



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 | v1 |
| This version publication date | 31 July 2022 |
| First version publication date | 31 July 2022 |

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 |
| 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) | EMA-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 | Spain: 12 |
| Country: Number of subjects enrolled | Estonia: 8 |
| 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 (\pm 1.35) | -19.20 (\pm 1.37) | -19.94 (\pm 1.37) | -20.78 (\pm 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 (\pm 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 $\geq 50\%$ 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: | |
| <p>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.</p> | |
| 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 | |
|-------------------------------------|-----------------------|----------------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 153 | 148 | 146 | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Change at Week 1 (n=153,148,146) | -0.22 (± 0.06) | -0.24 (± 0.07) | -0.25 (± 0.07) | |
| Change at Week 2 (n=153,146,144) | -0.47 (± 0.08) | -0.57 (± 0.08) | -0.62 (± 0.08) | |
| Change at Week 3 (n=150,145,145) | -0.64 (± 0.08) | -0.59 (± 0.08) | -0.75 (± 0.08) | |
| Change at Week 4 (n=145,137,139) | -0.92 (± 0.09) | -0.97 (± 0.09) | -1.03 (± 0.09) | |
| Change at Week 6 (n=143,136,137) | -1.10 (± 0.10) | -1.19 (± 0.10) | -1.23 (± 0.10) | |
| Change at Week 8 (n=137,132,134) | -1.28 (± 0.10) | -1.37 (± 0.10) | -1.40 (± 0.10) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression - Global Improvement (CGI-I) Score

| | |
|-----------------|---|
| End point title | Clinical Global Impression - Global Improvement (CGI-I) Score |
|-----------------|---|

End point description:

The CGI-I provides the clinician's impression of the 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

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: | |
| <p>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.</p> | |
| 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: | |
| <p>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.</p> | |
| 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: 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.

| | |
|-----------------------|----------------------------------|
| 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: 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.

| Serious adverse events | Single-Blind: Placebo | Double-Blind: Placebo | Double-Blind: Fluoxetine 20 mg |
|---|--------------------------|--------------------------|-----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 677 (0.89%) | 3 / 153 (1.96%) | 1 / 83 (1.20%) |
| 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 / 83 (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%) | 1 / 83 (1.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 / 83 (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 / 83 (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 / 83 (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 / 83 (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 / 83 (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 / 83 (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 / 83 (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 / 83 (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 / 83 (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 / 83 (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%) | 0 / 83 (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 |

| Serious adverse events | Double-Blind: Vortioxetine 20 mg | Double-Blind: Vortioxetine 10 mg | |
|---|-------------------------------------|-------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 153 (1.31%) | 1 / 151 (0.66%) | |
| 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 / 151 (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%) | 0 / 151 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 153 (0.00%) | 0 / 151 (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 / 151 (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 / 151 (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 / 151 (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 / 151 (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 / 151 (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 / 151 (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 / 151 (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 / 151 (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 / 151 (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%) | 1 / 151 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| 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: Fluoxetine 20 mg |
|---|--------------------------|--------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 106 / 677 (15.66%) | 45 / 153 (29.41%) | 27 / 83 (32.53%) |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 677 (0.15%) | 0 / 153 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 0 | 2 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 677 (0.15%) | 4 / 153 (2.61%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 4 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 39 / 677 (5.76%) | 17 / 153 (11.11%) | 4 / 83 (4.82%) |
| occurrences (all) | 54 | 23 | 5 |
| Dizziness | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 9 / 677 (1.33%) 10 | 5 / 153 (3.27%) 5 | 3 / 83 (3.61%) 4 |
| General disorders and administration site conditions Illness subjects affected / exposed occurrences (all) | 0 / 677 (0.00%) 0 | 0 / 153 (0.00%) 0 | 0 / 83 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 15 / 677 (2.22%) 16 23 / 677 (3.40%) 23 9 / 677 (1.33%) 9 9 / 677 (1.33%) 9 5 / 677 (0.74%) 5 13 / 677 (1.92%) 13 | 4 / 153 (2.61%) 4 7 / 153 (4.58%) 7 2 / 153 (1.31%) 2 4 / 153 (2.61%) 5 4 / 153 (2.61%) 4 3 / 153 (1.96%) 3 | 3 / 83 (3.61%) 3 5 / 83 (6.02%) 6 2 / 83 (2.41%) 2 3 / 83 (3.61%) 6 0 / 83 (0.00%) 0 3 / 83 (3.61%) 3 |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 2 / 677 (0.30%) 2 | 0 / 153 (0.00%) 0 | 2 / 83 (2.41%) 2 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all) | 13 / 677 (1.92%) 13 3 / 677 (0.44%) 3 | 5 / 153 (3.27%) 8 0 / 153 (0.00%) 0 | 3 / 83 (3.61%) 3 2 / 83 (2.41%) 2 |

| | | | |
|--|----------------------|----------------------|---------------------|
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 0 / 677 (0.00%) 0 | 2 / 153 (1.31%) 2 | 3 / 83 (3.61%) 4 |
|--|----------------------|----------------------|---------------------|

| Non-serious adverse events | Double-Blind: Vortioxetine 20 mg | Double-Blind: Vortioxetine 10 mg | |
|---|-------------------------------------|-------------------------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 42 / 153 (27.45%) | 55 / 151 (36.42%) | |
| Investigations Weight decreased subjects affected / exposed occurrences (all) | 1 / 153 (0.65%) 1 | 0 / 151 (0.00%) 0 | |
| Weight increased subjects affected / exposed occurrences (all) | 3 / 153 (1.96%) 3 | 1 / 151 (0.66%) 1 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 14 / 153 (9.15%) 16 | 14 / 151 (9.27%) 19 | |
| Dizziness subjects affected / exposed occurrences (all) | 5 / 153 (3.27%) 5 | 7 / 151 (4.64%) 7 | |
| General disorders and administration site conditions Illness subjects affected / exposed occurrences (all) | 5 / 153 (3.27%) 8 | 0 / 151 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 153 (1.96%) 4 | 4 / 151 (2.65%) 6 | |
| Nausea subjects affected / exposed occurrences (all) | 17 / 153 (11.11%) 25 | 19 / 151 (12.58%) 22 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 6 / 153 (3.92%) 8 | 9 / 151 (5.96%) 11 | |
| Diarrhoea | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 153 (0.65%) 1 | 5 / 151 (3.31%) 5 | |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 153 (0.65%) 1 | 4 / 151 (2.65%) 4 | |
| Vomiting subjects affected / exposed occurrences (all) | 10 / 153 (6.54%) 16 | 14 / 151 (9.27%) 20 | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 0 / 153 (0.00%) 0 | 1 / 151 (0.66%) 1 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 153 (2.61%) 4 | 6 / 151 (3.97%) 8 | |
| Viral infection subjects affected / exposed occurrences (all) | 0 / 153 (0.00%) 0 | 1 / 151 (0.66%) 1 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 2 / 153 (1.31%) 2 | 1 / 151 (0.66%) 2 | |

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