Clinical trial results:
A Randomized, 6-Week, Double-Blind, Placebo-Controlled, Flexible-Dose, Parallel-Group Study of Lurasidone for the Treatment of Major Depressive Disorder with Mixed Features

Summary

EudraCT number	2012-004132-33
Trial protocol	GB
Global end of trial date	01 October 2014

Results information

Result version number	v1 (current)
This version publication date	02 September 2016
First version publication date	02 September 2016

Trial information

Trial identification

Sponsor protocol code	D1050304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01421134
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sunovion Pharmaceuticals Inc.
Sponsor organisation address	One Bridge PlazaNorth, Suite 510, Fort Lee, United States, 07024
Public contact	Manager, Sunovion Pharmaceuticals Inc., 001 1-866-503-6351, clinicaltrialdisclosure@sunvion.com
Scientific contact	Director, Sunovion Pharmaceuticals Inc., 001 1-866-503-6351, clinicaltrialdisclosure@sunvion.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	01 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2014
Global end of trial reached?	Yes
Global end of trial date	01 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Lurasidone HCl is a compound that is a candidate for the treatment of major depressive with mixed features.This clinical study is designed to test how well Lurasidone works to treat major depressive disorder with mixed features.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	United States: 60
Country: Number of subjects enrolled	Ukraine: 62
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Serbia: 52
Worldwide total number of subjects	209
EEA total number of subjects	4

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)	203

From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A Randomized, 6-Week, Double-Blind, Placebo-Controlled, Flexible-Dose, Parallel-Group Study of lurasidone for the Treatment of Major Depressive Disorder with Mixed Features. This study enrolled subjects at 44 sites in 5 countries, enrollment started on 01Sept2011.

Pre-assignment

Screening details:

Subjects were evaluated for eligibility during a screening period of up to 14 days. Subjects were washed out from prior or concomitant medications, where applicable, prior to randomization.Treatment with prior psychotropic medications.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	lurasidone

Arm description:

lurasidone 20, 40 or 60 mg

lurasidone: 20, 40, 60 mg, flexible dose, once daily PM 6 weeks

Arm type	Experimental
Investigational medicinal product name	lurasidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

once daily

Arm title	Placebo

Arm description:

Placebo

Placebo: Placebo

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:

once daily

Number of subjects in period 1	lurasidone	Placebo
Started	109	100
Completed	102	85
Not completed	7	15
Consent withdrawn by subject	1	1
Administrative	-	1
Adverse event, non-fatal	3	5
Lost to follow-up	1	1
Lack of efficacy	2	4
Protocol deviation	-	3

Baseline characteristics

Reporting groups	
Reporting group title	lurasidone
Reporting group description: lurasidone 20, 40 or 60 mg lurasidone: 20, 40, 60 mg, flexible dose, once daily PM 6 weeks	
Reporting group title	Placebo
Reporting group description: Placebo Placebo: Placebo	

Reporting group values	lurasidone	Placebo	Total
Number of subjects	109	100	209
Age Categorical Units: participants			
<=18 years	1	0	1
Between 18 and 65 years	106	96	202
>=65 years	2	4	6
Age Continuous Units: years			
arithmetic mean	43.6	46.4	
standard deviation	± 12.08	± 12.01	-
Gender, Male/Female Units: participants			
Female	73	72	145
Male	36	28	64
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	14	12	26
White	94	86	180
More than one race	0	0	0
Unknown or Not Reported	1	1	2
Region of Enrollment Units: Subjects			
Russian Federation	18	13	31
United States	34	26	60
Ukraine	30	32	62
United Kingdom	1	3	4
Serbia	26	26	52

End points

End points reporting groups

Reporting group title	lurasidone
Reporting group description: lurasidone 20, 40 or 60 mg lurasidone: 20, 40, 60 mg, flexible dose, once daily PM 6 weeks	
Reporting group title	Placebo
Reporting group description: Placebo Placebo: Placebo	

Primary: Mean Change from baseline to the 6-week study endpoint in Montgomery-Asberg Depression Rating Scale (MADRS) total scores

End point title	Mean Change from baseline to the 6-week study endpoint in Montgomery-Asberg Depression Rating Scale (MADRS) total scores
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	Primary
End point timeframe: Baseline to Week 6	

End point values	lurasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	100		
Units: units on a scale				
least squares mean (standard error)	-20.5 (± 0.95)	-13 (± 1)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	lurasidone v Placebo
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-7.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	-4.8
Variability estimate	Standard error of the mean
Dispersion value	1.37

Secondary: Mean change from baseline to the 6-week study endpoint in the Clinical Global Impression-Severity of Illness (CGI-S) score

End point title	Mean change from baseline to the 6-week study endpoint in the Clinical Global Impression-Severity of Illness (CGI-S) score

End point description:

The CGI-S score is a single value, clinician-rated assessment of 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 to Week 6

End point values	lurasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	100		
Units: units on a scale				
least squares mean (standard error)	-1.83 (± 0.109)	-1.18 (± 0.115)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	lurasidone v Placebo
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.157

Secondary: Mean change from baseline to Week 6 in the Young Mania Rating Scale (YMRS) total score

End point title	Mean change from baseline to Week 6 in the Young Mania Rating Scale (YMRS) total score

End point description:

The YMRS is an 11-item clinician-rated instrument used to assess the severity of mania. Seven items are rated on a 5-point scale, ranging from 0 to 4, and four items are rated on a 9-point scale, ranging from 0 to 8. The YMRS total score is calculated as the sum of the 11 individual items and ranges from 0 to 60. Higher scores are associated with greater severity of mania.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	lurasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	100		
Units: units on a scale				
least squares mean (standard error)	-7 (± 0.35)	-4.9 (± 0.37)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE

Statistical analysis description:

last observation carried forward (LOCF)

Comparison groups	lurasidone v Placebo
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	0.5

Secondary: Mean change from baseline to week 6 in the Sheehan Disability Scale

(SDS) total score	
End point title	Mean change from baseline to week 6 in the Sheehan Disability Scale (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 (work/school, social life/leisure, and family life/home responsibility) in the patient's life are impaired by depressive symptoms. These three items are responded to on a visual analogue scale (VAS) ranging through 0 (no impairment), 1–3 (mild), 4–6 (moderate), 7–9 (marked) and 10 (extreme) disability. The SDS total score is calculated as the sum of the three items and ranges from 0 (unimpaired) to 30 (highly impaired).

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	lurasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	69		
Units: units on a scale				
least squares mean (standard error)	-11.2 (± 0.88)	-6.4 (± 0.88)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	lurasidone v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	-2.4
Variability estimate	Standard error of the mean
Dispersion value	1.21

Secondary: Mean change from baseline to week 6 in the Hamilton Rating Scale for Anxiety(HAM-A) total score	
End point title	Mean change from baseline to week 6 in the Hamilton Rating Scale for Anxiety(HAM-A) total score

End point description:

The HAM-A is used to quantify the severity of anxiety symptomatology and consists of 14 items. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe/disabling). The HAM-A total

score is calculated as the sum of the 14 individual items and ranges from 0 to 56. Higher scores are associated with greater degree of anxiety.

End point type	Secondary
End point timeframe: Baseline to Week 6	

End point values	lurasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	98		
Units: units on a scale				
least squares mean (standard error)	-9.9 (± 0.58)	-5.4 (± 0.59)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Statistical analysis description: last observation carried forward (LOCF)	
Comparison groups	lurasidone v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	-2.9
Variability estimate	Standard error of the mean
Dispersion value	0.81

Secondary: Percentage of subjects who achieve a response, defined as ≥ 50% reduction from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 6 (LOCF).

End point title	Percentage of subjects who achieve a response, defined as ≥ 50% reduction from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score at week 6 (LOCF).
End point description:	

End point type	Secondary
End point timeframe: Baseline to Week 6	

End point values	lurasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	100		
Units: percentage of subjects				
number (not applicable)	64.8	30		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	lurasidone v Placebo
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.615
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.251
upper limit	13.459

Secondary: Percentage of subjects who achieve a remission, defined as a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≤ 12 at Week 6 (LOCF)

End point title	Percentage of subjects who achieve a remission, defined as a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≤ 12 at Week 6 (LOCF)

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	lurasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	100		
Units: percentage of subjects				
number (not applicable)	49.1	23		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	lurasidone v Placebo
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.105
upper limit	8.663

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 6 Weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo Placebo: Placebo	
Reporting group title	Lurasidone
Reporting group description: Lurasidone 20, 40 or 60 mg Lurasidone: 20, 40, 60 mg, flexible dose, once daily PM 6 weeks	

Serious adverse events	Placebo	Lurasidone	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	1 / 109 (0.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Depression Suicidal			
subjects affected / exposed	0 / 100 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Lurasidone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 100 (29.00%)	31 / 109 (28.44%)	
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	2 / 100 (2.00%)	0 / 109 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 100 (6.00%)	6 / 109 (5.50%)	
occurrences (all)	7	6	
Somnoelence			
subjects affected / exposed	1 / 100 (1.00%)	5 / 109 (4.59%)	
occurrences (all)	1	6	
Akathisia			
subjects affected / exposed	2 / 100 (2.00%)	4 / 109 (3.67%)	
occurrences (all)	2	4	
Dizziness			
subjects affected / exposed	3 / 100 (3.00%)	4 / 109 (3.67%)	
occurrences (all)	3	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 100 (2.00%)	7 / 109 (6.42%)	
occurrences (all)	2	7	
Abdominal discomfort			
subjects affected / exposed	1 / 100 (1.00%)	4 / 109 (3.67%)	
occurrences (all)	1	5	
Dry mouth			
subjects affected / exposed	1 / 100 (1.00%)	3 / 109 (2.75%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 100 (2.00%)	1 / 109 (0.92%)	
occurrences (all)	2	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 100 (11.00%)	6 / 109 (5.50%)	
occurrences (all)	11	7	
Anxiety			
subjects affected / exposed	9 / 100 (9.00%)	4 / 109 (3.67%)	
occurrences (all)	12	4	
Renal and urinary disorders			

Haemarturia subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 2	0 / 109 (0.00%) 0	
Infections and infestations Urinary Tract Infection subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 3	1 / 109 (0.92%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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: