Clinical trial results:
Interventional, randomised, double-blind, parallel-group, placebo-controlled, exploratory study investigating the effects of vortioxetine on cognition and blood oxygen level dependent (BOLD) fMRI signals in subjects remitted from depression and controls

Summary

EudraCT number	2011-001839-23
Trial protocol	GB
Global end of trial date	23 September 2013

Results information

Result version number	v1 (current)
This version publication date	19 July 2016
First version publication date	05 July 2015

Trial information

Trial identification

Sponsor protocol code	14137A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01607125
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, LundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, 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	23 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2013
Global end of trial reached?	Yes
Global end of trial date	23 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether vortioxetine compared to placebo in subjects remitted from depression modulates the blood oxygen level dependent (BOLD) signal in functional magnetic resonance imaging (fMRI) of the brain areas associated with executive function (working memory) during performance of the N-back task. The regions of interest are within the prefrontal cortex and anterior cingulate.
To determine whether vortioxetine compared to placebo in subjects remitted from depression modulates the blood oxygen level dependent (BOLD) signal in functional magnetic resonance imaging (fMRI) of the brain areas associated with spatial memory during performance of the Arena task. The region of interest is hippocampus.
To evaluate the effects of vortioxetine compared to placebo in subjects remitted from depression on the BOLD signal in fMRI in other brain regions involved in the regulation of cognitive processes during working memory and planning performance (N-back and Arena task).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 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	United Kingdom: 101
Worldwide total number of subjects	101
EEA total number of subjects	101

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)	101
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited by 4 investigators at 3 centres in the United Kingdom

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	Vortioxetine 20 mg qd (controls)

Arm description:

Subjects in the control group had no history of major depressive episodes (MDEs) and no history of MDEs in a biological parent or other first degree relative (as reported by the subject). Subjects had not reported subjective cognitive dysfunction and had never been treated with antidepressants or psychotherapy

Arm type	Experimental
Investigational medicinal product name	Vortioxetine
Investigational medicinal product code	
Other name	Lu AA21004
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

encapsulated 20 mg tablets, orally, once daily for 13 to 14 days

Arm title	Placebo (controls)

Arm description:

Subjects in the control group had no history of MDEs and no history of MDEs in a biological parent or other first degree relative (as reported by the subject). Subjects had not reported subjective cognitive dysfunction and had never been treated with antidepressants or psychotherapy

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

capsules, orally, once daily for 13 to 14 days

Arm title	Vortioxetine 20 mg qd (subjects remitted from depression)

Arm description:

Subjects remitted from depression had been in remission from recurrent depression, had suffered from at least two previous major depressive episodes (MDEs), and had received prescribed treatment with an antidepressant or a recognised psychotherapy for depression for a previous MDE. The subjects reported present subjective cognitive dysfunction. They had not been treated with antidepressants or received other psychotherapy for depression for at least six weeks prior to the screening visit.

Arm type	Experimental
Investigational medicinal product name	Vortioxetine
Investigational medicinal product code	
Other name	Lu AA21004
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

encapsulated 20 mg tablets, orally, once daily for 13 to 14 days

Arm title	Placebo (subjects remitted from depression)

Arm description:

Subjects remitted from depression had been in remission from recurrent depression, had suffered from at least two previous major depressive episodes (MDEs), and had received prescribed treatment with an antidepressant or a recognised psychotherapy for depression for a previous MDE. The subjects reported present subjective cognitive dysfunction. They had not been treated with antidepressants or received other psychotherapy for depression for at least six weeks prior to the screening visit.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

capsules, orally, once daily for 13 to 14 days

Number of subjects in period 1	Vortioxetine 20 mg qd (controls)	Placebo (controls)	Vortioxetine 20 mg qd (subjects remitted from depression)
Started	25	25	26
Completed	24	24	24
Not completed	1	1	2
Physician decision	1	1	2

Number of subjects in period 1	Placebo (subjects remitted from depression)
Started	25
Completed	24
Not completed	1
Physician decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Vortioxetine 20 mg qd (controls)
Reporting group description:	
Subjects in the control group had no history of major depressive episodes (MDEs) and no history of MDEs in a biological parent or other first degree relative (as reported by the subject). Subjects had not reported subjective cognitive dysfunction and had never been treated with antidepressants or psychotherapy	
Reporting group title	Placebo (controls)
Reporting group description:	
Subjects in the control group had no history of MDEs and no history of MDEs in a biological parent or other first degree relative (as reported by the subject). Subjects had not reported subjective cognitive dysfunction and had never been treated with antidepressants or psychotherapy	
Reporting group title	Vortioxetine 20 mg qd (subjects remitted from depression)
Reporting group description:	
Subjects remitted from depression had been in remission from recurrent depression, had suffered from at least two previous major depressive episodes (MDEs), and had received prescribed treatment with an antidepressant or a recognised psychotherapy for depression for a previous MDE. The subjects reported present subjective cognitive dysfunction. They had not been treated with antidepressants or received other psychotherapy for depression for at least six weeks prior to the screening visit.	
Reporting group title	Placebo (subjects remitted from depression)
Reporting group description:	
Subjects remitted from depression had been in remission from recurrent depression, had suffered from at least two previous major depressive episodes (MDEs), and had received prescribed treatment with an antidepressant or a recognised psychotherapy for depression for a previous MDE. The subjects reported present subjective cognitive dysfunction. They had not been treated with antidepressants or received other psychotherapy for depression for at least six weeks prior to the screening visit.	

Reporting group values	Vortioxetine 20 mg qd (controls)	Placebo (controls)	Vortioxetine 20 mg qd (subjects remitted from depression)
Number of subjects	25	25	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	25	25	26
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34	35	34
standard deviation	± 8.9	± 9.6	± 9.1
Gender categorical Units: Subjects			
Female	16	12	18

Male	9	13	8

Race Units: Subjects			
Asian	1	3	2
Black or African American	0	0	1
White	23	20	23
Other	1	2	0

Reporting group values	Placebo (subjects remitted from depression)	Total	
Number of subjects	25	101	
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)	25	101	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	39		
standard deviation	± 8.8	-	
Gender categorical Units: Subjects			
Female	11	57	
Male	14	44	
Race Units: Subjects			
Asian	3	9	
Black or African American	0	1	
White	21	87	
Other	1	4	

End points

End points reporting groups

Reporting group title	Vortioxetine 20 mg qd (controls)

Reporting group description:

Subjects in the control group had no history of major depressive episodes (MDEs) and no history of MDEs in a biological parent or other first degree relative (as reported by the subject). Subjects had not reported subjective cognitive dysfunction and had never been treated with antidepressants or psychotherapy

Reporting group title	Placebo (controls)

Reporting group description:

Subjects in the control group had no history of MDEs and no history of MDEs in a biological parent or other first degree relative (as reported by the subject). Subjects had not reported subjective cognitive dysfunction and had never been treated with antidepressants or psychotherapy

Reporting group title	Vortioxetine 20 mg qd (subjects remitted from depression)

Reporting group description:

Subjects remitted from depression had been in remission from recurrent depression, had suffered from at least two previous major depressive episodes (MDEs), and had received prescribed treatment with an antidepressant or a recognised psychotherapy for depression for a previous MDE. The subjects reported present subjective cognitive dysfunction. They had not been treated with antidepressants or received other psychotherapy for depression for at least six weeks prior to the screening visit.

Reporting group title	Placebo (subjects remitted from depression)

Reporting group description:

Subjects remitted from depression had been in remission from recurrent depression, had suffered from at least two previous major depressive episodes (MDEs), and had received prescribed treatment with an antidepressant or a recognised psychotherapy for depression for a previous MDE. The subjects reported present subjective cognitive dysfunction. They had not been treated with antidepressants or received other psychotherapy for depression for at least six weeks prior to the screening visit.

Primary: N-Back Task: BOLD fMRI activity during the 0 (control), 1, 2 and 3 back conditions of the task

End point title	N-Back Task: BOLD fMRI activity during the 0 (control), 1, 2 and 3 back conditions of the task[1]

End point description:

Of the pre-defined Regions of interest (ROIs), analyses showed a statistically significant effect in the hippocampus only. Thus, in remitted subjects, vortioxetine statistically significantly reduced the blood oxygen level dependent (BOLD) signal in the left hippocampus compared to placebo during the N-back task.

End point type	Primary

End point timeframe:

Day 1 to Day 13

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Main objectives of the study were to study effects of vortioxetine compared to placebo in subjects remitted from depression.

End point values	Vortioxetine 20 mg qd (subjects remitted from depression)	Placebo (subjects remitted from depression)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Activity				
number (not applicable)	0.2	0		

Statistical analyses

Statistical analysis title	Effect of treatment in remitted subjects

Statistical analysis description:

The effect of treatment was tested using an ANCOVA model with the 'change from baseline' as the dependent variable. Only the contrast was available from the analysis in the statistical software program SPM, and therefore the treatment contrast is presented in the vortioxetine group, while the placebo group effect has been set to zero.

Comparison groups	Placebo (subjects remitted from depression) v Vortioxetine 20 mg qd (subjects remitted from depression)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	ANCOVA

Primary: Arena Task: BOLD fMRI activity while performing the encoding and retrieval trials

End point title	Arena Task: BOLD fMRI activity while performing the encoding and retrieval trials[2]

End point description:

Vortioxetine did not influence BOLD activity or the performance measures of spatial memory. Only the p-value for left hippocampus is given since all p-values for regions of interest were non-significant.

End point type	Primary

End point timeframe:

Day 1 to 13

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Main objectives of the study were to study effects of vortioxetine compared to placebo in subjects remitted from depression.

End point values	Vortioxetine 20 mg qd (subjects remitted from depression)	Placebo (subjects remitted from depression)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Activity				
number (not applicable)	0.06	0		

Statistical analyses

Statistical analysis title	Effect of treatment in remitted subjects

Statistical analysis description:

The effect of treatment was tested using an ANCOVA model with the 'change from baseline' as the dependent variable. Only the contrast was available from the analysis in the statistical software program SPM, and therefore the treatment contrast is presented in the vortioxetine group, while the placebo group effect has been set to zero.

Comparison groups	Vortioxetine 20 mg qd (subjects remitted from depression) v Placebo (subjects remitted from depression)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.57
Method	ANCOVA

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	16.1
Reporting groups	
Reporting group title	Vortioxetine 20 mg qd
Reporting group description: 20 mg vortioxetine once daily for 13 to 14 days	
Reporting group title	Placebo qd
Reporting group description: Placebo qd	

Serious adverse events	Vortioxetine 20 mg qd	Placebo qd	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (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	Vortioxetine 20 mg qd	Placebo qd	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 48 (54.17%)	22 / 48 (45.83%)	
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 48 (12.50%)	2 / 48 (4.17%)	
occurrences (all)	6	2	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 48 (29.17%)	14 / 48 (29.17%)	
occurrences (all)	17	17	

General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 48 (10.42%)	1 / 48 (2.08%)	
occurrences (all)	5	1	
Irritability			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 48 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 48 (6.25%)	4 / 48 (8.33%)	
occurrences (all)	4	4	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 48 (20.83%)	4 / 48 (8.33%)	
occurrences (all)	12	4	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 48 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 48 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Initial insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 48 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Middle insomnia			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	1 / 48 (2.08%) 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

None reported