Clinical trial results:
Interventional, randomised, double-blind, parallel-group study of the efficacy and safety of initial administration of 17 mg vortioxetine intravenously with 10 mg/day vortioxetine orally in patients with Major Depressive Disorder

Summary

EudraCT number	2015-005081-30
Trial protocol	EE LT FI SK
Global end of trial date	27 April 2017

Results information

Result version number	v1 (current)
This version publication date	12 May 2018
First version publication date	12 May 2018

Trial information

Trial identification

Sponsor protocol code	16903A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02919501
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	Lundbeck Clinical Trials, H. Lundbeck A/S, +45 36 3013 11, LundbeckClinicalTrials@lundbeck.com
Scientific contact	Lundbeck Clinical Trials, H. Lundbeck A/S, +45 36 3013 11, LundbeckClinicalTrials@lundbeck.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 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2017
Global end of trial reached?	Yes
Global end of trial date	27 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the early onset of efficacy of vortioxetine 17 mg IV and vortioxetine 10 mg/day oral dose regimen versus placebo IV and vortioxetine 10 mg/day oral dose regimen on depressive symptoms

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996).

Background therapy:

The study consisted of a:
• Screening Period – 2 to 14-day period from screening to randomisation
• Treatment Period – 15-day double-blind treatment period with one initial IV administration of 17mg vortioxetine or placebo and daily oral treatment with vortioxetine 10mg.
• Safety Follow-up Period – 4-week period after end of treatment or after withdrawal from the study

Evidence for comparator: -

Actual start date of recruitment	11 September 2016
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	Estonia: 27
Country: Number of subjects enrolled	Finland: 28
Worldwide total number of subjects	55
EEA total number of subjects	55

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)	51
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who met each of the inclusion and none of the exclusion criteria were eligible to participate in the study

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo IV + vortioxetine oral

Arm description:

placebo to vortioxetine IV and oral vortioxetine

Arm type	Placebo
Investigational medicinal product name	Placebo IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Saline: isotonic sodium chloride, administered, over 2 hours as single dose

Investigational medicinal product name	Vortioxetine 10 mg/day
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vortioxetine (tablet): 10 mg, tablets, oral administration once daily for 15 days (open labelled)

Arm title	Vortioxetine IV + vortioxetine oral

Arm description:

vortioxetine IV and oral vortioxetine

Arm type	Experimental
Investigational medicinal product name	Vortioxetine IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Drug: vortioxetine (IV): 17 mg, solution for infusion, administered, over 2 hours as single dose

Investigational medicinal product name	Vortioxetine 10 mg/day
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vortioxetine (tablet): 10 mg, tablets, oral administration once daily for 15 days (open labelled)

Number of subjects in period 1	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral
Started	28	27
Completed	28	26
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	55	55	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	51	51	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	43	43	
Male	12	12	

End points

End points reporting groups	
Reporting group title	Placebo IV + vortioxetine oral
Reporting group description: placebo to vortioxetine IV and oral vortioxetine	
Reporting group title	Vortioxetine IV + vortioxetine oral
Reporting group description: vortioxetine IV and oral vortioxetine	

Primary: Change from baseline to week 1 in MADRS total score	
End point title	Change from baseline to week 1 in MADRS total score
End point description: Change from baseline to week 1 in MADRS total score. The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated 0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in symptoms.	
End point type	Primary
End point timeframe: From baseline to week 1 (Day 7)	

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: units on a scale				
least squares mean (standard error)	-13.8 (± 1.8)	-14.0 (± 1.9)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Placebo IV + vortioxetine oral v Vortioxetine IV + vortioxetine oral
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9197
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	4.5
Variability estimate	Standard error of the mean
Dispersion value	2.3

Secondary: Change From baseline to Day 14 in MADRS Total Score

End point title	Change From baseline to Day 14 in MADRS Total Score

End point description:

Change From baseline to Day 14 in MADRS Total Score. The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated 0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in symptoms.

End point type	Secondary

End point timeframe:

from baseline to Day 14

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: units on a scale				
least squares mean (standard error)	-18.2 (± 1.7)	-17.1 (± 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Day 3 in MADRS total score

End point title	Change from baseline to Day 3 in MADRS total score

End point description:

Change from baseline to Day 3 in MADRS total score. The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated 0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in symptoms.

End point type	Secondary

End point timeframe:

from baseline to Day 3

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: units on a scale				
least squares mean (standard error)	-10.7 (± 1.6)	-12.3 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Day 1 in MADRS total score

End point title	Change from baseline to Day 1 in MADRS total score

End point description:

Change from baseline to Day 1 in MADRS total score. The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated 0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in symptoms.

End point type	Secondary

End point timeframe:

from baseline to Day 1

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: unita on a scale				
least squares mean (standard error)	-5.9 (± 1.2)	-7.2 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Day 7

End point title	Response at Day 7

End point description:

Response (defined as a ≥50% decrease in MADRS total score from baseline) at Day 7. The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated

0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in symptoms.

End point type	Secondary

End point timeframe:

At Day 7

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: patients	8	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Remission at Day 7

End point title	Remission at Day 7

End point description:

Remission (defined as a MADRS total score ≤10) at Day 7. The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated 0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in symptoms.

End point type	Secondary

End point timeframe:

At Day 7

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: patients	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Day 7 in HADS depression subscale score

End point title	Change from baseline to Day 7 in HADS depression subscale score

End point description:

Change from baseline to Day 7 in Hospital Anxiety and Depression subscale Score. The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. The anxiety and depression subscales each range from 0 to 21, with higher scores indicating higher anxiety/depression complains. Patients were defined as having anxiety or depression or both if the score was 8 or more in the corresponding subscale.

End point type	Secondary

End point timeframe:

from baseline to Day 7

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: units on a scale				
least squares mean (standard deviation)	-3.3 (± 0.8)	-3.4 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-I score at Day 7

End point title	CGI-I score at Day 7

End point description:

The Clinical Global Impression (CGI-I) at Day 7 - global improvement CGI-I provides the clinician's impression of the patient's improvement (or worsening). The clinician assesses the patient's condition relative to a baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

at Day 7

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	26		
Units: units on a scale				
least squares mean (standard error)	2.6 (± 0.2)	2.5 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Day 7 in CGI-S score

End point title	Change from baseline to Day 7 in CGI-S score

End point description:

Change from baseline to Day 7 in Clinical Global Impression severity of illness (CGI-S) score. This scale provides the clinician's impression of the patient's current state of mental illness. The clinician uses his or her clinical experience of this patient population to rate the severity of the patient's current mental illness on a 7-point scale ranging from 1 (normal - not at all ill) to 7 (among the most extremely ill patients).

End point type	Secondary

End point timeframe:

from baseline to Day 7

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: units on a scale				
least squares mean (standard error)	-1.4 (± 0.3)	-1.4 (± 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Day 7 in HADS anxiety subscale score

End point title	Change from baseline to Day 7 in HADS anxiety subscale score

End point description:

Change from baseline to Day 7 in Hospital Anxiety and Depression subscale Score. The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression. The anxiety and depression subscales each range from 0 to 21, with higher scores indicating higher anxiety/depression complains. Patients were defined as having anxiety or depression or both if the score was 8 or more in the corresponding subscale.

End point type	Secondary

End point timeframe:

From baseline to Day 7

End point values	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: units on a scale				
least squares mean (standard error)	-3.9 (± 0.8)	-4.7 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: First dose to follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Placebo IV + vortioxetine oral
Reporting group description: Placebo IV and vortioxetine oral	
Reporting group title	Vortioxetine IV + vortioxetine oral
Reporting group description: Vortioxetine IV and vortioxetine oral	

Serious adverse events	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo IV + vortioxetine oral	Vortioxetine IV + vortioxetine oral	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 28 (60.71%)	20 / 27 (74.07%)	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 28 (14.29%)	4 / 27 (14.81%)	
occurrences (all)	5	4	
Somnolence			

subjects affected / exposed	1 / 28 (3.57%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 28 (14.29%)	2 / 27 (7.41%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 28 (3.57%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	9 / 28 (32.14%)	13 / 27 (48.15%)	
occurrences (all)	9	14	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed[1]	1 / 5 (20.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 28 (3.57%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 28 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	4	1	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This Non Serious Adverse Event is only applicable for male subjects.

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

None reported