-P: 240

[6] - No. subjects analysed for the below questionnaires:
CGI, YMRS, MADRS: 250
QIDS: 243

Statistical analyses

Statistical analysis title	CGI-BP-S overall score: change from DB Phase BL

Statistical analysis description:

The CGI-BP-S overall score is a single value, clinician-rated assessment of overall bipolar illness severity and ranges from 1= 'Normal, not at all ill' to 7= 'Among the most extremely ill patients'. A higher score is associated with greater illness severity.
Subjects were analyzed based on the treatment they were randomized. 2 lurasidone + Li/VPA subjects did not have post-DB baseline CGI-BP-S overall score.

Results at DB Week 28 (LOCF).

Comparison groups	Placebo + lithium / divalproex v Lurasidone + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.406 [8]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.12

Notes:

[7] - 2 lurasidone + Li/VPA subjects did not have post-DB baseline CGI-BP-S overall score therefore number of subjects included in analysis for the CGI-BP-S overall score were finally 494.
[8] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Statistical analysis title	CGI-BP-S mania score: change from DB Phase BL

Statistical analysis description:

The CGI-BP-S mania score is a single value, clinician-rated assessment of mania illness severity and ranges from 1= 'Normal, not at all ill' to 7= 'Among the most extremely ill patients'. A higher score is associated with greater illness severity.

Results at DB Week 28 (LOCF)

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.162 [10]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.04

Notes:

[9] - 2 lurasidone + Li/VPA subjects did not have post-DB baseline CGI-BP-S mania score therefore number of subjects included in analysis for the CGI-BP-S mania score were finally 494.
[10] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Statistical analysis title	CGI-BP-S depression score: change from DB Phase BL

Statistical analysis description:

The CGI-BP-S depression score is a single value, clinician-rated assessment of depression illness severity and ranges from 1= 'Normal, not at all ill' to 7= 'Among the most extremely ill patients'. A higher score is associated with greater illness severity.

Results at DB Week 28 (LOCF)

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.496 [12]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.13

Notes:

[11] - 2 lurasidone + Li/VPA subjects did not have post-DB baseline CGI-BP-S depression score therefore the number of subjects included in analysis for the CGI-BP-S depression score were finally 494.
[12] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Statistical analysis title	YMRS total score: change from DB Phase BL

Statistical analysis description:

The YMRS is an 11 item instrument used to assess the severity of mania in subjects with a diagnosis of bipolar disorder. Ratings are based on patient self reporting, combined with clinician observation (accorded greater score). The YMRS total score is calculated as the sum of the 11 items. The YMRS total score ranges from 0 to 60. Higher scores are associated with greater severity of mania.

Results at DB Week 28 (LOCF)

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.128 [14]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.2

Notes:

[13] - 2 lurasidone + Li/VPA subjects did not have post-DB baseline YMRS total score therefore the number of subjects included in analysis for the YMRS total score were finally 494.
[14] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Statistical analysis title	MADRS total score: change from DB Phase BL

Statistical analysis description:

The MADRS consists of 10 items, each rated on a Likert scale, from 0=”Normal” to 6=”Most Severe”. The MADRS total score is calculated as the sum of the 10 items. The MADRS total score ranges from 0 to 60. Higher scores are associated with greater severity of depressive symptoms.

Results at DB Week 28 (LOCF)

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.485 [16]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.9

Notes:

[15] - 2 lurasidone + Li/VPA subjects did not have post-DB baseline MADRS total score therefore the number of subjects included in analysis for the MADRS total score were finally 494.
[16] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Statistical analysis title	QIDS-SR16 total score: change from DB Phase BL

Statistical analysis description:

The QIDS-SR16 is a 16-item self-report measure of depressive symptomatology which uses a computerized assessment interface for administration. The scoring system for the QIDS-SR16 converts responses to 16 separate items into nine DSM-IV symptom criterion domains. Nine domains comprise: depressed mood; concentration/decision making; self outlook; suicidal ideation; decreased interest; decreased energy; sleep disturbance; appetite/weight disturbance; and psychomotor disturbance.

LOCF results

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.582 [18]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.5

Notes:

[17] - QIDS-SR16 total score is calculated as the sum of the 9 domain scores. QIDS-SR16 total score ranges from 0 to 27 with a high score indicating more severe symptoms.

7 lurasidone + Li/VPA subjects and 7 placebo +Li/VPA subjects did not have post-DB baseline QIDS-SR16 total score therefore the number of subjects included in analysis for the QIDS-SR16 total score were finally 482.
[18] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Statistical analysis title	PANSS-P subscale score: change from DB Phase BL

Statistical analysis description:

The PANSS-P is a subset of items in the PANSS, an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The measure contains seven questions to assess delusions, conceptual disorganization, hallucinations behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. An anchored Likert scale from 1-7, where values of 2 and above indicate the presence of progressively more severe symptoms, is used to score each item.

LOCF Results

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.42 [20]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.2

Notes:

[19] - The PANSS-P subscale score is the sum of the 7 items and ranges from 7 through 49. A higher score is associated with greater illness severity.

6 lurasidone + Li/VPA subjects and 3 placebo +Li/VPA subjects did not have post-DB baseline PANSS-P score therefore the number of subjects included in analysis for the PANSS-P score were finally 487.
[20] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Secondary: SDS Total Score: change from DB phase BL

End point title	SDS Total Score: change from DB phase BL

End point description:

The SDS is a composite of 3 self-rated items designed to measure the extent to which 3 major sectors in the patient's life are impaired by depressive symptoms. This anchored visual analog scale uses spatiovisual, numeric, and verbal descriptive anchors simultaneously to assess disability across 3 domains (work, social life, and family life) on a 10-point visual analog scale. The total score of global functional impairment ranges from 0 to 30, with higher scores indicating a greater degree of disability.

End point type	Secondary

End point timeframe:

28 weeks

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	193		
Units: scores				
least squares mean (standard error)	0.4 (± 0.59)	0.6 (± 0.61)		

Statistical analyses

Statistical analysis title	SDS total score: change from DB Phase BL

Statistical analysis description:

The SDS total score is a composite of three self-rated items designed to measure the extent to which three major sectors in the patient's life are impaired by depressive symptoms. The SDS total score is calculated as the sum of the 3 items. The SDS total score ranges from 0 to 30. Higher scores are associated with greater severity of global functional impairments.

Results at DB Week 28 (LOCF)

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.788
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.2

Notes:

[21] - If a subject has not worked/studied at all during the past week for reasons unrelated to the disorder, the SDS total score will be set to missing.

63 lurasidone + Li/VPA subjects and 57 placebo +Li/VPA subjects did not have post-DB baseline SDS total score therefore the number of subjects included in analysis for the SDS total score were finally 376 .

Secondary: Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form

End point title	Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form

End point description:

The Q-LES-Q-SF is a 16-item self-report measure of the degree of enjoyment and satisfaction in various areas of daily living. Q-LES-Q-SF percent maximum possible scores range from 0-100, where higher scores indicate better quality of life.

End point type	Secondary

End point timeframe:

28 weeks

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	239		
Units: score				
least squares mean (standard error)	-1.7 (± 1.022)	-2.07 (± 1.035)		

Statistical analyses

Statistical analysis title	Q-LES-Q-SF: change from DB Phase BL

Statistical analysis description:

Q-LES-Q-SF is a 16-item self-report measure of the degree of enjoyment and satisfaction in various areas of daily living. The questionnaire was developed and validated for use in depressed outpatient subjects and has eight summary scales that reflect major areas of functioning: physical health, mood, leisure time activities, social relationships, general activities, work, household duties and school/coursework. Each item is rated on a 5-point scale, ranging from 1 (very poor) to 5 (very good).

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.772 [23]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.14
upper limit	2.88

Notes:

[22] - The Q-LES-Q-SF percentage maximum possible score is calculated as 100 × (Raw Score – 14 [Minimum Score]) / (70 [Maximum Score] – 14 [Minimum Score]). Higher percent maximum scores indicate better quality of life.
12 lurasidone + Li/VPA subjects and 11 placebo +Li/VPA subjects did not have post-DB baseline Q-LES-Q-SF percent maximum possible score therefore the number of subjects included in this analysis were finally 473.
Results at DB Week 28 (LOCF)
[23] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Secondary: Sleep quality assessed by the Pittsburgh Insomnia Rating Scale (PIRS-2).

End point title	Sleep quality assessed by the Pittsburgh Insomnia Rating Scale (PIRS-2).

End point description:

The PIRS-2 is a 2-item self-report of insomnia. The PIRS-2 total score ranges from 0-6, where higher scores indicating greater impairment.

End point type	Secondary

End point timeframe:

28 weeks

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	243		
Units: score				
least squares mean (standard error)	0.4 (± 0.1)	0.5 (± 0.1)		

Statistical analyses

Statistical analysis title	PIRS-2 total score: change from DB Phase BL

Statistical analysis description:

The PIRS-2 is a 2-item self-report of insomnia assessed via a computer interface. Each item is scored from 0-3. The PIRS-2 total score is calculated as the sum of the 2 items. The PIRS total score ranges from 0 to 6. Higher scores are associated with greater severity of insomnia.

Results at DB Week 28 (LOCF)

Comparison groups	Lurasidone + lithium / divalproex v Placebo + lithium / divalproex
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.38 [25]
Method	ANCOVA
Parameter estimate	LS mean difference of luras. vs placebo
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

Notes:

[24] - 7 lurasidone + Li/VPA subjects and 7 placebo +Li/VPA subjects did not have post-DB baseline PIRS-2 total score therefore the number of subjects included in this analysis were finally 482 .
[25] - Analysis of Covariance (ANCOVA) model contains treatment, and pooled country, and mood stabilizer (lithium or divalproex) as fixed factors and baseline as a covariate.

Secondary: SF-12 Health Survey

End point title	SF-12 Health Survey

End point description:

The SF-12 is a multipurpose short-form generic measure of health status. It was developed to be a much shorter, yet valid, alternative to the SF-36 for use in large surveys of general and specific populations as well as large longitudinal studies of health outcomes. The standard (4-week) recall version was utilized. Higher scores indicate better quality of life.

End point type	Secondary

End point timeframe:

28 weeks

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	244		
Units: score				
arithmetic mean (standard deviation)				
SF-12 Health Survey Component Scores: Mental	47.3 (± 10.97)	46.1 (± 11.19)		
SF-12 Health Survey Component Scores: Physical	51.5 (± 7.44)	51.7 (± 7.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Medication Satisfaction Questionnaire

End point title	Medication Satisfaction Questionnaire

End point description:

The MSQ is a single-item assessment that requires the subject to use a 7-point, Likert-type scale to rate how satisfied they are with their current medication used to treat bipolar disorder, with a higher score indicating higher satisfaction.

End point type	Secondary

End point timeframe:

28 weeks

End point values	Lurasidone + lithium / divalproex	Placebo + lithium / divalproex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: score				
arithmetic mean (standard deviation)	5.2 (± 1.45)	5.1 (± 1.44)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

- During open label phase (up to 20 weeks)
- During double blind phase (up to 28 weeks)

Adverse event reporting additional description:

Adverse Events were collected and recorded from the date the informed consent form was signed until the end of participation in the study. SAEs were collected for each subject through 14 days after the subject's last dose of study drug: after the 14-day timeframe, investigator did report SAEs "spontaneously if considered at least PS related

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Open-label safety

Reporting group description:

Open-label safety population included all subjects who received at least 1 dose of study medication (lurasidone (20-80 mg/day, and either lithium or divalproex), in the open-label phase.

Reporting group title	Placebo + Li/VPA

Reporting group description:

subjects who were randomized and received at least 1 dose of study medication (placebo + Li/VPA) in the double-blind phase

Reporting group title	Lurasidone + Li/VPA

Reporting group description:

subjects who were randomized and received at least 1 dose of study medication (Lurasidone + Li/VPA) in the double-blind phase

Serious adverse events	Open-label safety	Placebo + Li/VPA	Lurasidone + Li/VPA
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 962 (4.26%)	11 / 250 (4.40%)	13 / 246 (5.28%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ovarian tumour			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Ovarian cancer			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (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

Vascular disorders			
Brain neoplasm			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Hypotension			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (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			
Chest discomfort			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Ovarian cyst			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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			
Mania			
subjects affected / exposed	5 / 962 (0.52%)	3 / 250 (1.20%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 5	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	10 / 962 (1.04%)	1 / 250 (0.40%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	5 / 10	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	2 / 962 (0.21%)	0 / 250 (0.00%)	0 / 246 (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
Bipolar I disorder			
subjects affected / exposed	2 / 962 (0.21%)	2 / 250 (0.80%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 962 (0.00%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive symptoms			
subjects affected / exposed	2 / 962 (0.21%)	0 / 250 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	2 / 962 (0.21%)	0 / 250 (0.00%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal attempt			
subjects affected / exposed	2 / 962 (0.21%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 962 (0.00%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute psychosis			

subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Insomnia			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Panic attack			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Somatoform disorder			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	2 / 962 (0.21%)	0 / 250 (0.00%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Clavicle fracture			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Facial bones fracture			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Lower limb fracture			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Toxicity to various agents			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Headache			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Cholecystitis chronic			
subjects affected / exposed	1 / 962 (0.10%)	1 / 250 (0.40%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelitiasis			
subjects affected / exposed	0 / 962 (0.00%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 962 (0.00%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Chondromalacia			
subjects affected / exposed	1 / 962 (0.10%)	0 / 250 (0.00%)	0 / 246 (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
Back pain			
subjects affected / exposed	0 / 962 (0.00%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint swelling			
subjects affected / exposed	0 / 962 (0.00%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Patellofemoral pain syndrome			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 962 (0.00%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (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
Postoperative wound infection			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (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
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	0 / 962 (0.00%)	0 / 250 (0.00%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 962 (0.00%)	1 / 250 (0.40%)	0 / 246 (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: 3 %

Non-serious adverse events	Open-label safety	Placebo + Li/VPA	Lurasidone + Li/VPA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	474 / 962 (49.27%)	151 / 250 (60.40%)	153 / 246 (62.20%)
Investigations			
Weight increased			

subjects affected / exposed	22 / 962 (2.29%)	13 / 250 (5.20%)	24 / 246 (9.76%)
occurrences (all)	22	13	24
Nervous system disorders			
Headache			
subjects affected / exposed	88 / 962 (9.15%)	17 / 250 (6.80%)	21 / 246 (8.54%)
occurrences (all)	88	17	21
Akathisia			
subjects affected / exposed	80 / 962 (8.32%)	8 / 250 (3.20%)	9 / 246 (3.66%)
occurrences (all)	80	8	9
Somnolence			
subjects affected / exposed	69 / 962 (7.17%)	2 / 250 (0.80%)	4 / 246 (1.63%)
occurrences (all)	69	2	4
Tremor			
subjects affected / exposed	43 / 962 (4.47%)	11 / 250 (4.40%)	15 / 246 (6.10%)
occurrences (all)	43	11	15
Sedation			
subjects affected / exposed	34 / 962 (3.53%)	1 / 250 (0.40%)	0 / 246 (0.00%)
occurrences (all)	34	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 962 (3.01%)	3 / 250 (1.20%)	3 / 246 (1.22%)
occurrences (all)	29	3	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	111 / 962 (11.54%)	4 / 250 (1.60%)	7 / 246 (2.85%)
occurrences (all)	111	4	7
Vomiting			
subjects affected / exposed	59 / 962 (6.13%)	4 / 250 (1.60%)	5 / 246 (2.03%)
occurrences (all)	59	4	5
Diarrhoea			
subjects affected / exposed	53 / 962 (5.51%)	7 / 250 (2.80%)	5 / 246 (2.03%)
occurrences (all)	53	7	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	77 / 962 (8.00%)	16 / 250 (6.40%)	9 / 246 (3.66%)
occurrences (all)	77	16	9

Anxiety			
subjects affected / exposed	41 / 962 (4.26%)	11 / 250 (4.40%)	4 / 246 (1.63%)
occurrences (all)	41	11	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	39 / 962 (4.05%)	12 / 250 (4.80%)	15 / 246 (6.10%)
occurrences (all)	39	12	15
Upper respiratory tract infection			
subjects affected / exposed	10 / 962 (1.04%)	9 / 250 (3.60%)	2 / 246 (0.81%)
occurrences (all)	10	9	2
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	30 / 962 (3.12%)	2 / 250 (0.80%)	0 / 246 (0.00%)
occurrences (all)	30	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2011	Amendment 1, 06 May 2011, implemented the following non-administrative changes: - The BMI was changed to a system-derived value in the eCRF; therefore, the BMI criterion was removed from the inclusion/exclusion criteria and visit assessments and the BMI determination appendix was deleted. - Additional visits were added to the DB phase in order to monitor the subject's postrandomization status more frequently (weekly for the first 2 weeks immediately after randomization visit, and every 2 weeks thereafter). In addition, an interim telephone call was added during the DB phase to assess the subject's status (AEs and concomitant medications) at weekly intervals. In addition to scheduled visits, subject 's would be contacted via an interim telephone call by site staff to monitor AEs and concomitant medications at Week 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27. - The allowed hospitalization period during the screening/wash-out phase was extended from 24 hours to up-to a maximum of 7 days. - Safety reporting requirements were updated to include a 14-day follow-up period requirement post last dose of study drug. - Removed the exclusion criteria requiring subject scores ≥ 4 on MADRS item number 10 (suicidal thoughts) at screening. - The key secondary analysis was revised to use heterogenous compound symmetry, which is more appropriate than the spatial exponential covariance pattern model that was originally planned.
17 January 2013	Amendment 2, 17 Jan 2013, implemented the following non-administrative changes: - Safety reporting and monitoring contact information was updated. - Various contact information was updated. - The key secondary endpoint, CG-BP-S, was changed to a secondary endpoint. - The C-SSRS was changed from an efficacy to a safety assessment. - The YMRS/MADRS inclusion criterion was modified to allow the open-label baseline time point in addition to screening. - Subjects who experience a protocol-specified recurrence of any mood event during the double-blind phase were also allowed the option to enroll in a separate 3-month, open-label lurasidone extension study. - Adjustments for multiplicity were deleted. - Pharmacogenomic blood sample collection, processing, storage, and shipment information was updated.
06 January 2014	Amendment 3, 06 Jan 2014, implemented the following non-administrative changes: - Updated the number of recurrence events and the resulting number of subjects needed to be randomized. - Updated the safety reporting information. - Updated various contact information. Various typographical and grammatical edits to improve consistency and overall readability have been incorporated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported