Clinical trial results:
A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Active-Referenced, Flexible Dose Study on the Efficacy of Lu AA21004 on Cognitive Dysfunction in Adult Subjects with Major Depressive Disorder (MDD)

Summary

EudraCT number	2011-005298-22
Trial protocol	DE FI BG
Global end of trial date	05 February 2014

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	28 May 2015

Trial information

Trial identification

Sponsor protocol code	Lu_AA21004_202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01564862
WHO universal trial number (UTN)	U1111-1126-0091

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	One Takeda Parkway, Deerfield, IL, United States, 60015
Public contact	Clinical Study Manager, Takeda Global Research & Development Centre (Europe) Ltd, 44 (0)2031168000, clinicaloperations@tgrd.com
Scientific contact	Clinical Study Manager, Takeda Global Research & Development Centre (Europe) Ltd, 44 (0)2031168000, clinicaloperations@tgrd.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	24 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2014
Global end of trial reached?	Yes
Global end of trial date	05 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the effects of Lu AA21004, once daily (QD), on cognitive dysfunction in patients with major depressive disorder (MDD).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 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	Ukraine: 19
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Bulgaria: 127
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	Germany: 90
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	United States: 306
Worldwide total number of subjects	602
EEA total number of subjects	266

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)	597
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 80 investigative sites in Bulgaria, Finland, Germany, Poland, Russia Federation, Ukraine.and the United States from 09 April 2012 to 05 February 2014.

Pre-assignment

Screening details:

Participants with a diagnosis of major depressive disorder were enrolled equally in 1 of 3 treatment groups, once a day placebo, 10 to 20 mg flexible dose of vortioxetine, or 60 mg duloxetine.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Vortioxetine (Lu AA21004)

Arm description:

Vortioxetine (Lu AA21004) 10 mg, capsules, orally, once daily for one week; then dose adjustment to a maximum 20 mg, capsules, orally, once daily for up to 7 weeks.

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

Dosage and administration details:

Vortioxetine capsules

Arm title	Duloxetine

Arm description:

Duloxetine 60 mg, capsules, orally, for up to 8 weeks. Duloxetine 30 mg, capsule, orally, once daily for 1 week taper-down period.

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

Dosage and administration details:

Duloxetine capsules

Arm title	Placebo

Arm description:

Placebo matching capsules, orally, once daily for up to 9 weeks (includes 1 week taper down period).

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:

Placebo matching capsules

Number of subjects in period 1	Vortioxetine (Lu AA21004)	Duloxetine	Placebo
Started	198	210	194
Received Treatment	196	207	191
Completed	168	176	164
Not completed	30	34	30
Major Protocol Deviation	3	3	4
Voluntary Withdrawal	9	6	8
Other Reasons	1	-	-
Pretreatment Event or Adverse Event	6	12	6
Lost to follow-up	10	8	6
Lack of efficacy	1	5	6

Baseline characteristics

Reporting groups	
Reporting group title	Vortioxetine (Lu AA21004)
Reporting group description:	
Vortioxetine (Lu AA21004) 10 mg, capsules, orally, once daily for one week; then dose adjustment to a maximum 20 mg, capsules, orally, once daily for up to 7 weeks.	
Reporting group title	Duloxetine
Reporting group description:	
Duloxetine 60 mg, capsules, orally, for up to 8 weeks. Duloxetine 30 mg, capsule, orally, once daily for 1 week taper-down period.	
Reporting group title	Placebo
Reporting group description:	
Placebo matching capsules, orally, once daily for up to 9 weeks (includes 1 week taper down period).	

Reporting group values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo
Number of subjects	198	210	194
Age categorical Units: Subjects			
≤ 55 years	158	164	152
> 55 years	40	46	42
Age continuous Units: years			
arithmetic mean	44.2	45.7	45
standard deviation	± 12.21	± 11.46	± 12.07
Gender categorical Units: Subjects			
Female	135	138	119
Male	63	72	75
Race/Ethnicity Units: Subjects			
Hispanic or Latino	8	7	15
Non-Hispanic and Non-Latino	90	104	82
Not-Specified	100	99	97
Race/Ethnicity Units: Subjects			
Caucasian (or White, including Hispanic)	169	176	171
Black	28	27	20
Asian	1	6	1
American Indian or Alaska Native	0	1	2
Smoking Classification Units: Subjects			
Never Smoked	95	109	105
Current Smoker	73	68	56
Past Smoker	30	33	33
Alcohol Consumption Units: Subjects			
Never	89	84	87

Once Monthly or Less Often	67	73	51
Once a Week	23	31	29
2 to 6 Times per Week	15	19	24
Daily	4	3	3
Height			
Units: cm			
arithmetic mean	168.2	169.7	169
standard deviation	± 9.17	± 9.14	± 9.43
Weight			
Units: kg			
arithmetic mean	81.84	81.68	80.96
standard deviation	± 22.068	± 20.965	± 20.316
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	28.86	28.39	28.27
standard deviation	± 7.334	± 7.312	± 6.354

Reporting group values	Total		
Number of subjects	602		
Age categorical			
Units: Subjects			
≤ 55 years	474		
> 55 years	128		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	392		
Male	210		
Race/Ethnicity			
Units: Subjects			
Hispanic or Latino	30		
Non-Hispanic and Non-Latino	276		
Not-Specified	296		
Race/Ethnicity			
Units: Subjects			
Caucasian (or White, including Hispanic)	516		
Black	75		
Asian	8		
American Indian or Alaska Native	3		
Smoking Classification			
Units: Subjects			
Never Smoked	309		
Current Smoker	197		
Past Smoker	96		
Alcohol Consumption			
Units: Subjects			
Never	260		
Once Monthly or Less Often	191		

Once a Week	83		
2 to 6 Times per Week	58		
Daily	10		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Vortioxetine (Lu AA21004)
Reporting group description:	
Vortioxetine (Lu AA21004) 10 mg, capsules, orally, once daily for one week; then dose adjustment to a maximum 20 mg, capsules, orally, once daily for up to 7 weeks.	
Reporting group title	Duloxetine
Reporting group description:	
Duloxetine 60 mg, capsules, orally, for up to 8 weeks. Duloxetine 30 mg, capsule, orally, once daily for 1 week taper-down period.	
Reporting group title	Placebo
Reporting group description:	
Placebo matching capsules, orally, once daily for up to 9 weeks (includes 1 week taper down period).	

Primary: Change From Baseline to Week 8 in the Digit Symbol Substitution Test (DSST)

End point title	Change From Baseline to Week 8 in the Digit Symbol Substitution Test (DSST)
End point description:	
The DSST assesses relative contributions of speed, memory, executive function and visual scanning. Participants are required to copy symbols that are paired with simple geometric shapes or numbers within a specific time for a total possible score of 0 to 133. Higher scores-correct number of symbols reflects greater objective cognitive functioning. An increase in score represents an improvement in an integrated measure of cognitive function. An Analysis of Covariance (ANCOVA) model was used with treatment and center as fixed factors and the Baseline value as a covariate.	
End point type	Primary
End point timeframe:	
Baseline and Week 8	

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	187	167	
Units: Correct symbols				
least squares mean (standard error)	4.6 (± 0.53)	4.06 (± 0.511)	2.85 (± 0.542)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Vortioxetine (Lu AA21004) v Placebo

Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [1]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	3.21
Variability estimate	Standard error of the mean
Dispersion value	0.744

Notes:

[1] - P-value was from an ANCOVA model with treatment and center as fixed factors and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Duloxetine
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.099 [2]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	2.65
Variability estimate	Standard error of the mean
Dispersion value	0.733

Notes:

[2] - P-value was from an ANCOVA model with treatment and center as fixed factors and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Duloxetine v Vortioxetine (Lu AA21004)
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46 [3]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	1.96

Variability estimate	Standard error of the mean
Dispersion value	0.725

Notes:

[3] - P-value was from an ANCOVA model with treatment and center as fixed factors and the baseline value as a covariate.

Secondary: Change From Baseline to Week 8 in the Perceived Deficits Questionnaire (PDQ) Attention/Concentration and Planning/Organization Subscore

End point title	Change From Baseline to Week 8 in the Perceived Deficits Questionnaire (PDQ) Attention/Concentration and Planning/Organization Subscore

End point description:

PDQ is a patient-rated scale designed to subjectively assess cognitive dysfunction, comprising four 5-item subscales: Attention/Concentration, Retrospective Memory, Prospective Memory, and Planning/Organization for a total possible score of 0 to 40. The subscale Attention/Concentration is the sum of items 1, 5, 9, 13, and 17 with a range of 0-20; while the subscale Planning/Organization is the sum of items 4, 8, 12, 16, and 20 with the score range of 0 to 20. The scores of the subscales Attention/Concentration and Planning/Organization were combined. Higher scores reflect greater participant-perceived cognitive dysfunction in the domains identified. A decrease in score represents an improvement in subjective cognitive function in the domains identified. A Mixed Model Repeated Measures (MMRM) model was used with baseline*week, center, week, treatment and week*treatment as factors in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169	179	160	
Units: score on a scale				
least squares mean (standard error)	-8.9 (± 0.55)	-9.3 (± 0.53)	-6.3 (± 0.57)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Vortioxetine (Lu AA21004) v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	-1

Variability estimate	Standard error of the mean
Dispersion value	0.78

Notes:

[4] - P-value was from a MMRM model with baseline*week, center, week, treatment and week*treatment as factors in the analysis.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Duloxetine
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	-1.5
Variability estimate	Standard error of the mean
Dispersion value	0.77

Notes:

[5] - P-value was from a MMRM model with baseline*week, center, week, treatment and week*treatment as factors in the analysis.

Secondary: Clinical Global Impressions-Improvement (CGI-I) Score at Week 8

End point title	Clinical Global Impressions-Improvement (CGI-I) Score at Week 8

End point description:

The CGI-I assesses the clinician's impression of the subject's state of mental illness improvement and consists of one question for the investigator: "Compared to his condition at the start of the study, how much has this patient changed?" which is rated on a seven-point scale (1=very much improved; 2=much improved; 3=minimally improved; 4=no change relative to baseline; 5=minimally worse; 6= much worse; 7=very much worse). Higher scores indicate greater worsening of illness. Values closest to 1 for this outcome measure indicate the greatest improvement of symptoms. A MMRM model was used with baseline*week, center, week, treatment and week*treatment as factors in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169	179	161	
Units: score on a scale				
least squares mean (standard error)	2.349 (± 0.0852)	2.235 (± 0.0826)	2.639 (± 0.0872)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Vortioxetine (Lu AA21004) v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.528
upper limit	-0.052
Variability estimate	Standard error of the mean
Dispersion value	0.1211

Notes:

[6] - P-value was from a MMRM model with baseline*week, center, week, treatment and week*treatment as factors in the analysis.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Duloxetine
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean difference
Point estimate	-0.404
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.638
upper limit	-0.169
Variability estimate	Standard error of the mean
Dispersion value	0.1194

Notes:

[7] - P-value was from a MMRM model with baseline*week, center, week, treatment and week*treatment as factors in the analysis.

Secondary: Change From Baseline to Week 8 in the Trail Making Test (TMT-A)

End point title	Change From Baseline to Week 8 in the Trail Making Test (TMT-A)

End point description:

The TMT is a two-part cognitive test. TMT-A assesses cognitive processing speed and consists of 25 circles distributed over a sheet of paper. Participants have 4 minutes to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Tester informs participant immediately whenever they make an error and allows for corrections by participants. Lower scores represent better speed of processing. A decrease in score over the study represents an improvement in speed in processing. An ANCOVA model was used with treatment and center as fixed factors and the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	180	162	
Units: seconds				
least squares mean (standard error)	-7.7 (± 0.98)	-8.06 (± 0.955)	-6.65 (± 1.009)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in the Trail Making Test B (TMT-B)

End point title	Change From Baseline to Week 8 in the Trail Making Test B (TMT-B)

End point description:

The TMT is a two-part cognitive test. TMT-B assesses executive functioning and consists of 25 circles distributed over a sheet of paper. Participants have 4 minutes to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Tester informs participant immediately whenever they make an error and allows for corrections by participants. Lower score for TMT-B represents better executive function. A decrease in score over the study represents an improvement in executive function. An ANCOVA model was used with treatment and center as fixed factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	157	170	157	
Units: seconds				
least squares mean (standard error)	-18.73 (± 2.096)	-14.6 (± 2.011)	-9.06 (± 2.101)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Time From Baseline to Week 8 in the Stroop Test

End point title	Change in Time From Baseline to Week 8 in the Stroop Test

End point description:

The STROOP test assesses the ability to inhibit a prepotent response to reading words while performing a task that requires attention control. It comprises of 2 sheets with 50 words each, up to 50 correct responses for each of the congruent and incongruent Stroop tests. Participants have 4 minutes to name the ink color of each word. Lower time to complete the test indicates better performance. Higher number of correct responses indicates better responses. A decrease in the time to complete the tests and an increase in the number of correct responses both indicate improvement over the course of the study. An ANCOVA model was used with treatment and center as fixed factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	187	167	
Units: seconds				
least squares mean (standard error)				
Congruent (n=174,187,167)	-3.3 (± 1.086)	-4.54 (± 1.044)	-4.37 (± 1.105)	
Incongruent (n=172,186,166)	-8.17 (± 1.56)	-9.83 (± 1.498)	-8.11 (± 1.586)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in the Groton Maze Learning Test (GMLT)

End point title	Change From Baseline to Week 8 in the Groton Maze Learning Test (GMLT)

End point description:

The GMLT measures executive functioning and spatial problem solving. Participants learn a hidden pathway through a maze of 10 x 10 grid of tiles on a computer touch screen using step-by-step guess, with trial and error feedback after each step. Once the pathway is learned, participants repeat the same pathway four more times. It usually takes 5-6 minutes to administer this test. Lower score equals better performance. A decrease in score over the course of the study indicates improved executive function. An ANCOVA model was used with treatment and center as fixed factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169	179	159	
Units: errors				
least squares mean (standard error)	-5.43 (± 1.355)	-5.16 (± 1.314)	-3.49 (± 1.397)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in the Detection Task (DT)

End point title	Change From Baseline to Week 8 in the Detection Task (DT)

End point description:

The DT is a computerized test that measures simple reaction time and psychomotor speed. The task requires participants to respond by pressing a "yes" button as soon as an onscreen playing card is turned over and is red, and by pressing a "no" button if the card is not red. It takes 2 minutes to be administered. There is no minimum or maximum scores since it is a time-based assessment. Lower score equals better performance. A decrease in score over the course of the study indicates improved speed of processing and psychomotor function. An ANCOVA model was used with treatment and center as fixed factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	182	167	
Units: Log10 milliseconds				
least squares mean (standard error)	-0.05 (± 0.008)	-0.039 (± 0.0078)	-0.033 (± 0.0082)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in the Identification Task (IT)

End point title	Change From Baseline to Week 8 in the Identification Task (IT)

End point description:

The IT measured choice reaction time: the participant pressed a "yes" button whenever an onscreen playing card turned face up and was red, or a "no" button if the card was not red. The IT took on average 2 minutes to complete. Lower scores equal better performance. A decrease in score over the course of the study indicates improved visual attention/vigilance. An ANCOVA model was used with treatment and center as fixed factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	182	167	
Units: Log10 milliseconds				
least squares mean (standard error)	-0.037 (± 0.006)	-0.03 (± 0.0059)	-0.024 (± 0.0062)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in the One-Back Task

End point title	Change From Baseline to Week 8 in the One-Back Task

End point description:

The One-Back test measures the cognitive domain of attention and working memory through yes or no responses to 30 trials. The task requires participants to report when a stimulus item presented serially is the same as an item one step back from the item at hand for a total correct responses 0 to 100. It usually takes 2-3 minutes to be administered. Higher scores equal better performance. An increase in score over the course of the study indicates improved attention/working memory. An ANCOVA model was used with treatment and center as fixed factors and the Baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	182	167	
Units: Log10 milliseconds				
least squares mean (standard error)	-0.028 (± 0.0062)	-0.024 (± 0.006)	-0.022 (± 0.0063)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Cognitive Dysfunction Improvement Due to Improvement of Depression

End point title	Proportion of Cognitive Dysfunction Improvement Due to Improvement of Depression[8]

End point description:

Improvement of Cognitive Dysfunction is determined using the change from Baseline to Week 8 in the Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score and the Digital Symbol Substitution Test (DSST) total number of correct symbols. The MADRS is a 10-item clinician rated scale to measure overall severity of depressive symptoms (such as apparent sadness, reported sadness, inner tension) rated on a 7-point Likert scale from 0 (symptoms absent) to 6 (severe depression). The DSST assesses relative contributions of speed, memory, executive function and visual scanning. The proportion of direct effect from treatment = DSST difference / (DSST difference + coefficient*MADRS difference).

End point type	Secondary

End point timeframe:

Baseline and Week 8

Notes:

[8] - 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: Participants in the Placebo arm were not included in this analysis.

End point values	Vortioxetine (Lu AA21004)	Duloxetine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	187		
Units: proportion of direct effect				
number (not applicable)	75.66	48.69		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in the MADRS Total Score

End point title	Change From Baseline to Week 8 in the MADRS Total Score

End point description:

MADRS is a 10-item clinician rated scale to measure overall severity of depressive symptoms (such as apparent sadness, reported sadness, inner tension) rated on a 7-point Likert scale from 0 (symptoms absent) to 6 (severe depression) with a total possible score range from 0 to 60. Higher scores indicate greater severity of symptoms. A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 4 and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	187	167	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 1	-3.7 (± 4.8)	-4.6 (± 5.29)	-3.4 (± 5.03)	
Change at Week 4	-9.8 (± 6.85)	-11.6 (± 7.94)	-8 (± 7.98)	
Change at Week 8	-14.3 (± 8.97)	-15.5 (± 9.23)	-12.3 (± 9.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With MADRS Response at Week 8

End point title	Percentage of Participants With MADRS Response at Week 8

End point description:

MADRS is a 10-item clinician rated scale to measure overall severity of depressive symptoms (such as apparent sadness, reported sadness, inner tension) rated on a 7-point Likert scale from 0 (symptoms absent) to 6 (severe depression) with a total possible score range from 0 to 60. Higher scores indicate greater severity of symptoms. MADRS Response was defined as a ≥50% decrease in MADRS Total Score from Baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	187	167	
Units: percentage of participants				
number (not applicable)	50.9	54.5	41.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants in MADRS Remission at Week 8

End point title	Percentage of Participants in MADRS Remission at Week 8

End point description:

MADRS is a 10-item clinician rated scale to measure overall severity of depressive symptoms (such as apparent sadness, reported sadness, inner tension) rated on a 7-point Likert scale from 0 (symptoms absent) to 6 (severe depression) with a total possible score range from 0 to 60. Higher scores indicate greater severity of symptoms. MADRS Remission was defined as a MADRS total score ≤10.

End point type	Secondary

End point timeframe:

Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	187	167	
Units: percentage of participants				
number (not applicable)	30.3	33.7	21.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in the Clinical Global Impressions-Severity (CGI-S) Score

End point title	Change From Baseline to Week 8 in the Clinical Global Impressions-Severity (CGI-S) Score

End point description:

The CGI-S assesses the clinician's impression of the subject's current state of mental illness and consists of one question for the investigator: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on a seven-point scale (1=normal, not ill at all; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill). A MMRM model with baseline*week, center, week, treatment and week*treatment as factors was used for analyses.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 4 and Week 8

End point values	Vortioxetine (Lu AA21004)	Duloxetine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	187	167	
Units: score on a scale				
least squares mean (standard error)				
Change from Baseline at Week 1 (n=174, 187,167)	-0.289 (± 0.0426)	-0.353 (± 0.041)	-0.243 (± 0.0435)	
Change from Baseline at Week 4 (n=173,184,165)	-0.951 (± 0.0678)	-1.17 (± 0.0656)	-0.617 (± 0.0693)	
Change from Baseline at Week 8 (n=169,179,161)	-1.546 (± 0.0886)	-1.698 (± 0.0859)	-1.225 (± 0.0906)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of study drug and no more than 30 days after the last dose of study drug (Up to 12 Weeks)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Vortioxetine (Lu AA21004)

Reporting group description:

Vortioxetine (Lu AA21004) 10 mg, capsules, orally, once daily for one week; then dose adjustment to a maximum 20 mg, capsules, orally, once daily for up to 7 weeks.

Reporting group title	Duloxetine

Reporting group description:

Duloxetine 60 mg, capsules, orally, for up to 8 weeks. Duloxetine 30 mg, capsule, orally, once daily for 1 week taper-down period.

Reporting group title	Placebo

Reporting group description:

Placebo matching capsules, orally, once daily for up to 9 weeks (includes 1 week taper down period).

Serious adverse events	Vortioxetine (Lu AA21004)	Duloxetine	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 196 (0.51%)	1 / 207 (0.48%)	2 / 191 (1.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 196 (0.00%)	1 / 207 (0.48%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 196 (0.00%)	1 / 207 (0.48%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	0 / 196 (0.00%)	0 / 207 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 196 (0.00%)	0 / 207 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 196 (0.51%)	0 / 207 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Vortioxetine (Lu AA21004)	Duloxetine	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 196 (37.24%)	84 / 207 (40.58%)	41 / 191 (21.47%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 196 (3.06%)	11 / 207 (5.31%)	5 / 191 (2.62%)
occurrences (all)	6	11	5
Headache			
subjects affected / exposed	20 / 196 (10.20%)	24 / 207 (11.59%)	16 / 191 (8.38%)
occurrences (all)	22	25	20
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 196 (5.61%)	6 / 207 (2.90%)	5 / 191 (2.62%)
occurrences (all)	13	6	5
Dry mouth			
subjects affected / exposed	6 / 196 (3.06%)	16 / 207 (7.73%)	9 / 191 (4.71%)
occurrences (all)	6	17	9
Nausea			

subjects affected / exposed	40 / 196 (20.41%)	43 / 207 (20.77%)	8 / 191 (4.19%)
occurrences (all)	41	48	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 196 (3.57%)	8 / 207 (3.86%)	11 / 191 (5.76%)
occurrences (all)	7	8	11
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 196 (1.53%)	12 / 207 (5.80%)	1 / 191 (0.52%)
occurrences (all)	3	12	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2012	The primary purposes Amendment 1 were to change the dose for duloxetine titration during Week 1, add the CPFQ to the cognitive tests, and add a safety phone call at the end of Week 6.
05 November 2012	The primary purposes of amendment 2 were to remove hemoglobin A1C and alcohol exclusion requirements, clarify the exclusion criterion for subclinical hypothyroidism, andupdate unstable medical conditions in the exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported