Clinical trial results:
A Randomized, 6-Week, Double-blind, Placebo-Controlled, Flexible Dose, Parallel-Group Study to Evaluate the Efficacy and Safety of Lurasidone in Children and Adolescent Subjects With Bipolar I Depression

Summary

EudraCT number	2013-004903-37
Trial protocol	IT BG Outside EU/EEA HU DE GB FR
Global end of trial date	19 October 2015

Results information

Result version number	v1 (current)
This version publication date	14 May 2017
First version publication date	14 May 2017

Trial information

Trial identification

Sponsor protocol code	D1050326

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02046369
WHO universal trial number (UTN)	-
Other trial identifiers	D1050326: D1050326

Notes:

Sponsors

Sponsor organisation name	Sunovion Pharmaceuticals Inc.
Sponsor organisation address	ONE BRIDGE PLAZA NORTH, SUITE 510,, Fort Lee, United States, 07024
Public contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., 01 (1) 201-592-2050, clinicaltrialsdisclosure@sunovion.com
Scientific contact	CNS Medical Director, Sunovion Pharmaceuticals Inc., 01 (1) 201-592-2050, clinicaltrialsdisclosure@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	23 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2015
Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this research study is to evaluate the safety and effectiveness of lurasidone (20 mg/day to 80 mg/day) compared to a placebo for use in children and adolescent subjects with bipolar I depression

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2014
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	United States: 153
Country: Number of subjects enrolled	Ukraine: 66
Country: Number of subjects enrolled	Russian Federation: 42
Country: Number of subjects enrolled	Mexico: 33
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Colombia: 14
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 7
Country: Number of subjects enrolled	Philippines: 2
Worldwide total number of subjects	350
EEA total number of subjects	33

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)	44
Adolescents (12-17 years)	306
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

MALE AND FEMALE SUBJECTS 10 TO 17, INCLUSIVE,WITH DSM-5 PRIMARY DIAGNOSIS OF BIPOLAR 1 DISORDER, MOST RECENT EPISODE DEPRESSED, AND CONFIRMATION OF THE DIAGNOSIS BY MEANS OF THE SCHEDULE FOR AFFECTIVE DISORDERS AND SCHIZOPHRENIA FOR SCHOOL-AGE CHILDREN.

Pre-assignment

Screening details:

continued from above:
THE CURRENT EPISODE OF MAJOR DEPRESSION ASSOVIATED WITH BIPOLAR 1 DISORDER MUST HAVE BEEN CONFIRMED BY THE INVESTIGATOR AND NOTED IN THE SOURCE RECORDS. SUBJECTS MUST ALSO HAVE HAD CHILDREN'S DEPRESSION RATING SCALE SCORE OF ≥ 45 AT SCREENING AND BASELINE; YOUNG MANIA RATING SCALE SCORE OF ≤ 15 AT SCREENING AND BASELINE

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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Luradisone

Arm description:

Luradisone 20- 80 mg administered once daily

Lurasidone: Lurasidone flexibly dosed 20-80 mg once daily

Arm type	Experimental
Investigational medicinal product name	lurasidone
Investigational medicinal product code	
Other name	Latuda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

20mg - 80mg flexible dosing once daily

Arm title	Placebo

Arm description:

Placebo administered once daily

Placebo: Placebo Comparator once daily

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

placebo dosed once daily

Number of subjects in period 1	Luradisone	Placebo
Started	176	174
Completed	162	156
Not completed	14	18
Consent withdrawn by subject	3	6
non compliance	1	-
Adverse event, non-fatal	3	3
never received study drug	-	1
Lost to follow-up	3	3
Lack of efficacy	3	3
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Luradisone
Reporting group description: Luradisone 20- 80 mg administered once daily Lurasidone: Lurasidone flexibly dosed 20-80 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo administered once daily Placebo: Placebo Comparator once daily	

Reporting group values	Luradisone	Placebo	Total
Number of subjects	176	174	350
Age Categorical Units: Participants			
<=18 years	175	172	347
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Not recorded	1	2	3
Age Continuous Units: years			
arithmetic mean	14.2	14.3	
standard deviation	± 2.18	± 2.01	-
Gender categorical Units: Subjects			
Female	87	83	170
Male	88	89	177
not recorded	1	2	3
Sex: Female, Male Units: Subjects			
Female	87	83	170
Male	88	89	177
not recorded	1	2	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	175	172	347
Unknown or Not Reported	0	0	0
not recorded	1	2	3
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	0	2
Asian	7	4	11
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	16	20	36
White	135	125	260

More than one race	15	23	38
Unknown or Not Reported	0	0	0
not recorded	1	2	3
Region of Enrollment Units: Subjects			
Colombia	7	7	14
Puerto Rico	0	0	0
South Korea	4	3	7
Hungary	5	5	10
United States	75	75	150
Philippines	2	0	2
Ukraine	33	33	66
Poland	2	3	5
Mexico	16	17	33
Bulgaria	9	8	17
France	1	0	1
Russian Federation	21	21	42
not recorded	1	2	3
Bipolar I disorder history Units: Subjects			
Without rapid cycling (0-3 cycles past 12 months	149	147	296
Without rapid cycling(4-7 cycles past 12 months	26	24	50
With 8 or more cycles within past 12 months	0	1	1
not recorded	1	2	3
Psychiatric History Units: years			
arithmetic mean	12.44	12.17	
standard deviation	± 2.79	± 2.68	-

End points

End points reporting groups

Reporting group title	Luradisone

Reporting group description:

Luradisone 20- 80 mg administered once daily

Lurasidone: Lurasidone flexibly dosed 20-80 mg once daily

Reporting group title	Placebo

Reporting group description:

Placebo administered once daily

Placebo: Placebo Comparator once daily

Primary: Change in the Children's Depression Rating Scale, Revised (CDRS-R) total score as compared to placebo from Double-Blind Baseline to Week 6 (Day 43) baseline

End point title	Change in the Children's Depression Rating Scale, Revised (CDRS-R) total score as compared to placebo from Double-Blind Baseline to Week 6 (Day 43) baseline

End point description:

CDRS-R total score: changes from baseline over time - mixed model for repeated measures

LS Mean and SE for change from baseline are based on Mixed Model for Repeated Measures

End point type	Primary

End point timeframe:

baseline

End point values	Luradisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	170		
Units: units on a scale				
arithmetic mean (standard deviation)				
baseline	59.2 (± 8.24)	58.6 (± 8.26)		
week 6	-21 (± 1.06)	-15.3 (± 1.08)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE

Statistical analysis description:

A mean difference in change from Baseline in CDRS-R total score of 5.0 units was assumed for the lurasidone 20-80 mg/day arm over the placebo arm, and a common standard deviation of 14.2 units (effect size=0.35), a sample size of 145 subjects per treatment arm was calculated to yield a power of 85%. With an expected attrition rate of 15%, approximately 170 subjects per treatment arm (340 in total) were to be randomized in a 1:1 ratio .

Comparison groups	Luradisone v Placebo

Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	LS mean differnece (SE)
Parameter estimate	LS mean differnce (SE)
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	-3
Variability estimate	Standard error of the mean
Dispersion value	1.39

Secondary: Change from Baseline in Pediatric Anxiety Rating Scale (PARS) score as compared to placebo.

End point title	Change from Baseline in Pediatric Anxiety Rating Scale (PARS) score as compared to placebo.

End point description:

PARS score: changes from baseline over time - mixed model for repeated measures

LS Mean and SE for change from baseline are based on Mixed Model for Repeated Measures

End point type	Secondary

End point timeframe:

baseline

End point values	Luradisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	170		
Units: units on a scale				
arithmetic mean (standard deviation)				
baseline	10.9 (± 7.72)	11.5 (± 7.6)		
week 6	-3.4 (± 0.44)	-2.3 (± 0.45)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE

Statistical analysis description:

LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures (MMRM).

Comparison groups	Luradisone v Placebo

Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0385
Method	LS mean differnece (SE)
Parameter estimate	LS mean differnce (SE)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.54

Secondary: Change from Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) score as compared to placebo.

End point title	Change from Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) score as compared to placebo.

End point description:

PQ-LES-Q percentage maximum possible score: changes from baseline over time - mixed model for repeated measures

LS Mean and SE for change from baseline are based on Mixed Model for Repeated Measures

End point type	Secondary

End point timeframe:

baseline

End point values	Luradisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	169		
Units: units on a scale				
arithmetic mean (standard deviation)				
baseline	49.6 (± 15.49)	49.7 (± 17.31)		
week 6	11.8 (± 1.1)	7.9 (± 1.13)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE

Statistical analysis description:

LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures (MMRM).

Comparison groups	Luradisone v Placebo

Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044
Method	LS mean differnece (SE)
Parameter estimate	LS mean differnce (SE)
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	6.5
Variability estimate	Standard error of the mean
Dispersion value	1.35

Secondary: Change from Baseline in Clinician-rated Children's Global Assessment Scale (CGAS) score as compared to placebo.

End point title	Change from Baseline in Clinician-rated Children's Global Assessment Scale (CGAS) score as compared to placebo.

End point description:

CGAS Score: changes from baseline over time - mixed model for repeated measures

LS Mean and SE for change from baseline are based on Mixed Model for Repeated Measures

End point type	Secondary

End point timeframe:

baseline

End point values	Luradisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	170		
Units: units on a scale				
arithmetic mean (standard deviation)				
baseline	48.8 (± 8.73)	49.5 (± 6.99)		
week 6	14 (± 0.96)	9.3 (± 0.99)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE

Statistical analysis description:

LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures (MMRM).

Comparison groups	Luradisone v Placebo

Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	LS mean differnece (SE)
Parameter estimate	LS mean differnce (SE)
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.4
upper limit	7
Variability estimate	Standard error of the mean
Dispersion value	1.19

Secondary: Change from Baseline in Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) score as compared to placebo.

End point title	Change from Baseline in Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) score as compared to placebo.

End point description:

ADHD-RS total score: changes from baseline over time -ANCOVA

LS Mean and SE for change from baseline are based on ANCOVA

End point type	Secondary

End point timeframe:

baseline

End point values	Luradisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	167		
Units: units on a scale				
arithmetic mean (standard deviation)				
baseline	11.8 (± 10.85)	12.3 (± 11.62)		
week 6	-2.6 (± 7.26)	-2 (± 7.61)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE

Statistical analysis description:

LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures (MMRM).

Comparison groups	Luradisone v Placebo

Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3715
Method	ANCOVA
Parameter estimate	LS mean differnce (SE)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.77

Secondary: Change from baseline in Clinical Global Impressions-Bipolar-Severity (CGI-BP-S) depression score

End point title	Change from baseline in Clinical Global Impressions-Bipolar-Severity (CGI-BP-S) depression score

End point description:

Change from baseline in Clinical Global Impressions-Bipolar-Severity (CGI-BP-S) depression score changes from baseline over time - mixed model for repeated measures

LS Mean and SE for change from baseline are based on Mixed Model for Repeated Measures

End point type	Secondary

End point timeframe:

baseline

End point values	Luradisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	170		
Units: units on a scale				
arithmetic mean (standard deviation)				
baseline	4.6 (± 0.65)	4.5 (± 0.57)		
week 6	-1.49 (± 0.085)	-1.05 (± 0.087)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	Luradisone v Placebo

Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	LS mean differnece (SE)
Parameter estimate	LS mean differnce (SE)
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.112

Notes:

[1] - LS mean difference, and the associated 95% CI and p-value for change from baseline are based on Mixed Model for Repeated Measures (MMRM).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse event (TEAE) is defined as an AE with a start date on or after the date of first does through 7 days after study drug discontinuation (14 days for serious adverse events and deaths) for subjects who complete the double blind st

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Luradisone

Reporting group description:

Luradisone 20- 80 mg administered once daily

Lurasidone: Lurasidone flexibly dosed 20-80 mg once daily

Reporting group title	Placebo

Reporting group description:

Placebo administered once daily

Placebo: Placebo Comparator once daily

Serious adverse events	Luradisone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 175 (1.14%)	4 / 172 (2.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
humerus fracture			
subjects affected / exposed	1 / 175 (0.57%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
abortion spontaneous			
subjects affected / exposed	0 / 175 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar I disorder			

subjects affected / exposed	1 / 175 (0.57%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
depression			
subjects affected / exposed	0 / 175 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
psychotic disorder			
subjects affected / exposed	0 / 175 (0.00%)	1 / 172 (0.58%)	
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: 5 %

Non-serious adverse events	Luradisone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 175 (64.00%)	75 / 172 (43.60%)	
Investigations			
weight increased			
subjects affected / exposed	12 / 175 (6.86%)	3 / 172 (1.74%)	
occurrences (all)	12	3	
Nervous system disorders			
headache			
subjects affected / exposed	25 / 175 (14.29%)	26 / 172 (15.12%)	
occurrences (all)	30	38	
somnolence			
subjects affected / exposed	16 / 175 (9.14%)	8 / 172 (4.65%)	
occurrences (all)	20	9	
dizziness			
subjects affected / exposed	10 / 175 (5.71%)	8 / 172 (4.65%)	
occurrences (all)	12	8	
Gastrointestinal disorders			
nausea			
subjects affected / exposed	28 / 175 (16.00%)	10 / 172 (5.81%)	
occurrences (all)	35	13	
vomiting			

subjects affected / exposed occurrences (all)	11 / 175 (6.29%) 15	6 / 172 (3.49%) 8	
Psychiatric disorders insomnia subjects affected / exposed occurrences (all)	9 / 175 (5.14%) 9	4 / 172 (2.33%) 4	
Infections and infestations nasopharyngitis subjects affected / exposed occurrences (all)	7 / 175 (4.00%) 7	10 / 172 (5.81%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2014	AMENDMENT 2 INCLUDED THE FOLLOWING CHANGES: • Revise the description of select scales used in the protocol. • Clarify ADHD medication usage. • Clarify stimulant usage status in respect to the statistical analysis. • Update of Appendix G, Protocol Exclusion Criterion #7 CDRS-R Reference Chart.
19 March 2014	AMENDMENT 1 INCLUDED THE FOLLOWING CHANGES: • Removal of the YMRS assessment from the follow-up visit. • Update of Appendix G, Protocol Exclusion Criterion #7 CDRS-R Reference Chart.
29 April 2014	AMENDMENT 3 INCLUDED THE FOLLOWING CHANGES: •Clarify the criteria for hospitalization and discharge. •Clarify ADHD medication usage. •Clarify age inclusion criterion. •Clarify diagnosis exclusion criterion. •Clarify suicidal ideation exclusion criterion. •Clarify Type 2 diabetes exclusion criterion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported