Clinical trial results:
Interventional, randomised, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose study of vortioxetine in paediatric patients aged 12 to 17 years, with Major depressive disorder (MDD)

Summary

EudraCT number	2008-005354-20
Trial protocol	LV EE GB HU BG DE FI IT ES BE PL FR
Global end of trial date	30 July 2019

Results information

Result version number	v1 (current)
This version publication date	18 January 2020
First version publication date	18 January 2020

Trial information

Trial identification

Sponsor protocol code	12710A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02709746
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000455-PIP02-10
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	30 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2019
Global end of trial reached?	Yes
Global end of trial date	30 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo on depressive symptoms in adolescents with a DSM-5™ diagnosis of MDD.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2016
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: 311
Country: Number of subjects enrolled	Russian Federation: 100
Country: Number of subjects enrolled	Mexico: 57
Country: Number of subjects enrolled	Colombia: 32
Country: Number of subjects enrolled	Serbia: 27
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Poland: 69
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Bulgaria: 23
Country: Number of subjects enrolled	Estonia: 19
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Latvia: 29
Worldwide total number of subjects	784
EEA total number of subjects	228

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)	784
Adults (18-64 years)	0
From 65 to 84 years	0
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	Phase A (Single-blind treatment period)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Single-blind Treatment (SBT), Placebo

Arm description:

Single-blind Treatment, Placebo and Brief Psychosocial Intervention (BPI) for 4 weeks

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

Dosage and administration details:

Encapsulated, orally

Number of subjects in period 1	Single-blind Treatment (SBT), Placebo
Started	784
Completed	616
Not completed	168
non-compliance with IMP	12
Consent withdrawn by subject	12
Adverse event, non-fatal	2
Other	14
Did not fulfil rand criteria for DB period	103
Lost to follow-up	7
Enrolled but not treated	7
Lack of efficacy	7
Protocol deviation	4

Period 2

Period 2 title	Phase B (Double-blind treatment period)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	DBT, Vortioxetine 10 mg

Arm description:

Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Vortioxetine 10 mg/day, encapsulated tablets, orally.

Arm type	Experimental
Investigational medicinal product name	Vortioxetine 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vortioxetine 10 mg/day, encapsulated, orally

Arm title	DBT, Vortioxetine 20 mg

Arm description:

Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Vortioxetine 20 mg/day, encapsulated tablets, orally.

Arm type	Experimental
Investigational medicinal product name	Vortioxetine 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vortioxetine 20 mg/day, encapsulated, orally

Arm title	DBT, Fluoxetine 20 mg

Arm description:

Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Fluoxetine 20 mg/day, encapsulated tablets,

Arm type	Experimental
Investigational medicinal product name	Fluoxetine 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fluoxetine 20 mg/day, encapsulated, orally

Arm title	DBT, Placebo

Arm description:

Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Placebo, encapsulated tablets, orally.

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

Dosage and administration details:

Placebo, encapsulated, orally

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Patients are randomized at the start of Period 2, therefor Period 2 can be seen as a baseline period, whereas Period 1 is a lead-in period.

Number of subjects in period 2[2]	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg
Started	147	162	153
Completed	126	140	138
Not completed	21	22	15
non-compliance with IMP	1	4	1
Consent withdrawn by subject	2	2	2
Enrolled not treated	-	1	-
Adverse event, non-fatal	4	8	5
Other	6	5	6
Lost to follow-up	4	2	-
Lack of efficacy	3	-	1
Protocol deviation	1	-	-

Number of subjects in period 2[2]	DBT, Placebo
Started	154
Completed	138
Not completed	16
non-compliance with IMP	-
Consent withdrawn by subject	1
Enrolled not treated	-
Adverse event, non-fatal	2
Other	7
Lost to follow-up	2
Lack of efficacy	2
Protocol deviation	2

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Patients are randomized at the start of Period 2, therefor Period 2 can be seen as a baseline period, whereas Period 1 is a lead-in period.

Baseline characteristics

Reporting groups	
Reporting group title	DBT, Vortioxetine 10 mg
Reporting group description:	
Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Vortioxetine 10 mg/day, encapsulated tablets, orally.	
Reporting group title	DBT, Vortioxetine 20 mg
Reporting group description:	
Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Vortioxetine 20 mg/day, encapsulated tablets, orally.	
Reporting group title	DBT, Fluoxetine 20 mg
Reporting group description:	
Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Fluoxetine 20 mg/day, encapsulated tablets,	
Reporting group title	DBT, Placebo
Reporting group description:	
Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Placebo, encapsulated tablets, orally.	

Reporting group values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg
Number of subjects	147	162	153
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	147	162	153
Age continuous			
Units: years			
arithmetic mean	14.8	14.5	14.8
standard deviation	± 1.66	± 1.63	± 1.6
Gender categorical			
Units: Subjects			
Female	93	97	103
Male	54	65	50
CDSR-S total score at enrolment			
Units: Units on a scale			
arithmetic mean	64.82	65.29	64.06
standard deviation	± 9.38	± 9.73	± 8.65
CGI-S at Enrolment			
Units: Units on a scale			
arithmetic mean	4.99	5.00	4.97
standard deviation	± 0.77	± 0.71	± 0.68

Reporting group values	DBT, Placebo	Total	
Number of subjects	154	616	
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	154	616	

Age continuous Units: years arithmetic mean standard deviation	 14.6 ± 1.6	 -	
Gender categorical Units: Subjects			
Female Male	105 49	398 218	
CDSR-S total score at enrolment Units: Units on a scale arithmetic mean standard deviation	 64.02 ± 8.96	 -	
CGI-S at Enrolment Units: Units on a scale arithmetic mean standard deviation	 4.92 ± 0.69	 -	

End points

End points reporting groups

Reporting group title	Single-blind Treatment (SBT), Placebo
Reporting group description:	
Single-blind Treatment, Placebo and Brief Psychosocial Intervention (BPI) for 4 weeks	
Reporting group title	DBT, Vortioxetine 10 mg
Reporting group description:	
Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Vortioxetine 10 mg/day, encapsulated tablets, orally.	
Reporting group title	DBT, Vortioxetine 20 mg
Reporting group description:	
Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Vortioxetine 20 mg/day, encapsulated tablets, orally.	
Reporting group title	DBT, Fluoxetine 20 mg
Reporting group description:	
Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Fluoxetine 20 mg/day, encapsulated tablets,	
Reporting group title	DBT, Placebo
Reporting group description:	
Eligible patients from Phase A (patients with incomplete improvement), will be randomly assigned (1:1:1:1) double-blind treatment in DBT Period, 8 weeks. Placebo, encapsulated tablets, orally.	
Subject analysis set title	Vortioxetine average (Avg. VOR)
Subject analysis set type	Full analysis
Subject analysis set description:	
The primary comparison was the average effect of the two vortioxetine (Avg. VOR) doses versus placebo at Week 8 in the DB Period. The testing strategy also included comparisons of the individual vortioxetine doses versus placebo. First, the comparison of the average effect of the two vortioxetine doses versus placebo was tested at a two-sided 5% significance level. If significance was achieved, each vortioxetine dose was tested separately versus placebo at a two-sided 5% significance level. Statistical significance could be claimed on the individual doses only if significance was claimed for the average vortioxetine doses.	

Primary: Change in Children Depression Rating Scale - Revised (CDRS-R) total score after treatment

End point title	Change in Children Depression Rating Scale - Revised (CDRS-R) total score after treatment
End point description:	
The CDRS-R is a clinician-rated scale to measure the severity of depression of children and adolescents. The CDRS-R consists of 17 items: 14 items rate verbal observations, and three items rate nonverbal observations (tempo of language, hypoactivity, and nonverbal expression of depressed affect). Depression symptoms are rated on a 5-point scale from 1 to 5 for the verbal observations, and a 7-point scale from 1 to 7 for the nonverbal observations. The total score ranges from 17 (normal) to 113 (severe depression). Children and parents answer separately. Rater judges and selects 'Best'.	
End point type	Primary
End point timeframe:	
From randomization to Week 8	

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: units on a scale				
least squares mean (standard error)	-17.09 (± 1.27)	-18.94 (± 1.22)	-21.95 (± 1.23)	-18.22 (± 1.22)

End point values	Vortioxetine average (Avg. VOR)			
Subject group type	Subject analysis set			
Number of subjects analysed	265[1]			
Units: units on a scale				
least squares mean (standard error)	-18.01 (± 0.98)			

Notes:

[1] - 126 patients for 10 mg vortioxetine and 139 patients for 20 mg vortioxetine

Statistical analyses

Statistical analysis title	Vortioxetine 10 mg vs placebo

Statistical analysis description:

Only patients randomized to receive double-blind treatment in the DBT Period are analyzed. Overall Number of Participants analyzed is number of patients in the FAS with a week 8 observation.

Comparison groups	DBT, Placebo v DBT, Vortioxetine 10 mg
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.4702
Method	Mixed Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	4.2

Notes:

[2] - The change from Randomization in CDRS-R total score at Week 8 was analysed using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included the fixed, categorical effects of treatment, country, and week, the continuous covariate of CDRS-R total score at Randomization, the treatment-by-week interaction, and the CDRS-R at Randomization-by-week interaction. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Statistical analysis title	Vortioxetine 20 mg vs placebo

Statistical analysis description:

Only patients randomized to receive double-blind treatment in the DBT Period are analyzed. Overall Number of Participants analyzed is number of patients in the FAS with a week 8 observation.

Comparison groups	DBT, Vortioxetine 20 mg v DBT, Placebo

Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.6373
Method	Mixed Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.71
upper limit	2.27

Notes:

[3] - The change from Randomization in CDRS-R total score at Week 8 was analysed using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included the fixed, categorical effects of treatment, country, and week, the continuous covariate of CDRS-R total score at Randomization, the treatment-by-week interaction, and the CDRS-R at Randomization-by-week interaction. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Statistical analysis title	Fluoxetine 20 mg vs placebo

Statistical analysis description:

Only patients randomized to receive double-blind treatment in the DBT Period are analyzed. Overall Number of Participants analyzed is number of patients in the FAS with a week 8 observation.

Comparison groups	DBT, Fluoxetine 20 mg v DBT, Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0152
Method	Mixed Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-3.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.74
upper limit	-0.72

Notes:

[4] - The change from Randomization in CDRS-R total score at Week 8 was analysed using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included the fixed, categorical effects of treatment, country, and week, the continuous covariate of CDRS-R total score at Randomization, the treatment-by-week interaction, and the CDRS-R at Randomization-by-week interaction. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Statistical analysis title	Vortioxetine average vs placebo

Statistical analysis description:

The primary comparison was the average effect of the two vortioxetine (Avg. VOR) doses versus placebo at Week 8 in the DB Period based on the SAS lsmestimate statement. The testing strategy also included comparisons of the individual vortioxetine doses versus placebo. First, the comparison of the average effect of the two vortioxetine doses versus placebo was tested at a two-sided 5% significance level. If significance was achieved, each vortioxetine dose was tested separately versus placebo

Comparison groups	DBT, Placebo v Vortioxetine average (Avg. VOR)

Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8778
Method	Mixed Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	2.82

Secondary: Change in CDRS-R total score during treatment (at Week 2)

End point title	Change in CDRS-R total score during treatment (at Week 2)

End point description:

The CDRS-R is a clinician-rated scale to measure the severity of depression of children and adolescents. The CDRS-R consists of 17 items: 14 items rate verbal observations, and three items rate nonverbal observations (tempo of language, hypoactivity, and nonverbal expression of depressed affect). Depression symptoms are rated on a 5-point scale from 1 to 5 for the verbal observations, and a 7-point scale from 1 to 7 for the nonverbal observations. The total score ranges from 17 (normal) to 113 (severe depression).

End point type	Secondary

End point timeframe:

At week 2

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	158	150	153
Units: units on a scale				
least squares mean (standard error)	-9.58 (± 1.02)	-10.15 (± 0.99)	-10.34 (± 1.00)	-8.83 (± 0.98)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDRS-R MOOD Score

End point title	Change in CDRS-R MOOD Score

End point description:

Change in Children Depression Rating Scale - Revised (CDRS-R) Mood. The CDRS-R has been widely used for the evaluation of children and adolescents with major depressive disorder (MDD). The CDRS-R total score is the sum of the responses to 17 items. Each item is graded on a 5- or 7-point scale. Mood is one of four subscores defined in the CDRS-R: sum of items 8, 11, 14, 15; score range 4 to 28. The highest possible score indicates the most severe measure of depression.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: units on a scale				
least squares mean (standard error)	-5.05 (± 0.40)	-5.47 (± 0.38)	-6.53 (± 0.38)	-5.32 (± 0.38)

Statistical analyses

No statistical analyses for this end point

Secondary: CDRS-R response

End point title	CDRS-R response

End point description:

Children Depression Rating Scale - Response: defined as a >= 50% decrease in CDRS-R total score, calculated as (change from baseline [Randomization])/(baseline value - 17).

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: Number of patients	53	60	68	49

Statistical analyses

No statistical analyses for this end point

Secondary: CDRS-R remission

End point title	CDRS-R remission

End point description:

Remission defined as a CDRS-R total score<= 28.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: Number of patients	21	24	32	20

Statistical analyses

No statistical analyses for this end point

Secondary: Change in General Behaviour Inventory (GBI) depression sub scale score assessed by the Parents

End point title	Change in General Behaviour Inventory (GBI) depression sub scale score assessed by the Parents

End point description:

Using the 10-item depression subscale, assessed by parent (PGBI-10D). Change from Baseline to Week 30 in GBI Total Parent/Guardian Version Depression score, using LOCF. GBI is a self-report inventory with 73 items focused on mood-related behaviors including depressive, hypomanic, and biphasic symptoms. One 20-item subscale completed by parent/guardian. Symptoms rated on 4-point Likert scale from 0 (never/hardly ever) to 3 (often/almost constantly). Minimum score 0=better outcome, maximum score 60=worse outcome

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: units on a scale				
least squares mean (standard error)	-6.23 (± 0.56)	-6.48 (± 0.54)	-8.00 (± 0.54)	-6.62 (± 0.53)

Statistical analyses

No statistical analyses for this end point

Secondary: Parent Global Assessment–Global Improvement (PGA) score

End point title	Parent Global Assessment–Global Improvement (PGA) score

End point description:

The PGA is a parent-rated variation of the CGI-I to evaluate the severity of the child's symptoms. The PGA reflects assessments of change from Baseline symptoms using a 7 point scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

From Randomizationto Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	139	137	137
Units: Units on a scale				
least squares mean (standard error)	2.80 (± 0.10)	2.74 (± 0.09)	2.49 (± 0.09)	2.72 (± 0.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Symbol Digit Modalities Test (SDMT)

End point title	Change in Symbol Digit Modalities Test (SDMT)

End point description:

The Symbol Digit Modalities Test (SDMT) is a cognitive test designed to assess speed of performance requiring visual perception, spatial decision-making and psychomotor skills. The SDMT consists of 110 geometric symbols that the patient has to substitute with a corresponding digit in a 90-second period. Each correct digit is counted, and the total score ranges from 0 (less than normal functioning) to 110 (greater than normal functioning).

End point type	Secondary

End point timeframe:

From Randomizationto Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	140	138	137
Units: units on a scale				
least squares mean (standard error)	3.75 (± 1.02)	2.64 (± 0.98)	2.69 (± 0.98)	2.41 (± 0.97)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Clinical Global Impression severity of illness (CGI-S) score

End point title	Change in Clinical Global Impression severity of illness (CGI-S) score

End point description:

The CGI-S 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 Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: Units on a scale				
least squares mean (standard error)	-1.23 (± 0.10)	-1.38 (± 0.10)	-1.59 (± 0.10)	-1.21 (± 0.10)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression - global improvement (CGI-I) score

End point title	Clinical Global Impression - global improvement (CGI-I) score

End point description:

The 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). In all cases, the assessment should be made independent of whether the rater believes the improvement is drug-related or not.

End point type	Secondary

End point timeframe:

At Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	139	137	137
Units: Units on a scale				
least squares mean (standard error)	2.81 (± 0.10)	2.69 (± 0.09)	2.50 (± 0.09)	2.73 (± 0.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Children’s Global Assessment Scale (CGAS) score

End point title	Change in Children’s Global Assessment Scale (CGAS) score

End point description:

The Children's Global Assessment Score (CGAS) is a rating scale which measures psychological, social and school functioning for children. The CGAS is a clinician-rated global scale to measure the lowest level of functioning for a child (4 to 16 years) during a specified time period. The CGAS contains behaviourally oriented descriptors at each anchor point that depict behaviours and life situations applicable to a child. The items range in value from 1 (most functionally impaired child) to 100 (the healthiest). A total score above 70 indicates normal function.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	140	138	137
Units: Units on a scale				
least squares mean (standard error)	12.24 (± 1.25)	13.89 (± 1.20)	16.43 (± 1.20)	14.52 (± 1.19)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pediatric Quality of Life Inventory (PedsQL) Visual Analogue Scales (VAS): afraid or scared Score

End point title	Change in Pediatric Quality of Life Inventory (PedsQL) Visual Analogue Scales (VAS): afraid or scared Score

End point description:

The PedsQL™ VAS is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	140	138	137
Units: Units on a scale				
least squares mean (standard error)	-0.47 (± 0.19)	-0.76 (± 0.18)	-0.78 (± 0.18)	-0.71 (± 0.18)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PedsQL VAS total average score

End point title	Change in PedsQL VAS total average score

End point description:

The PedsQL™ VAS is designed to measure at-that-moment functioning in children and adolescents. The PedsQL™ VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue, and pain using visual analogue scales. The functionality for each domain is measured on a 10cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	140	138	137
Units: Units on a scale				
least squares mean (standard error)	-1.00 (± 0.17)	-1.13 (± 0.16)	-1.33 (± 0.16)	-1.14 (± 0.16)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PedsQL emotional distress summary average score

End point title	Change in PedsQL emotional distress summary average score

End point description:

The PedsQL™ VAS is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	140	138	137
Units: Units on a scale				
least squares mean (standard error)	-0.93 (± 0.18)	-1.09 (± 0.17)	-1.33 (± 0.17)	-1.18 (± 0.17)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) total scores

End point title	Change in Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) total scores

End point description:

(items 1 to 14). The PQ-LES-Q is a patient-rated scale designed to assess satisfaction with life. It is an adaptation of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), which is used to measure quality of life in adults. The PQ LES Q consist of 15 items, item 1-14 assess the degree of satisfaction experienced by subjects in various areas of daily functioning and item 15 allows subjects to summarize their experience in a global rating. Each item is rated on a 5-point scale from 1 (very poor) to 5 (very good). The total score range of item 1-14 is 14 to 70, with higher scores indicating greater satisfaction.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	140	137	137
Units: Units on a scale				
least squares mean (standard error)	7.62 (± 0.97)	7.56 (± 0.93)	9.26 (± 0.94)	7.06 (± 0.92)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDRS-R SOMATIC Score

End point title	Change in CDRS-R SOMATIC Score

End point description:

Change in Children Depression Rating Scale - Revised (CDRS-R) Somatic. The CDRS-R has been widely used for the evaluation of children and adolescents with major depressive disorder (MDD). The CDRS-R total score is the sum of the responses to 17 items. Each item is graded on a 5- or 7-point scale. Somatic is one of four subscores defined in the CDRS-R: sum of items 4, 5, 6, 7, 16, 17; score ranges from 6 to 36. The highest possible score indicates the most severe measure of depression.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: units on a scale				
least squares mean (standard error)	-5.63 (± 0.46)	-6.03 (± 0.44)	-6.79 (± 0.45)	-5.78 (± 0.44)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDRS-R BEHAVIOUR Score

End point title	Change in CDRS-R BEHAVIOUR Score

End point description:

Change in Children Depression Rating Scale - Revised (CDRS-R): Behaviour. The CDRS-R has been widely used for the evaluation of children and adolescents with major depressive disorder (MDD). The CDRS-R total score is the sum of the responses to 17 items. Each item is graded on a 5- or 7-point scale. Somatic is one of four subscores defined in the CDRS-R:sum of items 1, 2, 3; score ranges from 3 to 21. The highest possible score indicates the most severe measure of depression.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: Units on a scale				
least squares mean (standard error)	-4.32 (± 0.38)	-4.90 (± 0.36)	-5.52 (± 0.37)	-4.73 (± 0.36)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDRS-R SUBJECTIVE Score

End point title	Change in CDRS-R SUBJECTIVE Score

End point description:

Change in Children Depression Rating Scale - Revised (CDRS-R): Subjective. The CDRS-R has been widely used for the evaluation of children and adolescents with major depressive disorder (MDD). The CDRS-R total score is the sum of the responses to 17 items. Each item is graded on a 5- or 7-point scale. Somatic is one of four subscores defined in the CDRS-R: sum of items 9, 10, 12, 13; score ranges from 4 to 28. The highest possible score indicates the most severe measure of depression.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: Units on a scale				
least squares mean (standard error)	-2.41 (± 0.22)	-2.63 (± 0.21)	-3.23 (± 0.21)	-2.66 (± 0.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Change General Behaviour Inventory (GBI) Depression Subscale Score assessed by the Child

End point title	Change General Behaviour Inventory (GBI) Depression Subscale Score assessed by the Child

End point description:

The GBI 10-item mania scale is a parent- and subject-rated scale designed to screen for manic symptoms in children and adolescents. The 10 items are rated on a scale from 0 (never or hardly ever) to 3 (very often or almost constantly). The total score ranges from 0 to 30 points, with high scores indicating greater pathology.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: Units on a scale				
least squares mean (standard error)	-5.48 (± 0.61)	-5.55 (± 0.59)	-6.30 (± 0.59)	-6.03 (± 0.58)

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-S Remission

End point title	CGI-S Remission

End point description:

Remission defined as CGI-S score of 1 or 2.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	139	137	137
Units: Number of patients	26	33	36	24

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PQ-LES-Q overall Score

End point title	Change in PQ-LES-Q overall Score

End point description:

(items 1 to 14). The PQ-LES-Q is a patient-rated scale designed to assess satisfaction with life. It is an adaptation of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), which is used to measure quality of life in adults. The PQ LES Q consist of 15 items, item 1-14 assess the degree of satisfaction experienced by subjects in various areas of daily functioning and item 15 allows subjects to summarize their experience in a global rating. Each item is rated on a 5-point scale from 1 (very poor) to 5 (very good). The total score range of item 1-14 is 14 to 70, with higher scores indicating greater satisfaction.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	140	137	137
Units: Units on a scale				
least squares mean (standard error)	0.54 (± 0.08)	0.43 (± 0.08)	0.67 (± 0.08)	0.51 (± 0.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PedsQL VAS: sad or blue Score

End point title	Change in PedsQL VAS: sad or blue Score

End point description:

The PedsQL™ VAS is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	140	138	137
Units: Units on a scale				
least squares mean (standard error)	-1.90 (± 0.26)	-1.71 (± 0.25)	-2.45 (± 0.25)	-2.12 (± 0.24)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PedsQL VAS: angry Score

End point title	Change in PedsQL VAS: angry Score

End point description:

The PedsQL™ VAS is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	140	138	137
Units: Units on a scale				
least squares mean (standard error)	-0.51 (± 0.23)	-0.70 (± 0.23)	-1.01 (± 0.23)	-0.59 (± 0.23)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PedsQL VAS: worry Score

End point title	Change in PedsQL VAS: worry Score

End point description:

The PedsQL™ VAS is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	140	138	137
Units: Units on a scale				
least squares mean (standard error)	-0.96 (± 0.25)	-1.17 (± 0.24)	-0.91 (± 0.24)	-1.33 (± 0.24)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PedsQL VAS: tired Score

End point title	Change in PedsQL VAS: tired Score

End point description:

The PedsQL™ VAS is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	140	138	137
Units: Units on a scale				
least squares mean (standard error)	-1.18 (± 0.29)	-1.40 (± 0.28)	-1.55 (± 0.28)	-1.27 (± 0.28)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PedsQL VAS: pain or hurt Score

End point title	Change in PedsQL VAS: pain or hurt Score

End point description:

The PedsQL™ VAS is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	140	138	137
Units: Units on a scale				
least squares mean (standard error)	-1.12 (± 0.22)	-0.97 (± 0.21)	-0.83 (± 0.21)	-0.76 (± 0.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDRS-R total score during treatment (at Week 4)

End point title	Change in CDRS-R total score during treatment (at Week 4)

End point description:

The CDRS-R is a clinician-rated scale to measure the severity of depression of children and adolescents. The CDRS-R consists of 17 items: 14 items rate verbal observations, and three items rate nonverbal observations (tempo of language, hypoactivity, and nonverbal expression of depressed affect). Depression symptoms are rated on a 5-point scale from 1 to 5 for the verbal observations, and a 7-point scale from 1 to 7 for the nonverbal observations. The total score ranges from 17 (normal) to 113 (severe depression).

End point type	Secondary

End point timeframe:

At Week 4

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	137	153	145	149
Units: Units on a scale				
least squares mean (standard error)	-14.32 (± 1.14)	-15.03 (± 1.10)	-16.25 (± 1.11)	-13.71 (± 1.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDRS-R total score during treatment (at Week 6)

End point title	Change in CDRS-R total score during treatment (at Week 6)

End point description:

The CDRS-R is a clinician-rated scale to measure the severity of depression of children and adolescents. The CDRS-R consists of 17 items: 14 items rate verbal observations, and three items rate nonverbal observations (tempo of language, hypoactivity, and nonverbal expression of depressed affect). Depression symptoms are rated on a 5-point scale from 1 to 5 for the verbal observations, and a 7-point scale from 1 to 7 for the nonverbal observations. The total score ranges from 17 (normal) to 113 (severe depression).

End point type	Secondary

End point timeframe:

At Week 6

End point values	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg	DBT, Fluoxetine 20 mg	DBT, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	127	145	143	142
Units: Units on a scale				
least squares mean (standard error)	-15.43 (± 1.24)	-17.78 (± 1.19)	-19.20 (± 1.20)	-16.71 (± 1.19)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 38 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Phase A
Reporting group description: -	
Reporting group title	DBT, Vortioxetine 10 mg
Reporting group description: -	
Reporting group title	DBT, Vortioxetine 20 mg
Reporting group description: -	
Reporting group title	DBT, Fluoxetine 20 mg
Reporting group description: -	
Reporting group title	DBT, Placebo
Reporting group description: -	

Serious adverse events	Phase A	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 777 (1.67%)	4 / 147 (2.72%)	7 / 161 (4.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 777 (0.00%)	0 / 147 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 777 (0.13%)	0 / 147 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysmenorrhoea			

subjects affected / exposed	1 / 777 (0.13%)	0 / 147 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 777 (0.00%)	0 / 147 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised anxiety disorder			
subjects affected / exposed	1 / 777 (0.13%)	0 / 147 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal behaviour			
subjects affected / exposed	1 / 777 (0.13%)	0 / 147 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	6 / 777 (0.77%)	1 / 147 (0.68%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 6	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	2 / 777 (0.26%)	0 / 147 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 777 (0.13%)	1 / 147 (0.68%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	0 / 777 (0.00%)	1 / 147 (0.68%)	0 / 161 (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
Gastroenteritis			

subjects affected / exposed	0 / 777 (0.00%)	1 / 147 (0.68%)	0 / 161 (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
Gastrointestinal viral infection			
subjects affected / exposed	0 / 777 (0.00%)	0 / 147 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 777 (0.13%)	0 / 147 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 777 (0.00%)	0 / 147 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 777 (0.00%)	0 / 147 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 777 (0.00%)	0 / 147 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DBT, Fluoxetine 20 mg	DBT, Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 153 (1.96%)	1 / 154 (0.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised anxiety disorder			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	2 / 153 (1.31%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 153 (0.00%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase A	DBT, Vortioxetine 10 mg	DBT, Vortioxetine 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	128 / 777 (16.47%)	47 / 147 (31.97%)	57 / 161 (35.40%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 777 (2.70%)	11 / 147 (7.48%)	7 / 161 (4.35%)
occurrences (all)	23	14	7
Headache			
subjects affected / exposed	65 / 777 (8.37%)	23 / 147 (15.65%)	20 / 161 (12.42%)
occurrences (all)	85	37	46
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 777 (1.67%)	5 / 147 (3.40%)	9 / 161 (5.59%)
occurrences (all)	14	5	10
Nausea			
subjects affected / exposed	28 / 777 (3.60%)	21 / 147 (14.29%)	31 / 161 (19.25%)
occurrences (all)	31	23	48
Vomiting			
subjects affected / exposed	13 / 777 (1.67%)	7 / 147 (4.76%)	15 / 161 (9.32%)
occurrences (all)	13	7	20
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 777 (3.35%)	6 / 147 (4.08%)	10 / 161 (6.21%)
occurrences (all)	28	7	11

Non-serious adverse events	DBT, Fluoxetine 20 mg	DBT, Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 153 (26.14%)	30 / 154 (19.48%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 153 (3.92%)	5 / 154 (3.25%)	
occurrences (all)	8	6	
Headache			
subjects affected / exposed	10 / 153 (6.54%)	12 / 154 (7.79%)	
occurrences (all)	16	19	

Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 7 / 153 (4.58%) 11 10 / 153 (6.54%) 16 8 / 153 (5.23%) 10	 5 / 154 (3.25%) 5 7 / 154 (4.55%) 9 1 / 154 (0.65%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 10 / 153 (6.54%) 12	 5 / 154 (3.25%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2015	PA1: Revised interim analysis (blinded sample size re-assessment) and sample size sections to reflect that the power for having at least one significant dose with an effect of 4 points instead of 5 points for the primary endpoint is given. Added: Lipids testing
18 January 2016	PA2: Inclusion criterion 12: changed urine pregnancy test to blood pregnancy test Exclusion criterion 7: specified that patients who receive formal psychotherapy or CBT are not included in the study. Added that the window between screening and Enrolment was extended for up to 30 days.
05 July 2018	PA3: Modified the testing strategy for the primary analysis such that the primary comparison was between the average doses (rather than the individual doses) of vortioxetine to placebo to increase the power of the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported