



Clinical trial results:

A Multicenter, Open-Label, Flexible-Dose Extension Study of Lurasidone Adjunctive to Lithium or Divalproex in Subjects with Bipolar I Disorder (PERSIST EXTENSION STUDY)

Summary

EudraCT number	2011-004789-14
Trial protocol	HU CZ SK BG PL HR
Global end of trial date	01 July 2015

Results information

Result version number	v1 (current)
This version publication date	19 August 2016
First version publication date	19 August 2016

Trial information

Trial identification

Sponsor protocol code	D1050308
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01575561
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	27 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2015
Global end of trial reached?	Yes
Global end of trial date	01 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the longer term safety, tolerability, and effectiveness of lurasidone, flexibly dosed at 20, 40, 60 or 80 mg/day in subjects with bipolar disorder who had either completed double-blind treatment or experienced a protocol-specified recurrence of any mood event during the Double-blind Phase in Study D1050296 (EudraCT No.: 2011-000986-10).

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 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 and Concomitant Therapy:

Potent inducers or inhibitors of the CYP3A4 enzyme system and any medications that consistently prolong the QTc interval were prohibited during the study. The use of herbal supplements or other complementary or alternative medications was not permitted during the study.

Initiation of new psychotherapeutic interventions was permitted during the study. Subjects who participated in ongoing psychotherapy treatment during Study D1050296 were permitted to continue it during the study.

Psychotropic Medications:

Subjects may have been treated with benzodiazepines, or antidepressants (no CYP3A4 inhibitors/inducers), at the discretion of Investigator (Inv.) Monoamine oxidase (MAO) inhibitors and other antipsychotic medications (exception: lurasidone) were prohibited.

Benzotropine (up to 6 mg/day) was permitted for movement disorders: if it was not available or if inadequate response or intolerability, the following medications were used to treat acute extrapyramidal symptoms (EPS): biperiden (up to 16 mg/day), trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Propranolol (up to 120 mg/day) was permitted as needed for akathisia.

Use of lorazepam, or equivalent benzodiazepine, was permitted at the discretion of Inv. (up to 6 mg/day) for intolerable anxiety/agitation. Oral benzodiazepines or rapid-acting IM injection were used sparingly (only when clinically required per Investigator judgment). Zolpidem (≤ 10 mg/day), zolpidem controlled release (≤ 12.5 mg/day), eszopiclone (≤ 3 mg/day), zaleplon (≤ 20 mg/day), and temazepam (≤ 30 mg/day) may have been used at bedtime for insomnia. Hypnotic agents were used max. once nightly and not in combination.

If lorazepam or zolpidem or other medications not available, a similar agent at equivalent doses was permitted as specified by the Medical Monitor (MM) and/or the Operations Manual. Opiates were allowed rarely for a limited period of time with prior authorization from MM.

Evidence for comparator:

Not applicable (Intervention Model: Single Group Assignment)

Actual start date of recruitment	12 June 2012
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	France: 8
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Russian Federation: 42
Country: Number of subjects enrolled	Serbia: 35
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Czech Republic: 40
Country: Number of subjects enrolled	United States: 95
Country: Number of subjects enrolled	Argentina: 30
Country: Number of subjects enrolled	Bulgaria: 34
Worldwide total number of subjects	377
EEA total number of subjects	145

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)	360
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who had either completed double-blind treatment or experienced a protocol-specified recurrence of any mood event during the Double-blind Phase in study D1050296 had the option to participate in this study. Subjects who had at least entered the Open-label Phase of Study D1050296 when the Sponsor stopped the study were also eligible.

Pre-assignment

Screening details:

Of the 428 subjects who either completed the double-blind phase of the D1050296 study or had a recurrence of a mood event, 372 continued into this extension study: a total of 5 subjects who were receiving open-label study medication when the D1050296 study was stopped by the Sponsor also continued into this study.

338 subjects completed this study

Period 1

Period 1 title	Open-Label Extension (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable: Open-Label Extension Study

Arms

Arm title	Lurasidone + lithium / valproate
Arm description: -	
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:

Subjects were initially treated with open-label lurasidone 40 mg/day (Day 1). Dose adjustment of study drug (20, 40, 60 or 80 mg/day) was to occur at the regularly scheduled visits and in increments/decrements of 1 dose level. If dose adjustment was required in between regular study visits, the subject came in for an unscheduled visit and returned all used/unused medication kits at the time of dose adjustment. Dose reductions for tolerability or safety purposes were permitted to occur starting on the second day of extension study treatment (Day 2). These dose reductions may have occurred more frequently than the regular study visits and at more than 1 dose level at a time (maximum of 2 dose levels at a time) to optimize effectiveness and tolerability, based on Investigator judgment. Subjects were treated with open-label lithium or divalproex for the duration of the study and were treated with the same drug (either lithium or divalproex) they received in the D1050296 study.

Number of subjects in period 1	Lurasidone + lithium / valproate
Started	377
Completed	338
Not completed	39
Consent withdrawn by subject	11
Administrative	1

Adverse event, non-fatal	9
Lost to follow-up	6
Lack of efficacy	8
Protocol deviation	4

Baseline characteristics

Reporting groups

Reporting group title	Lurasidone + lithium / valproate
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Reporting group description: -

Reporting group values	Lurasidone + lithium / valproate	Total	
Number of subjects	377	377	
Age categorical			
Units: Subjects			
Between 18 and 64 years	360	360	
≥ 65 years	17	17	
Age continuous			
Units: years			
arithmetic mean	45.5		
standard deviation	± 12.27	-	
Gender categorical			
Units: Subjects			
Female	206	206	
Male	171	171	
Race			
Units: Subjects			
White	327	327	
Black or African American	28	28	
Asian	15	15	
American Indian or Alaska Native	1	1	
Other	6	6	
Ethnicity			
Units: Subjects			
Hispanic or Latino	62	62	
Not Hispanic or Latino	315	315	
Region on Enrollment			
Units: Subjects			
North America/ US	95	95	
South America/ Argentina	30	30	
Europe/ Bulgaria	34	34	
South America/ Chile	17	17	
Europe/ Czech Republic	40	40	
Europe/ France	8	8	
Europe/ Hungary	21	21	
Asia/ Japan	13	13	
Europe/ Poland	37	37	
Europe/ Russia	42	42	
Europe/ Serbia	35	35	
Europe/ Slovakia	5	5	

End points

End points reporting groups

Reporting group title	Lurasidone + lithium / valproate
Reporting group description: -	

Primary: Number of subjects with treatment emergent AEs, SAEs, and TEAEs leading to discontinuation

End point title	Number of subjects with treatment emergent AEs, SAEs, and TEAEs leading to discontinuation ^[1]
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End point description:

End point type	Primary
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End point timeframe:

During 12 weeks treatment period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is the extension study of Study D1050296 (EudraCT No.: 2011-000986-10): every subject took lurasidone during this extension study, and thus only one treatment group is reported and no statistical analyses could be performed.

End point values	Lurasidone + lithium / valproate			
Subject group type	Reporting group			
Number of subjects analysed	377			
Units: Subjects				
At least 1 TEAE	155			
At least 1 TEAE potentially related to study drug	69			
Deaths	0			
At least 1 treatment-emergent SAE (TESAE)	14			
At least 1 TESAE related to study drug	1			
At least one TEAE leading to discontinuation	9			

Attachments (see zip file)	DB750001/Cardiac Safety Data Review Meeting Summary -
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Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 12 (LOCF) in the MADRS total score

End point title	Change from baseline to Week 12 (LOCF) in the MADRS total score
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End point 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.

End point type	Secondary
End point timeframe:	
Baseline, Week 12 (LOCF)	

End point values	Lurasidone + lithium / valproate			
Subject group type	Reporting group			
Number of subjects analysed	375			
Units: Score				
arithmetic mean (standard deviation)	-1.9 (± 6.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 12 (LOCF) in the CGI-BP-S score

End point title	Change from baseline to Week 12 (LOCF) in the CGI-BP-S score
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End point 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.

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.

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.

End point type	Secondary
End point timeframe:	
Baseline, Week 12 (LOCF)	

End point values	Lurasidone + lithium / valproate			
Subject group type	Reporting group			
Number of subjects analysed	375			
Units: Score				
arithmetic mean (standard deviation)				
CGI-BP-S Overall Score	-0.31 (± 1.068)			
CGI-BP-S Mania Score	-0.13 (± 0.807)			
CGI-BP-S Depression Score	-0.27 (± 0.969)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 12 (LOCF) in the YMRS total score

End point title	Change from baseline to Week 12 (LOCF) in the YMRS total score
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End point 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.

End point type	Secondary
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End point timeframe:

Baseline, Week 12 (LOCF)

End point values	Lurasidone + lithium / valproate			
Subject group type	Reporting group			
Number of subjects analysed	375			
Units: Score				
arithmetic mean (standard deviation)	-1 (± 5.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 12 (LOCF) in the QIDS-SR16 total score

End point title	Change from baseline to Week 12 (LOCF) in the QIDS-SR16 total score
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End point 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. The nine domains comprise: depressed mood (Item 5); concentration/decision making (Item 10); self outlook (Item 11); suicidal ideation (Item 12); decreased interest (Item 13); decreased energy (Item 14); sleep disturbance (initial, middle, and late insomnia or hypersomnia) (highest score of Items 1 to 4); appetite/weight disturbance (highest score of Items 6 to 9); and psychomotor disturbance (highest score of Items 15 and 16). The QIDS-SR16 total score is calculated as the sum of the 9 domain scores. The QIDS-SR16 total score ranges from 0 to 27 with a high score indicating more severe symptoms.

End point type	Secondary
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End point timeframe:

Baseline, Week 12 (LOCF)

End point values	Lurasidone + lithium / valproate			
Subject group type	Reporting group			
Number of subjects analysed	351			
Units: Score				
arithmetic mean (standard deviation)	-1 (\pm 3.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 12 (LOCF) in the PANSS-P score

End point title	Change from baseline to Week 12 (LOCF) in the PANSS-P score
End point 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. 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.	
End point type	Secondary
End point timeframe:	
Baseline, Week 12 (LOCF)	

End point values	Lurasidone + lithium / valproate			
Subject group type	Reporting group			
Number of subjects analysed	359			
Units: Score				
arithmetic mean (standard deviation)	-0.2 (\pm 1.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 12 (LOCF) in the SDS total score

End point title	Change from baseline to Week 12 (LOCF) in the SDS total score	
End point description:		
The SDS 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. 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.

End point type	Secondary
End point timeframe:	
Baseline, Week 12 (LOCF)	

End point values	Lurasidone + lithium / valproate			
Subject group type	Reporting group			
Number of subjects analysed	297			
Units: Score				
arithmetic mean (standard deviation)	-1.4 (\pm 5.98)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

Adverse event reporting additional description:

Safety population was used for all safety analyses and summaries. Summaries of adverse events were limited to treatment-emergent adverse events, which were defined as adverse events with a start date on or after the first study dose date, through 7 days post last study dose date for non-serious adverse events (AE), or 14 days for serious AEs (SAEs)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Lurasidone + lithium / valproate
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Reporting group description: -

Serious adverse events	Lurasidone + lithium / valproate		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 377 (3.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intentional overdose			

subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia megaloblastic			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 377 (1.06%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	2 / 377 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bipolar disorder			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Emotional distress			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Panic attack			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Persecutory delusion			
subjects affected / exposed	1 / 377 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lurasidone + lithium / valproate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 377 (13.53%)		
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 377 (3.98%)		
occurrences (all)	18		
Akathisia			
subjects affected / exposed	12 / 377 (3.18%)		
occurrences (all)	13		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 377 (2.12%)		
occurrences (all)	9		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 377 (2.92%)		
occurrences (all)	12		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 377 (3.45%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2012	Protocol Amendment 1, 19 March 2012, implemented the following changes: <ul style="list-style-type: none">- Data and Safety Monitoring Board (DSMB) did not monitor this study, therefore this information was removed.- Contact information was updated.- Because Concomitant medication review and Adverse event (AE) monitoring were performed in the last visit of Study D1050296, these assessments were removed from the Visit 1E (Day 1) visit.- Wording concerning concomitant psychotropic medications was updated for clarity.- Collection of the Health Services Utilization Questionnaire (HSUQ) assessment was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes: