Clinical trial results:
Interventional, Randomized, Double-blind, Placebo-controlled, Active-reference (Fluoxetine), Fixed-dose Study of Vortioxetine in Paediatric Patients Aged 7 to 11 Years, With Major Depressive Disorder (MDD)

Summary

EudraCT number	2008-005353-38
Trial protocol	LV EE GB HU FI DE IT ES BG PL FR
Global end of trial date	21 January 2022

Results information

Result version number	v2 (current)
This version publication date	14 September 2022
First version publication date	31 July 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	12709A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02709655
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
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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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2022
Global end of trial reached?	Yes
Global end of trial date	21 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to evaluate the efficacy of vortioxetine 10 milligrams (mg)/day and 20 mg/day versus placebo after 8 weeks of treatment on depressive symptoms in children 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	18 May 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: 22
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Colombia: 144
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Latvia: 14
Country: Number of subjects enrolled	Mexico: 109
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Serbia: 26
Country: Number of subjects enrolled	Russian Federation: 93
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United States: 179
Country: Number of subjects enrolled	South Africa: 1
Worldwide total number of subjects	683
EEA total number of subjects	107

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)	683
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study included 2 periods: single-blind (SB) (treatment with standardized brief psychosocial intervention [BPI] and placebo) and double-blind (DB) (treatment with BPI and placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day, or fluoxetine 20 mg/day).

Pre-assignment

Screening details:

Prior to the interim analysis, participants were randomized in a 1:1:1:1 ratio to placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day, or fluoxetine 20 mg/day. After interim analysis, participants were randomized in a 1:1:1 ratio to placebo, vortioxetine 10 mg/day, or vortioxetine 20 mg/day.

Period 1

Period 1 title	Single-Blind Phase (4 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Single-Blind: Placebo

Arm description:

Participants received BPI (3 sessions) and placebo capsules orally once daily for 4 weeks.

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 capsule was administered per schedule specified in the arm description.

Number of subjects in period 1[1]	Single-Blind: Placebo
Started	677
Received at least 1 dose of study drug	677
Completed	540
Not completed	137
Consent withdrawn by subject	15
Failure to meet randomization criteria	85
Adverse event, non-fatal	2
Non-compliance with study drug	3
Other than specified	20
Lost to follow-up	1
Lack of efficacy	8

Protocol deviation	3

Notes:

[1] - 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: A total of 683 participants were enrolled, out of which 6 were not treated.

Period 2

Period 2 title	Double-Blind Phase (8 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind: Placebo

Arm description:

Participants received placebo capsules orally once daily for 8 weeks. Participants received 2 sessions of BPI also.

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 capsule was administered per schedule specified in the arm description.

Arm title	Double-Blind: Vortioxetine 10 mg

Arm description:

Participants initiated treatment with vortioxetine capsules 5 mg/day orally for 2 days and thereafter they received 10 mg/day for up to Week 8. Based on the tolerability, vortioxetine dose could be reduced by 5 mg/day at Week 4. Participants received 2 sessions of BPI also.

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

Dosage and administration details:

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

Arm title	Double-Blind: Vortioxetine 20 mg

Arm description:

Participants initiated treatment with vortioxetine capsules 5 mg/day orally for 2 days followed by 10 mg/day for 2 days and 15 mg/day for 2 days, and thereafter they received vortioxetine 20 mg/day for up to Week 8. Based on the tolerability, vortioxetine dose could be reduced by 5 mg/day at Week 4. Participants received 2 sessions of BPI also.

Arm type	Experimental

Investigational medicinal product name	Vortioxetine
Investigational medicinal product code	
Other name	Brintellix ®, Lu AA21004
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

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

Arm title	Double-Blind: Fluoxetine 20 mg

Arm description:

Participants initiated treatment with fluoxetine 10 mg/day orally for 6 days and thereafter they received 20 mg/day. for up to Week 8. Based on the tolerability, fluoxetine dose could be reduced by 10 mg/day at Week 4. Participants received 2 sessions of BPI also.

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

Dosage and administration details:

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

Number of subjects in period 2	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg
Started	153	151	153
Received at least 1 dose of study drug	153	151	153
Full analysis set (FAS)	153	148	148
Completed	138	135	133
Not completed	15	16	20
Consent withdrawn by subject	4	4	4
Adverse event, non-fatal	1	2	3
Non-compliance with study drug	1	3	6
Other than specified	5	7	5
Lost to follow-up	1	-	2
Lack of efficacy	2	-	-
Protocol deviation	1	-	-

Number of subjects in period 2	Double-Blind: Fluoxetine 20 mg
Started	83
Received at least 1 dose of study drug	83
Full analysis set (FAS)	81
Completed	78
Not completed	5
Consent withdrawn by subject	1
Adverse event, non-fatal	-

Non-compliance with study drug	1
Other than specified	2
Lost to follow-up	-
Lack of efficacy	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Single-Blind: Placebo
Reporting group description:	
Participants received BPI (3 sessions) and placebo capsules orally once daily for 4 weeks.	

Reporting group values	Single-Blind: Placebo	Total	
Number of subjects	677	677	
Age categorical Units: Subjects			
Children (2-11 years)	677	677	
Age Continuous Units: years			
arithmetic mean	9.3		
standard deviation	± 1.42	-	
Sex: Female, Male Units: participants			
Female	312	312	
Male	365	365	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	2	2	
Black or African American	112	112	
Not Reported	12	12	
Other	229	229	
White	321	321	
Children Depression Rating Scale - Revised (CDRS-R) Total Score			
The CDRS-R was rated by a clinician following interviews with the child and parent and 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. The total score ranged from 17 (normal) to 113 (severe depression).			
Units: units on a scale			
arithmetic mean	63.4		
standard deviation	± 9.12	-	

End points

End points reporting groups

Reporting group title	Single-Blind: Placebo
Reporting group description:	
Participants received BPI (3 sessions) and placebo capsules orally once daily for 4 weeks.	
Reporting group title	Double-Blind: Placebo
Reporting group description:	
Participants received placebo capsules orally once daily for 8 weeks. Participants received 2 sessions of BPI also.	
Reporting group title	Double-Blind: Vortioxetine 10 mg
Reporting group description:	
Participants initiated treatment with vortioxetine capsules 5 mg/day orally for 2 days and thereafter they received 10 mg/day for up to Week 8. Based on the tolerability, vortioxetine dose could be reduced by 5 mg/day at Week 4. Participants received 2 sessions of BPI also.	
Reporting group title	Double-Blind: Vortioxetine 20 mg
Reporting group description:	
Participants initiated treatment with vortioxetine capsules 5 mg/day orally for 2 days followed by 10 mg/day for 2 days and 15 mg/day for 2 days, and thereafter they received vortioxetine 20 mg/day for up to Week 8. Based on the tolerability, vortioxetine dose could be reduced by 5 mg/day at Week 4. Participants received 2 sessions of BPI also.	
Reporting group title	Double-Blind: Fluoxetine 20 mg
Reporting group description:	
Participants initiated treatment with fluoxetine 10 mg/day orally for 6 days and thereafter they received 20 mg/day. for up to Week 8. Based on the tolerability, fluoxetine dose could be reduced by 10 mg/day at Week 4. Participants received 2 sessions of BPI also.	
Subject analysis set title	Vortioxetine Average (Avg. VOR)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Avg. VOR is the average dose effect of the 2 vortioxetine doses (Vortioxetine 10 mg and Vortioxetine 20 mg).	

Primary: Change From Baseline in Children Depression Rating Scale - Revised (CDRS-R) Total Score at Week 8 of Phase B

End point title	Change From Baseline in Children Depression Rating Scale - Revised (CDRS-R) Total Score at Week 8 of Phase B
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 estimated using a restricted maximum likelihood (REML)-based Mixed Model Repeated Measurements (MMRM) approach. Full analysis set (FAS) included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of CDRS-R total score. Overall number of participants analyzed = participants evaluated for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline (Week 4 of Phase A), Week 8 of Phase B	

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	132	134	78
Units: units on a scale				
least squares mean (standard error)	-17.48 (± 1.35)	-19.20 (± 1.37)	-19.94 (± 1.37)	-20.78 (± 1.60)

End point values	Vortioxetine Average (Avg. VOR)			
Subject group type	Subject analysis set			
Number of subjects analysed	266			
Units: units on a scale				
least squares mean (standard error)	-19.57 (± 1.16)			

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using an REML-based MMRM approach with freely varying mean and covariance structure and with country, treatment (vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine, and placebo), and Week as fixed factors and Baseline CDRS-R total score as a continuous covariate, the treatment-by-week interaction, and Baseline CDRS-R-by-Week interaction.

Comparison groups	Double-Blind: Placebo v Vortioxetine Average (Avg. VOR)
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0937
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.54
upper limit	0.36
Variability estimate	Standard error of the mean
Dispersion value	1.24

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using an REML-based MMRM approach with freely varying mean and covariance structure and with country, treatment (vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine, and placebo), and Week as fixed factors and Baseline CDRS-R total score as a continuous covariate, the treatment-by-week interaction, and Baseline CDRS-R-by-Week interaction.

Comparison groups	Double-Blind: Placebo v Double-Blind: Vortioxetine 10 mg
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2336
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.56
upper limit	1.11
Variability estimate	Standard error of the mean
Dispersion value	1.44

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis was performed using an REML-based MMRM approach with freely varying mean and covariance structure and with country, treatment (vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine, and placebo), and Week as fixed factors and Baseline CDRS-R total score as a continuous covariate, the treatment-by-week interaction, and Baseline CDRS-R-by-Week interaction.

Comparison groups	Double-Blind: Placebo v Double-Blind: Vortioxetine 20 mg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0879
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.29
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	1.44

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Analysis was performed using an REML-based MMRM approach with freely varying mean and covariance structure and with country, treatment (vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine, and placebo), and Week as fixed factors and Baseline CDRS-R total score as a continuous covariate, the treatment-by-week interaction, and Baseline CDRS-R-by-Week interaction.

Comparison groups	Double-Blind: Placebo v Double-Blind: Fluoxetine 20 mg

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0531
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.65
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	1.7

Secondary: Change From Baseline in CDRS-R Total Score at Weeks 2, 4, and 6 of Phase B

End point title	Change From Baseline in CDRS-R Total Score at Weeks 2, 4, and 6 of Phase B

End point description:

The CDRS-R was rated by a clinician following interviews with the child and parent and 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. The total score ranged from 17 (normal) to 113 (severe depression). FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this endpoint. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 2, 4, and 6 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	153	147	146	80
Units: units on a scale				
least squares mean (standard error)				
Change at Week 2 (n=153,147,146,80)	-9.20 (± 1.17)	-9.54 (± 1.18)	-10.30 (± 1.19)	-10.17 (± 1.32)
Change at Week 4 (n=145,137,139,78)	-13.15 (± 1.28)	-14.56 (± 1.30)	-15.62 (± 1.30)	-13.97 (± 1.50)
Change at Week 6 (n=143,136,137,78)	-16.00 (± 1.32)	-17.64 (± 1.34)	-18.28 (± 1.34)	-17.75 (± 1.56)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CDRS-R Subscores (Mood, Somatic, Subjective, and Behaviour) at Weeks 2, 4, 6, and 8 of Phase B

End point title	Change From Baseline in CDRS-R Subscores (Mood, Somatic, Subjective, and Behaviour) at Weeks 2, 4, 6, and 8 of Phase B

End point description:

CDRS-R consisted of 17 items. 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. Four subscores were defined based on the CDRS-R: Mood: sum of items 8, 11, 14, 15; score range 4 to 28, Somatic: sum of items 4, 5, 6, 7, 16, 17; score range 6 to 36, Subjective: sum of items 9, 10, 12, 13; score range 4 to 28, and Behaviour: sum of items 1, 2, 3; score range 3 to 21. Higher scores indicated the most severe measure of depression. FAS: all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of CDRS-R total score. Overall number of participants analyzed = participants evaluated for this endpoint. n = participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 2, 4, 6, and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	153	147	146	80
Units: units on a scale				
least squares mean (standard error)				
Mood Score: Change at Week 2 (n=153,147,146,80)	-2.82 (± 0.40)	-3.10 (± 0.40)	-3.47 (± 0.40)	-3.02 (± 0.45)
Mood Score: Change at Week 4 (n=145,137,139,78)	-3.69 (± 0.42)	-4.39 (± 0.43)	-4.77 (± 0.43)	-3.73 (± 0.49)
Mood Score: Change at Week 6 (n=143,136,137,78)	-4.67 (± 0.43)	-5.39 (± 0.44)	-5.52 (± 0.44)	-4.97 (± 0.51)
Mood Score: Change at Week 8 (n=136,132,134,78)	-5.08 (± 0.44)	-5.64 (± 0.44)	-5.95 (± 0.45)	-5.84 (± 0.51)
Somatic Score: Change at Week 2 (n=153,147,146,80)	-2.81 (± 0.44)	-2.61 (± 0.44)	-2.88 (± 0.44)	-3.02 (± 0.50)
Somatic Score: Change at Week 4 (n=145,137,139,78)	-4.08 (± 0.47)	-4.30 (± 0.48)	-4.70 (± 0.48)	-4.26 (± 0.56)
Somatic Score: Change at Week 6 (n=143,136,137,78)	-4.86 (± 0.48)	-5.53 (± 0.49)	-5.33 (± 0.49)	-5.57 (± 0.57)
Somatic Score: Change at Week 8 (n=136,132,134,78)	-5.38 (± 0.49)	-6.15 (± 0.50)	-6.08 (± 0.50)	-6.44 (± 0.57)
Subjective Score:Change at Week 2(n=153,147,146,80	-1.44 (± 0.22)	-1.46 (± 0.22)	-1.43 (± 0.22)	-1.56 (± 0.25)
Subjective Score:Change at Week 4(n=145,137,139,78	-2.04 (± 0.23)	-2.12 (± 0.23)	-2.20 (± 0.23)	-2.17 (± 0.27)
Subjective Score:Change at Week 6(n=143,136,137,78	-2.43 (± 0.24)	-2.42 (± 0.24)	-2.65 (± 0.24)	-2.38 (± 0.28)
Subjective Score:Change at Week 8(n=136,132,134,78	-2.56 (± 0.24)	-2.59 (± 0.24)	-2.84 (± 0.24)	-2.65 (± 0.28)
Behaviour Score:Change at Week 2(n=153,147,146,80)	-2.16 (± 0.34)	-2.40 (± 0.34)	-2.56 (± 0.35)	-2.61 (± 0.39)

Behaviour Score:Change at Week 4(n=145,137,139,78)	-3.39 (± 0.38)	-3.77 (± 0.39)	-4.00 (± 0.39)	-3.80 (± 0.45)
Behaviour Score:Change at Week 6(n=143,136,137,78)	-4.09 (± 0.39)	-4.31 (± 0.39)	-4.83 (± 0.40)	-4.80 (± 0.46)
Behaviour Score:Change at Week 8(n=136,132,134,78)	-4.47 (± 0.40)	-4.80 (± 0.41)	-5.09 (± 0.41)	-5.83 (± 0.48)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With CDRS-R Response

End point title	Percentage of Participants With CDRS-R Response

End point description:

CDRS-R response was defined as a ≥50% decrease in CDRS-R total score, calculated as: (change from baseline [Randomization])/(baseline value – 17). The CDRS-R consisted of 17 items out of which 3 items rated nonverbal observations. 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. The total score ranged from 17 (normal) to 113 (severe depression). FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 6, and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	153	147	146	80
Units: percentage of participants				
number (not applicable)				
Week 2 (n = 153, 147, 146, 80)	7.8	10.2	11.6	16.3
Week 4 (n = 145, 137, 139, 78)	20.7	23.4	26.6	26.9
Week 6 (n = 143, 136, 137, 78)	30.8	31.6	37.2	33.3
Week 8 (n = 136, 132, 134, 78)	29.4	36.4	41.0	47.4

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With CDRS-R Remission

End point title	Percentage of Participants With CDRS-R Remission

End point description:

CDRS-R remission was defined as a CDRS-R total score ≤28. The CDRS-R consisted of 17 items out of

which 3 items rated nonverbal observations. 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. The total score ranged from 17 (normal) to 113 (severe depression). FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 6, and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	153	147	146	80
Units: percentage of participants				
number (not applicable)				
Week 2 (n = 153, 147, 146, 80)	2.0	5.4	2.7	3.8
Week 4 (n = 145, 137, 139, 78)	9.0	9.5	10.1	9.0
Week 6 (n = 143, 136, 137, 78)	14.7	15.4	15.3	14.1
Week 8 (n = 136, 132, 134, 78)	14.7	16.7	20.1	26.9

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in General Behaviour Inventory (GBI) Depression Subscale Score, Using the 10-Item Depression Subscale Assessed by Parent (PGBI-10D) and Child (CGBI-10D) at Weeks 2, 4, 6, and 8 of Phase B

End point title	Change From Baseline in General Behaviour Inventory (GBI) Depression Subscale Score, Using the 10-Item Depression Subscale Assessed by Parent (PGBI-10D) and Child (CGBI-10D) at Weeks 2, 4, 6, and 8 of Phase B

End point description:

The GBI 10-item depression scale was developed to screen for depressive symptoms in children and adolescents. Two versions of the GBI 10-item depression scale were used, the child rated version (CGBI) and the parent rated version (PGBI). The 10 depression items were rated on a 4-point scale from 0 (never or hardly ever) to 3 (very often or almost constantly). The total score ranged from 0 to 30, with higher scores indicating greater pathology. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 2, 4, 6, and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	147	146	80
Units: units on a scale				
least squares mean (standard error)				
PGBI: Change at Week 2 (n=152,147,146,80)	-3.33 (± 0.55)	-3.38 (± 0.55)	-3.78 (± 0.56)	-3.78 (± 0.63)
PGBI: Change at Week 4 (n=143,137,137,78)	-4.11 (± 0.58)	-4.72 (± 0.59)	-5.33 (± 0.59)	-4.45 (± 0.68)
PGBI: Change at Week 6 (n=142,136,137,78)	-5.32 (± 0.58)	-5.58 (± 0.59)	-5.82 (± 0.59)	-6.05 (± 0.68)
PGBI: Change at Week 8 (n=136,132,134,78)	-5.81 (± 0.61)	-6.51 (± 0.62)	-6.46 (± 0.62)	-6.56 (± 0.72)
CGBI: Change at Week 2 (n=149,145,143,76)	-2.66 (± 0.61)	-3.32 (± 0.61)	-3.27 (± 0.61)	-2.94 (± 0.70)
CGBI: Change at Week 4 (n=141,136,134,75)	-3.65 (± 0.65)	-4.15 (± 0.65)	-4.16 (± 0.65)	-3.16 (± 0.76)
CGBI: Change at Week 6 (n=139,134,135,75)	-4.62 (± 0.63)	-5.43 (± 0.64)	-5.17 (± 0.63)	-5.14 (± 0.73)
CGBI: Change at Week 8 (n=134,131,132,75)	-5.26 (± 0.65)	-6.12 (± 0.66)	-5.48 (± 0.65)	-5.46 (± 0.76)

Statistical analyses

No statistical analyses for this end point

Secondary: Parent Global Assessment (PGA) Score

End point title	Parent Global Assessment (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 symptoms using a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 6, and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	152	147	145	80
Units: units on a scale				
least squares mean (standard error)				
Week 2 (n = 152, 147, 145, 80)	3.31 (± 0.09)	3.25 (± 0.09)	3.18 (± 0.09)	3.13 (± 0.11)
Week 4 (n = 143, 137, 136, 78)	2.97 (± 0.10)	2.90 (± 0.10)	2.84 (± 0.10)	2.90 (± 0.12)
Week 6 (n = 142, 136, 136, 78)	2.73 (± 0.10)	2.73 (± 0.10)	2.68 (± 0.10)	2.80 (± 0.12)

Week 8 (n = 136, 132, 133, 78)	2.68 (± 0.11)	2.62 (± 0.11)	2.61 (± 0.11)	2.59 (± 0.13)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression - Severity of Illness (CGI-S) Score at Weeks 1, 2, 3, 4, 6, and 8 of Phase B

End point title	Change From Baseline in Clinical Global Impression - Severity of Illness (CGI-S) Score at Weeks 1, 2, 3, 4, 6, and 8 of Phase B

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). FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 1, 2, 3, 4, 6, and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	153	148	146	81
Units: units on a scale				
least squares mean (standard error)				
Change at Week 1 (n=153,148,146,81)	-0.25 (± 0.07)	-0.27 (± 0.07)	-0.28 (± 0.07)	-0.22 (± 0.08)
Change at Week 2 (n=153,146,144,81)	-0.50 (± 0.08)	-0.60 (± 0.08)	-0.65 (± 0.08)	-0.63 (± 0.10)
Change at Week 3 (n=150,145,145,78)	-0.67 (± 0.08)	-0.62 (± 0.08)	-0.79 (± 0.08)	-0.77 (± 0.10)
Change at Week 4 (n=145,137,139,78)	-0.95 (± 0.09)	-1.00 (± 0.09)	-1.06 (± 0.09)	-1.01 (± 0.12)
Change at Week 6 (n=143,136,137,78)	-1.13 (± 0.10)	-1.22 (± 0.10)	-1.27 (± 0.10)	-1.23 (± 0.12)
Change at Week 8 (n=137,132,134,78)	-1.31 (± 0.10)	-1.40 (± 0.11)	-1.44 (± 0.11)	-1.57 (± 0.13)

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). FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 6, and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	153	148	145	81
Units: units on a scale				
least squares mean (standard error)				
Week 1 (n = 153, 148, 145, 81)	3.66 (± 0.07)	3.63 (± 0.07)	3.60 (± 0.07)	3.72 (± 0.08)
Week 2 (n = 153, 146, 143, 81)	3.32 (± 0.08)	3.30 (± 0.08)	3.19 (± 0.08)	3.26 (± 0.10)
Week 3 (n = 150, 145, 144, 78)	3.20 (± 0.08)	3.20 (± 0.08)	3.14 (± 0.08)	3.23 (± 0.10)
Week 4 (n = 145, 137, 138, 78)	2.93 (± 0.09)	2.93 (± 0.09)	2.82 (± 0.09)	2.97 (± 0.11)
Week 6 (n = 143, 136, 136, 78)	2.70 (± 0.09)	2.64 (± 0.10)	2.65 (± 0.10)	2.78 (± 0.12)
Week 8 (n = 137, 132, 133, 78)	2.69 (± 0.10)	2.58 (± 0.08)	2.60 (± 0.10)	2.57 (± 0.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With CGI-S Remission

End point title	Percentage of Participants With CGI-S Remission

End point description:

CGI-S remission was defined as a CGI-S score of 1 or 2. 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). FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 6, and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	153	148	148	81
Units: percentage of participants				
number (not applicable)				
Week 1 (n = 153, 148, 146, 81)	0	0.7	0	0
Week 2 (n = 153, 148, 147, 81)	0.7	3.4	1.4	3.7
Week 3 (n = 153, 148, 148, 81)	3.3	4.1	4.7	7.4
Week 4 (n = 153, 148, 148, 81)	8.5	8.1	12.8	12.3
Week 6 (n = 153, 148, 148, 81)	14.4	16.2	16.2	14.8
Week 8 (n = 153, 148, 148, 81)	22.9	22.3	20.9	29.6

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children's Global Assessment Scale (CGAS) Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in Children's Global Assessment Scale (CGAS) Score at Weeks 4 and 8 of Phase B

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 randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	146	139	142	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=146,139,142,79)	8.93 (± 1.23)	9.84 (± 1.25)	8.73 (± 1.26)	10.54 (± 1.39)
Change at Week 8 (n=136,132,134,78)	12.71 (± 1.31)	12.98 (± 1.33)	13.22 (± 1.34)	16.35 (± 1.51)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pediatric Quality of Life Inventory (PedsQL) Visual Analogue Scales (VAS): Afraid or Scared (Anxiety) Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in Pediatric Quality of Life Inventory (PedsQL) Visual Analogue Scales (VAS): Afraid or Scared (Anxiety) Score at Weeks 4 and 8 of Phase B

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 (0-10 points). The participants are asked to mark on the line how they feel. A lower value represents a better outcome. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	141	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,141,79)	-0.48 (± 0.27)	-0.51 (± 0.27)	-0.48 (± 0.27)	-0.41 (± 0.31)
Change at Week 8 (n=136,130,134,78)	-0.73 (± 0.26)	-1.07 (± 0.27)	-1.01 (± 0.27)	-1.08 (± 0.29)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL VAS: Sad or Blue (Sadness) Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in PedsQL VAS: Sad or Blue (Sadness) Score at Weeks 4 and 8 of Phase B

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 (0-10 points). The participants are asked to mark on the line how they feel. A lower value represents a better outcome. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	141	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,141,79)	-1.20 (± 0.31)	-1.65 (± 0.31)	-1.78 (± 0.31)	-1.42 (± 0.35)
Change at Week 8 (n=136,130,134,78)	-1.72 (± 0.32)	-2.23 (± 0.32)	-2.05 (± 0.32)	-2.31 (± 0.36)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL VAS: Angry Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in PedsQL VAS: Angry Score at Weeks 4 and 8 of Phase B

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 (0-10 points). The participants are asked to mark on the line how they feel. A lower value represents a better outcome. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	144	139	140	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=144,139,140,79)	-0.98 (± 0.30)	-1.36 (± 0.31)	-1.33 (± 0.31)	-1.22 (± 0.35)
Change at Week 8 (n=136,130,133,78)	-1.24 (± 0.31)	-1.98 (± 0.32)	-1.36 (± 0.32)	-1.67 (± 0.36)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL VAS: Worry Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in PedsQL VAS: Worry Score at Weeks 4 and 8 of Phase B

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 (0-10 points). The participants are asked to mark on the line how they feel. A lower value represents a better outcome. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	141	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,141,79)	-0.63 (± 0.31)	-1.48 (± 0.32)	-1.21 (± 0.32)	-1.27 (± 0.36)
Change at Week 8 (n=136,130,134,78)	-1.08 (± 0.32)	-1.82 (± 0.33)	-1.45 (± 0.33)	-1.41 (± 0.36)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL VAS: Tired (Fatigue) Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in PedsQL VAS: Tired (Fatigue) Score at Weeks 4 and 8 of Phase B

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 (0-10 points). The participants are asked to mark on the line how they feel. A lower value represents a better outcome. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	141	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,141,79)	-1.22 (± 0.34)	-1.19 (± 0.35)	-1.63 (± 0.35)	-0.94 (± 0.39)
Change at Week 8 (n=136,130,134,78)	-1.39 (± 0.36)	-1.32 (± 0.37)	-1.74 (± 0.37)	-1.73 (± 0.41)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL VAS: Pain or Hurt Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in PedsQL VAS: Pain or Hurt Score at Weeks 4 and 8 of Phase B

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 (0-10 points). The participants are asked to mark on the line how they feel. A lower value represents a better outcome. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	141	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,141,79)	-0.22 (± 0.28)	-0.81 (± 0.28)	-0.45 (± 0.28)	-0.50 (± 0.32)
Change at Week 8 (n=136,130,134,78)	-0.70 (± 0.28)	-0.79 (± 0.28)	-1.02 (± 0.28)	-0.69 (± 0.32)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL VAS Total Average Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in PedsQL VAS Total Average Score at Weeks 4 and 8 of Phase B

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 (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 randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	141	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,141,79)	-0.81 (± 0.19)	-1.19 (± 0.19)	-1.17 (± 0.20)	-1.01 (± 0.22)
Change at Week 8 (n=136,130,134,78)	-1.17 (± 0.20)	-1.55 (± 0.20)	-1.47 (± 0.20)	-1.54 (± 0.23)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL Emotional Distress Summary Average Score at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in PedsQL Emotional Distress Summary Average Score at Weeks 4 and 8 of Phase B

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 (0-10 points). The participants are asked to mark on the line how they feel. The average emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items. A lower value represents a better outcome. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	141	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,141,79)	-0.84 (± 0.21)	-1.28 (± 0.21)	-1.22 (± 0.22)	-1.13 (± 0.24)
Change at Week 8 (n=136,130,134,78)	-1.22 (± 0.22)	-1.80 (± 0.22)	-1.51 (± 0.22)	-1.66 (± 0.25)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) Total Score (Items 1 to 14) at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) Total Score (Items 1 to 14) at Weeks 4 and 8 of Phase B

End point description:

The PQ-LES-Q is a patient-rated scale designed to assess satisfaction with life. The PQ-LES-Q consist of 15 items, item 1 to 14 assess the degree of satisfaction experienced by participants in various areas of daily functioning, and item 15 allows subjects to summarise 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 to 14 is 14 to 70, with higher scores indicating greater satisfaction. FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	140	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,140,79)	3.94 (± 0.95)	4.90 (± 0.96)	4.90 (± 0.97)	4.36 (± 1.09)
Change at Week 8 (n=136,132,134,78)	6.22 (± 0.98)	7.08 (± 0.99)	7.14 (± 1.00)	6.79 (± 1.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PQ-LES-Q Overall Evaluation Score (Item 15) at Weeks 4 and 8 of Phase B

End point title	Change From Baseline in PQ-LES-Q Overall Evaluation Score (Item 15) at Weeks 4 and 8 of Phase B

End point description:

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, which is used to measure quality of life in adults. The PQ-LES-Q consist of 15 items, item 1 to 14 assess the degree of satisfaction experienced by participants in various areas of daily functioning, and item 15 allows subjects to summarize their experience in a global rating. Item 15 is rated on a 5-point scale from 1 (very poor) to 5 (very good). FAS included all participants randomized to the DB, 8-week treatment period (Phase B) who took at least 1 dose of DB study drug and who had a valid baseline (Week 4 of Phase A) assessment and at least 1 valid post-baseline assessment of the CDRS-R total score. Overall number of participants analyzed = participants evaluated for this outcome measure. n = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Week 4 of Phase A), Weeks 4 and 8 of Phase B

End point values	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	145	139	140	79
Units: units on a scale				
least squares mean (standard error)				
Change at Week 4 (n=145,139,140,79)	0.28 (± 0.09)	0.37 (± 0.09)	0.43 (± 0.09)	0.24 (± 0.11)
Change at Week 8 (n=136,132,134,78)	0.41 (± 0.09)	0.49 (± 0.09)	0.52 (± 0.09)	0.45 (± 0.11)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 16

Adverse event reporting additional description:

All-patients-treated set Phase A (APTS_A) included all participants enrolled to the 4-week Single-blind period (Phase A) who received at least 1 dose of study drug. All-patients-treated set Phase B (APTS) included all participants randomized to the double-blind, 8-week treatment period (Phase B) who took at least 1 dose of double-blind study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Single-Blind: Placebo

Reporting group description:

Participants received BPI (3 sessions) and placebo capsules orally once daily for 4 weeks.

Reporting group title	Double-Blind: Placebo

Reporting group description:

Participants received placebo capsules orally once daily for 8 weeks. Participants received 2 sessions of BPI also.

Reporting group title	Double-Blind: Vortioxetine 10 mg

Reporting group description:

Participants initiated treatment with vortioxetine capsules 5 mg/day orally for 2 days and thereafter they received 10 mg/day for up to Week 8. Based on the tolerability, vortioxetine dose could be reduced by 5 mg/day at Week 4. Participants received 2 sessions of BPI also.

Reporting group title	Double-Blind: Vortioxetine 20 mg

Reporting group description:

Participants initiated treatment with vortioxetine capsules 5 mg/day orally for 2 days followed by 10 mg/day for 2 days and 15 mg/day for 2 days, and thereafter they received vortioxetine 20 mg/day for up to Week 8. Based on the tolerability, vortioxetine dose could be reduced by 5 mg/day at Week 4. Participants received 2 sessions of BPI also.

Reporting group title	Double-Blind: Fluoxetine 20 mg

Reporting group description:

Participants initiated treatment with fluoxetine 10 mg/day orally for 6 days and thereafter they received 20 mg/day. for up to Week 8. Based on the tolerability, fluoxetine dose could be reduced by 10 mg/day at Week 4. Participants received 2 sessions of BPI also.

Serious adverse events	Single-Blind: Placebo	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 677 (0.89%)	3 / 153 (1.96%)	1 / 151 (0.66%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Intentional overdose			

subjects affected / exposed	1 / 677 (0.15%)	0 / 153 (0.00%)	0 / 151 (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
Forearm fracture			
subjects affected / exposed	0 / 677 (0.00%)	0 / 153 (0.00%)	0 / 151 (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
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 677 (0.15%)	0 / 153 (0.00%)	0 / 151 (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			
Suicide attempt			
subjects affected / exposed	1 / 677 (0.15%)	1 / 153 (0.65%)	0 / 151 (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
Intentional self-injury			
subjects affected / exposed	1 / 677 (0.15%)	0 / 153 (0.00%)	0 / 151 (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	1 / 677 (0.15%)	0 / 153 (0.00%)	0 / 151 (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
Major depression			
subjects affected / exposed	0 / 677 (0.00%)	0 / 153 (0.00%)	0 / 151 (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
Mania			
subjects affected / exposed	0 / 677 (0.00%)	0 / 153 (0.00%)	0 / 151 (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
Infections and infestations			

Gastroenteritis			
subjects affected / exposed	1 / 677 (0.15%)	0 / 153 (0.00%)	0 / 151 (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
Viral pharyngitis			
subjects affected / exposed	1 / 677 (0.15%)	0 / 153 (0.00%)	0 / 151 (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
Cellulitis			
subjects affected / exposed	0 / 677 (0.00%)	1 / 153 (0.65%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 677 (0.00%)	1 / 153 (0.65%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed	0 / 677 (0.00%)	0 / 153 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 153 (1.31%)	1 / 83 (1.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			

subjects affected / exposed	0 / 153 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional self-injury			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (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	0 / 153 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 153 (0.65%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 153 (0.65%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Viral pharyngitis			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 153 (0.00%)	0 / 83 (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: 2 %

Non-serious adverse events	Single-Blind: Placebo	Double-Blind: Placebo	Double-Blind: Vortioxetine 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 677 (15.66%)	45 / 153 (29.41%)	55 / 151 (36.42%)
Investigations			
Weight decreased			
subjects affected / exposed	1 / 677 (0.15%)	0 / 153 (0.00%)	0 / 151 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 677 (0.15%)	4 / 153 (2.61%)	1 / 151 (0.66%)
occurrences (all)	1	4	1
Nervous system disorders			
Headache			
subjects affected / exposed	39 / 677 (5.76%)	17 / 153 (11.11%)	14 / 151 (9.27%)
occurrences (all)	54	23	19
Dizziness			

subjects affected / exposed	9 / 677 (1.33%)	5 / 153 (3.27%)	7 / 151 (4.64%)
occurrences (all)	10	5	7
General disorders and administration site conditions			
Illness			
subjects affected / exposed	0 / 677 (0.00%)	0 / 153 (0.00%)	0 / 151 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	15 / 677 (2.22%)	4 / 153 (2.61%)	4 / 151 (2.65%)
occurrences (all)	16	4	6
Nausea			
subjects affected / exposed	23 / 677 (3.40%)	7 / 153 (4.58%)	19 / 151 (12.58%)
occurrences (all)	23	7	22
Abdominal pain			
subjects affected / exposed	9 / 677 (1.33%)	2 / 153 (1.31%)	9 / 151 (5.96%)
occurrences (all)	9	2	11
Diarrhoea			
subjects affected / exposed	9 / 677 (1.33%)	4 / 153 (2.61%)	5 / 151 (3.31%)
occurrences (all)	9	5	5
Dry mouth			
subjects affected / exposed	5 / 677 (0.74%)	4 / 153 (2.61%)	4 / 151 (2.65%)
occurrences (all)	5	4	4
Vomiting			
subjects affected / exposed	13 / 677 (1.92%)	3 / 153 (1.96%)	14 / 151 (9.27%)
occurrences (all)	13	3	20
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 677 (0.30%)	0 / 153 (0.00%)	1 / 151 (0.66%)
occurrences (all)	2	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 677 (1.92%)	5 / 153 (3.27%)	6 / 151 (3.97%)
occurrences (all)	13	8	8
Viral infection			
subjects affected / exposed	3 / 677 (0.44%)	0 / 153 (0.00%)	1 / 151 (0.66%)
occurrences (all)	3	0	1

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 677 (0.00%)	2 / 153 (1.31%)	1 / 151 (0.66%)
occurrences (all)	0	2	2

Non-serious adverse events	Double-Blind: Vortioxetine 20 mg	Double-Blind: Fluoxetine 20 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 153 (27.45%)	27 / 83 (32.53%)	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 153 (0.65%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Weight increased			
subjects affected / exposed	3 / 153 (1.96%)	2 / 83 (2.41%)	
occurrences (all)	3	2	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 153 (9.15%)	4 / 83 (4.82%)	
occurrences (all)	16	5	
Dizziness			
subjects affected / exposed	5 / 153 (3.27%)	3 / 83 (3.61%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Illness			
subjects affected / exposed	5 / 153 (3.27%)	0 / 83 (0.00%)	
occurrences (all)	8	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 153 (1.96%)	3 / 83 (3.61%)	
occurrences (all)	4	3	
Nausea			
subjects affected / exposed	17 / 153 (11.11%)	5 / 83 (6.02%)	
occurrences (all)	25	6	
Abdominal pain			
subjects affected / exposed	6 / 153 (3.92%)	2 / 83 (2.41%)	
occurrences (all)	8	2	
Diarrhoea			

subjects affected / exposed	1 / 153 (0.65%)	3 / 83 (3.61%)	
occurrences (all)	1	6	
Dry mouth			
subjects affected / exposed	1 / 153 (0.65%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	10 / 153 (6.54%)	3 / 83 (3.61%)	
occurrences (all)	16	3	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 153 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 153 (2.61%)	3 / 83 (3.61%)	
occurrences (all)	4	3	
Viral infection			
subjects affected / exposed	0 / 153 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 153 (1.31%)	3 / 83 (3.61%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2018	Due to recruitment difficulties modified the study design to include an interim analysis to potentially stop the study early for either efficacy or futility. The interim analysis was performed when at least 240 randomized participants had either completed or been withdrawn from the study. If it was planned to continue the study after the interim analysis, the study would include only 3 arms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported