Clinical trial results:
Long-term, Open-label, Flexible-dose, Extension Study of Vortioxetine in Child and Adolescent Patients With Major Depressive Disorder (MDD) From 7 to 18 Years of Age

Summary

EudraCT number	2008-005356-25
Trial protocol	LV DE HU PL IT ES BG BE
Global end of trial date	19 April 2022

Results information

Result version number	v1
This version publication date	04 October 2022
First version publication date	04 October 2022

Trial information

Trial identification

Sponsor protocol code	12712A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02871297
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, +45 36301311, LundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, +45 36301311, LundbeckClinicalTrials@lundbeck.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2022
Global end of trial reached?	Yes
Global end of trial date	19 April 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the long-term safety and tolerability of vortioxetine in child and adolescent participants with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5®) diagnosis of MDD.

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice and in accordance with the ethical principles described in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 August 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	Bulgaria: 43
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Colombia: 105
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Estonia: 26
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Latvia: 31
Country: Number of subjects enrolled	Mexico: 104
Country: Number of subjects enrolled	Poland: 69
Country: Number of subjects enrolled	Russian Federation: 136
Country: Number of subjects enrolled	Serbia: 37
Country: Number of subjects enrolled	Ukraine: 20
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	South Africa: 2

Worldwide total number of subjects	662
EEA total number of subjects	229

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)	300
Adolescents (12-17 years)	352
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a long-term extension study in child and adolescent participants with MDD who completed 1 of the double-blind, placebo-controlled, active-reference Study 12709A (NCT02709655) or 12710A (NCT02709746).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Vortioxetine

Arm description:

Participants initiated treatment with vortioxetine 5 milligrams (mg)/day orally for the first 2 days and thereafter they received 10 mg/day vortioxetine. Based on the response and dose-limiting adverse events (AEs), vortioxetine dose could be up- or down-titrated with 5 mg/day but the maximum dose did not exceed 20 mg/day. The total duration of treatment was 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Vortioxetine
Investigational medicinal product code	
Other name	Brintellix ®, Lu AA21004
Pharmaceutical forms	Oral drops, solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Vortioxetine was administered per dose and schedule specified in the arm description.

Number of subjects in period 1	Vortioxetine
Started	662
Received at least 1 dose of study drug	662
Completed	526
Not completed	136
Consent withdrawn by subject	20
Adverse event, non-fatal	34
Rolled over to 13546A	2
Non-compliance with study drug	15
Other than specified	39
Lost to follow-up	13
Lack of efficacy	10
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Vortioxetine
Reporting group description:	
Participants initiated treatment with vortioxetine 5 milligrams (mg)/day orally for the first 2 days and thereafter they received 10 mg/day vortioxetine. Based on the response and dose-limiting adverse events (AEs), vortioxetine dose could be up- or down-titrated with 5 mg/day but the maximum dose did not exceed 20 mg/day. The total duration of treatment was 26 weeks.	

Reporting group values	Vortioxetine	Total	
Number of subjects	662	662	
Age Categorical Units: Subjects			
Children (2-11 years)	300	300	
Adolescents (12-17 years)	352	352	
Adults (18-64 years)	10	10	
Age Continuous Units: years			
arithmetic mean	12.33		
standard deviation	± 3.07	-	
Gender Categorical Units: Subjects			
Female	361	361	
Male	301	301	
Race Units: Subjects			
White	447	447	
Black	8	8	
Asian	5	5	
Other	188	188	
Unknown	9	9	
Not reported	5	5	

End points

End points reporting groups

Reporting group title	Vortioxetine

Reporting group description:

Participants initiated treatment with vortioxetine 5 milligrams (mg)/day orally for the first 2 days and thereafter they received 10 mg/day vortioxetine. Based on the response and dose-limiting adverse events (AEs), vortioxetine dose could be up- or down-titrated with 5 mg/day but the maximum dose did not exceed 20 mg/day. The total duration of treatment was 26 weeks.

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. SAEs included death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent 1 of the outcomes listed in this definition. TEAE was defined as an AE that started or increased in intensity on or after the date of first dose of study drug in this study 12712A. A summary of serious and non-serious AEs regardless of causality is located in 'Reported Adverse Events module'. All-patients-treated set (APTS) included all participants who took at least 1 dose of vortioxetine in this study 12712A.

End point type	Primary

End point timeframe:

Baseline up to Week 30

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis was descriptive in nature.

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	662			
Units: participants	404			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children Depression Rating Scale - Revised (CDRS-R) Total Score at Week 26

End point title	Change From Baseline in Children Depression Rating Scale - Revised (CDRS-R) Total Score at Week 26

End point description:

CDRS-R consisted of 17 items out of which 3 items rated nonverbal observations (listless speech, hypoactivity, and depressed affect). Fourteen items were rated on a 7-point scale from 1 to 7, and 3 items (sleep disturbance, appetite disturbance, and listless speech) were scored on a 5-point scale from 1 to 5. A rating of 1 indicated normal functioning and a higher number indicated a greater degree of depression. Total score ranged from 17 (normal) to 113 (severe depression). Least square (LS) mean

was calculated using using a restricted maximum likelihood-based mixed model for repeated measurements (MMRM) approach. Full analysis set (FAS) included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid open-label extension baseline (OLEXA) assessment and at least 1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	506			
Units: units on a scale				
least squares mean (standard error)	-16.05 (± 0.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Loss of Remission

End point title	Time to First Loss of Remission

End point description:

Remission was defined as a total score ≤28 on the CDRS-R. CDRS-R consisted of 17 items out of which 3 items rated nonverbal observations (listless speech, hypoactivity, and depressed affect). Fourteen items were rated on a 7-point scale from 1 to 7, and 3 items (sleep disturbance, appetite disturbance, and listless speech) were scored on a 5-point scale from 1 to 5. A rating of 1 indicated normal functioning and a higher number indicated a greater degree of depression. Total score ranged from 17 (normal) to 113 (severe depression). Due to change in planned analysis, this endpoint was not analyzed; hence, data were not collected for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: days				
median (full range (min-max))	(to)			

Notes:

[2] - Due to change in planned analysis, this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Relapse

End point title	Time to First Relapse

End point description:

Relapse was defined as a total score ≥40 on the CDRS-R. CDRS-R consisted of 17 items out of which 3 items rated nonverbal observations (listless speech, hypoactivity, and depressed affect). Fourteen items were rated on a 7-point scale from 1 to 7, and 3 items (sleep disturbance, appetite disturbance, and listless speech) were scored on a 5-point scale from 1 to 5. A rating of 1 indicated normal functioning and a higher number indicated a greater degree of depression. Total score ranged from 17 (normal) to 113 (severe depression). Due to change in planned analysis, this endpoint was not analyzed; hence, data were not collected for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: days				
median (full range (min-max))	(to)			

Notes:

[3] - Due to change in planned analysis, this endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression - Severity of Illness (CGI-S) Score at Week 26

End point title	Change From Baseline in Clinical Global Impression - Severity of Illness (CGI-S) Score at Week 26

End point description:

The CGI-S provides the clinician’s impression of the participant’s current state of mental illness. The clinician uses his or her clinical experience of this participant population to rate the severity of the participant’s current mental illness on a 7-point scale ranging from 1 (normal – not at all ill) to 7 (among the most extremely ill participants). LS mean was calculated using using a restricted maximum likelihood-based MMRM approach. FAS included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid OLEXA assessment and at least 1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	506			
Units: units on a scale				
least squares mean (standard error)	-1.48 (± 0.06)			

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 participant's improvement (or worsening). The clinician assesses the participant's condition relative to a baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). LS mean was calculated using using a restricted maximum likelihood-based MMRM approach. FAS included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid OLEXA assessment and at least 1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	506			
Units: units on a scale				
least squares mean (standard error)	1.72 (± 0.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Children (7-11 Years): Change From Baseline in Behaviour Rating Inventory of Executive Function - Preschool (BRIEF-P) Using the Global Executive Composite Score at Week 26

End point title	Children (7-11 Years): Change From Baseline in Behaviour Rating Inventory of Executive Function - Preschool (BRIEF-P) Using the Global Executive Composite Score at Week 26

End point description:

The BRIEF-P is an 86 item measure that assesses impairment in executive function with symptoms rated on a 3-point likert scale of 1 "never", 2 "sometimes" or 3 "often". There are 8 clinical sub-scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) and two validity scales (Inconsistency and Negativity). A Global Executive Composite score is obtained by summing all 8 clinical sub-scales. The Global Executive Composite ranges from 86-258 with higher scores indicating greater impairment in executive functions. The Global Executive Composite gets

converted to a T-score with T-scores of 65 or above considered in the clinical range. FAS included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid OLEXA assessment and at least 1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	217			
Units: T score				
arithmetic mean (standard deviation)	-7.41 (± 11.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adolescents (12-18 Years): Change From Baseline in Behaviour Rating Inventory of Executive Function - Self-report (BRIEF-SR) Using the Global Executive Composite Score at Week 26

End point title	Adolescents (12-18 Years): Change From Baseline in Behaviour Rating Inventory of Executive Function - Self-report (BRIEF-SR) Using the Global Executive Composite Score at Week 26

End point description:

The BRIEF-SR is an 86 item measure that assesses impairment in executive function with symptoms rated on a 3-point likert scale of 1 "never", 2 "sometimes" or 3 "often". There are 8 clinical sub-scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) and two validity scales (Inconsistency and Negativity). A Global Executive Composite score is obtained by summing all 8 clinical sub-scales. The Global Executive Composite ranges from 86-258 with higher scores indicating greater impairment in executive functions. The Global Executive Composite gets converted to a T-score with T-scores of 65 or above considered in the clinical range. FAS included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid OLEXA assessment and at least 1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	272			
Units: T score				
arithmetic mean (standard deviation)	-7.50 (± 13.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Children (7-11 Years): Change From Baseline in BRIEF-P Using the Metacognition Index Score at Week 26

End point title	Children (7-11 Years): Change From Baseline in BRIEF-P Using the Metacognition Index Score at Week 26

End point description:

The BRIEF-P is an 86 item measure that assesses impairment in executive function with symptoms rated on a 3-point likert scale of 1 "never", 2 "sometimes" or 3 "often". There are 8 clinical sub-scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) and two validity scales (Inconsistency and Negativity). The Metacognition Index (initiate, working memory, plan/organize, organisation of materials, and monitor) score is the total of 44 items and ranges from 44 to 132 with lower scores reflecting better functioning. FAS included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid OLEXA assessment and at least 1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	217			
Units: T score				
arithmetic mean (standard deviation)	-7.36 (± 11.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adolescents (12-18 Years): Change From Baseline in BRIEF-SR Using the Metacognition Index Score at Week 26

End point title	Adolescents (12-18 Years): Change From Baseline in BRIEF-SR Using the Metacognition Index Score at Week 26

End point description:

The BRIEF-SR is an 86 item measure that assesses impairment in executive function with symptoms rated on a 3-point likert scale of 1 "never", 2 "sometimes" or 3 "often". There are 8 clinical sub-scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) and two validity scales (Inconsistency and Negativity). The Metacognition Index (initiate, working memory, plan/organize, organisation of materials, and monitor) score is the total of 44 items and ranges from 44 to 132 with lower scores reflecting better functioning. FAS included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid OLEXA assessment and at least

1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	272			
Units: T score				
arithmetic mean (standard deviation)	-7.18 (± 13.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children's Global Assessment Scale (CGAS) Score at Week 26

End point title	Change From Baseline in Children's Global Assessment Scale (CGAS) Score at Week 26

End point description:

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 score ranges from 1 (most functionally impaired child) to 100 (the healthiest). A score greater than 70 indicates normal function. FAS included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid OLEXA assessment and at least 1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	506			
Units: units on a scale				
arithmetic mean (standard deviation)	14.78 (± 14.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pediatric Quality of Life Inventory Present Functioning Visual Analogue Scale (PedsQL VAS) Total Score at Week 26

End point title	Change From Baseline in Pediatric Quality of Life Inventory Present Functioning Visual Analogue Scale (PedsQL VAS) Total Score at Week 26

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 VAS. 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 (0-10 points). The participants are asked to mark on the line how they feel. The total score is the average of all 6 items. A lower value represents a better outcome. FAS included all participants who took at least 1 dose of vortioxetine in this study 12712A with valid OLEXA assessment and at least 1 valid post-OLEXA assessment of the CDRS-R total score. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	505			
Units: units on a scale				
arithmetic mean (standard deviation)	-1.50 (± 1.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Response to the Palatability Questionnaire

End point title	Number of Participants With Response to the Palatability Questionnaire

End point description:

The palatability of vortioxetine oral drops was assessed after intake of a single dose (5 to 20 mg) corresponding to the participant's current vortioxetine dose (replacing the vortioxetine tablet on that day). The palatability assessment included 4 questions on the overall appreciation of a medicinal product in relation to its taste (What do you think of the taste), mouthfeel (How does medicine feel in your mouth), aftertaste (What do you think of the after taste), and smell (What do you think of the smell). The items were rated on a 5-point hedonic scale; really bad, bad, neither good or bad, good, or very good. The oral drops were considered acceptable if the mean hedonic scores were ≤3 for each aspect of palatability (taste, aftertaste, smell, and mouthfeel). APTS included all participants who took at least 1 dose of vortioxetine in this study 12712A. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	153			
Units: participants				
Mouthfeel: Really bad	11			
Mouthfeel: Bad	17			
Mouthfeel: Neither good or bad	38			
Mouthfeel: Good	55			
Mouthfeel: Very good	32			
Aftertaste: Really bad	13			
Aftertaste: Bad	26			
Aftertaste: Neither good or bad	54			
Aftertaste: Good	32			
Aftertaste: Very good	28			
Smell: Really bad	4			
Smell: Bad	4			
Smell: Neither good or bad	37			
Smell: Good	59			
Smell: Very good	49			
Taste: Really bad	13			
Taste: Bad	15			
Taste: Neither good or bad	33			
Taste: Good	60			
Taste: Very good	32			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Response to the Acceptability Questionnaire

End point title	Number of Participants With Response to the Acceptability Questionnaire

End point description:

The acceptability of vortioxetine oral drops was assessed after intake of a single dose (5 to 20 mg) corresponding to the participant’s current vortioxetine dose (replacing the vortioxetine tablet on that day). The acceptability assessment was based on 3 items; acceptability of the taste, whether the drops were perceived as easy to take, willingness to take the drops every day (provided it was the only available formulation). For each item the response options were no, not sure, and yes. The oral drops were considered acceptable if <60% of participants responded "no" to each of the 3 questions regarding acceptability. APTS included all participants who took at least 1 dose of vortioxetine in this study 12712A. Here, 'overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Vortioxetine			
Subject group type	Reporting group			
Number of subjects analysed	153			
Units: participants				
Willingness to take the drops every day: No	27			
Willingness to take the drops every day: Not sure	17			
Willingness to take the drops every day: Yes	109			
Easy to take medicine: No	8			
Easy to take medicine: Neither easy or difficult	10			
Easy to take medicine: Yes	135			
Acceptability of the taste: No	31			
Acceptability of the taste: Not sure	24			
Acceptability of the taste: Yes	98			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 30

Adverse event reporting additional description:

APTS included all participants who took at least 1 dose of vortioxetine in this study 12712A.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Vortioxetine

Reporting group description:

Participants initiated treatment with vortioxetine 5 mg/day orally for the first 2 days and thereafter they received 10 mg/day vortioxetine. Based on the response and dose-limiting AEs, vortioxetine dose could be up- or down-titrated with 5 mg/day but the maximum dose did not exceed 20 mg/day. The total duration of treatment was 26 weeks.

Serious adverse events	Vortioxetine		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 662 (2.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	3 / 662 (0.45%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Psychomotor hyperactivity			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Mania			

subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychogenic seizure			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal behaviour			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	4 / 662 (0.60%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	4 / 662 (0.60%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteitis			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Torticollis			
subjects affected / exposed	1 / 662 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Vortioxetine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	255 / 662 (38.52%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	38 / 662 (5.74%)		
occurrences (all)	55		
Headache			
subjects affected / exposed	116 / 662 (17.52%)		
occurrences (all)	198		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	46 / 662 (6.95%)		
occurrences (all)	58		
Nausea			
subjects affected / exposed	138 / 662 (20.85%)		
occurrences (all)	212		
Vomiting			
subjects affected / exposed	69 / 662 (10.42%)		
occurrences (all)	100		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	46 / 662 (6.95%)		
occurrences (all)	61		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2017	Addition of efficacy assessments of the depressive symptoms by using CDRS-R at all study visits, scheduled and unscheduled. Pharmacokinetic (PK) sampling was also added at visits where clinical laboratory samples were collected, in order to evaluate compliance using population PK analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early based on new efficacy data from another study.

Notes: