



## Clinical trial results:

### A Randomized, Double-blind, Parallel-group, Active-controlled Study Evaluating the Efficacy of Vortioxetine Versus Desvenlafaxine in Adult Patients Suffering from Major Depressive Disorder with Partial Response to SSRI Treatment

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2019-002704-41       |
| Trial protocol           | CZ EE LV BG SK BE ES |
| Global end of trial date | 04 February 2022     |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 22 February 2023 |
| First version publication date | 22 February 2023 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 18498A |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04448431 |
| 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)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 04 February 2022 |
| Is this the analysis of the primary completion data? | No               |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 04 February 2022 |
| Was the trial ended prematurely? | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the trial was to compare the efficacy of vortioxetine versus desvenlafaxine after 8 weeks of treatment, on depressive symptoms in participants with major depressive disorder (MDD) who have responded partially to monotherapy with a selective serotonin reuptake inhibitor (SSRI).

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 June 2020 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 132          |
| Country: Number of subjects enrolled | Belgium: 1              |
| Country: Number of subjects enrolled | Bulgaria: 32            |
| Country: Number of subjects enrolled | Czechia: 73             |
| Country: Number of subjects enrolled | Estonia: 20             |
| Country: Number of subjects enrolled | Latvia: 10              |
| Country: Number of subjects enrolled | Mexico: 27              |
| Country: Number of subjects enrolled | Russian Federation: 150 |
| Country: Number of subjects enrolled | Slovakia: 53            |
| Country: Number of subjects enrolled | Spain: 8                |
| Country: Number of subjects enrolled | Sweden: 16              |
| Country: Number of subjects enrolled | Ukraine: 83             |
| Worldwide total number of subjects   | 605                     |
| EEA total number of subjects         | 213                     |

Notes:

### Subjects enrolled per age group

|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|   |     |
|---|-----|
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 598 |
| From 65 to 84 years                       | 7   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

605 participants were enrolled in the study. 603 participants received at least one dose of study treatment.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Vortioxetine |

Arm description:

Participants received 10 milligrams (mg) vortioxetine once daily for the first week. At the end of Week 1 (Day 7), the dose was increased to 20mg/day. The dose may have been adjusted (10 or 20mg/day) at unscheduled visits or at the end of Week 4 (Day 28) (only once) based on the participant's response and the investigator's clinical judgement. No dose changes were permitted after Week 4. The dose remained fixed until the end of the treatment period (Week 8, Day 56). From Week 8, participants received placebo once daily for one week.

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

Dosage and administration details:

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

|  |              |
|--|--------------|
| Investigational medicinal product name | Vortioxetine |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

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

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Desvenlafaxine |
|------------------|----------------|

Arm description:

Participants received a fixed dose of 50mg once daily during the treatment period. In order to maintain the blind, a dose adjustment could have been requested based on the participant's response and the investigator's clinical judgement, however, the dose of desvenlafaxine remained fixed. From Week 8, participants received 50mg desvenlafaxine or placebo every other day for one week.

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

Dosage and administration details:

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

|  |                |
|--|----------------|
| Investigational medicinal product name | Desvenlafaxine |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Capsule        |
| Routes of administration               | Oral use       |

Dosage and administration details:

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

| <b>Number of subjects in period 1</b>  | Vortioxetine | Desvenlafaxine |
|--|--------------|----------------|
| Started                                | 312          | 293            |
| Received at least 1 dose of study drug | 310          | 293            |
| Completed                              | 295          | 284            |
| Not completed                          | 17           | 9              |
| Consent withdrawn by subject           | 5            | 3              |
| Adverse event, non-fatal               | 6            | 3              |
| Not specified                          | 2            | 2              |
| Lost to follow-up                      | 1            | -              |
| Lack of efficacy                       | 1            | 1              |
| Not treated                            | 2            | -              |

## Baseline characteristics

### Reporting groups

|  |                |
|--|----------------|
| Reporting group title  | Vortioxetine   |
| Reporting group description:   |                |
| Participants received 10 milligrams (mg) vortioxetine once daily for the first week. At the end of Week 1 (Day 7), the dose was increased to 20mg/day. The dose may have been adjusted (10 or 20mg/day) at unscheduled visits or at the end of Week 4 (Day 28) (only once) based on the participant's response and the investigator's clinical judgement. No dose changes were permitted after Week 4. The dose remained fixed until the end of the treatment period (Week 8, Day 56). From Week 8, participants received placebo once daily for one week. |                |
| Reporting group title  | Desvenlafaxine |
| Reporting group description:   |                |
| Participants received a fixed dose of 50mg once daily during the treatment period. In order to maintain the blind, a dose adjustment could have been requested based on the participant's response and the investigator's clinical judgement, however, the dose of desvenlafaxine remained fixed. From Week 8, participants received 50mg desvenlafaxine or placebo every other day for one week.  |                |

| Reporting group values  | Vortioxetine | Desvenlafaxine | Total |
|---|--------------|----------------|-------|
| Number of subjects  | 312          | 293            | 605   |
| Age Categorical   |              |                |       |
| Units: Subjects   |              |                |       |
| In utero  | 0            | 0              | 0     |
| Preterm newborn infants (gestational age < 37 wks)  | 0            | 0              | 0     |
| Newborns (0-27 days)  | 0            | 0              | 0     |
| Infants and toddlers (28 days-23 months)  | 0            | 0              | 0     |
| Children (2-11 years)   | 0            | 0              | 0     |
| Adolescents (12-17 years)   | 0            | 0              | 0     |
| Adults (18-64 years)  | 307          | 291            | 598   |
| From 65-84 years  | 5            | 2              | 7     |
| 85 years and over   | 0            | 0              | 0     |
| Gender Categorical  |              |                |       |
| Units: Subjects   |              |                |       |
| Female  | 216          | 212            | 428   |
| Male  | 96           | 81             | 177   |
| Race  |              |                |       |
| Units: Subjects   |              |                |       |
| Asian   | 3            | 0              | 3     |
| Black   | 0            | 1              | 1     |
| Not reported  | 10           | 6              | 16    |
| Other   | 14           | 14             | 28    |
| White   | 285          | 272            | 557   |
| Montgomery and Åsberg Depression Rating Scale (MADRS) Total Score   |              |                |       |
| The MADRS is a 10-item rating scale designed to assess the severity of the symptoms in depressive illness and to be sensitive to treatment effects. Items in the scale assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The total score of the 10 items ranges from 0 (no symptoms) to 60 (severe symptoms), with higher scores indicating more severe symptoms. Participants with valid baseline scores are presented here (Vortioxetine n=309; Desvenlafaxine n=293) |              |                |       |
| Units: Score on a scale   |              |                |       |

|                    |         |         |   |
|--------------------|---------|---------|---|
| arithmetic mean    | 30.65   | 30.69   |   |
| standard deviation | ± 3.702 | ± 3.922 | - |

## End points

### End points reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Vortioxetine |
|-----------------------|--------------|

Reporting group description:

Participants received 10 milligrams (mg) vortioxetine once daily for the first week. At the end of Week 1 (Day 7), the dose was increased to 20mg/day. The dose may have been adjusted (10 or 20mg/day) at unscheduled visits or at the end of Week 4 (Day 28) (only once) based on the participant's response and the investigator's clinical judgement. No dose changes were permitted after Week 4. The dose remained fixed until the end of the treatment period (Week 8, Day 56). From Week 8, participants received placebo once daily for one week.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Desvenlafaxine |
|-----------------------|----------------|

Reporting group description:

Participants received a fixed dose of 50mg once daily during the treatment period. In order to maintain the blind, a dose adjustment could have been requested based on the participant's response and the investigator's clinical judgement, however, the dose of desvenlafaxine remained fixed. From Week 8, participants received 50mg desvenlafaxine or placebo every other day for one week.

### Primary: Change from Baseline to Week 8 in Montgomery and Åsberg Depression Rating Scale (MADRS) Total Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to Week 8 in Montgomery and Åsberg Depression Rating Scale (MADRS) Total Score |
|-----------------|---|

End point description:

The MADRS is a 10-item rating scale designed to assess the severity of the symptoms in depressive illness and to be sensitive to treatment effects. Items in the scale assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Symptoms are rated on a 7-point scale from 0 (no symptom) to 6 (severe symptom). Definitions of severity are provided at 2-point intervals. The total score of the 10 items ranges from 0 (no symptoms) to 60 (severe symptoms), with higher scores indicating more severe symptoms.

Analysis was performed on the Full-analysis set (FAS) – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 8

| End point values                    | Vortioxetine    | Desvenlafaxine  |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 295             | 286             |  |  |
| Units: Score on a scale             |                 |                 |  |  |
| least squares mean (standard error) | -13.61 (± 0.51) | -13.14 (± 0.52) |  |  |

## Statistical analyses



|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Vortioxetine vs. Desvenlafaxine          |
| Comparison groups                       | Vortioxetine v Desvenlafaxine            |
| Number of subjects included in analysis | 581                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | non-inferiority                          |
| P-value                                 | = 0.4196                                 |
| Method                                  | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate                      | Mean difference (final values)           |
| Point estimate                          | -0.47                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -1.61                                    |
| upper limit                             | 0.67                                     |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 0.58                                     |

### Secondary: Percentage of MADRS Responders at Week 8

|  |  |
|--|--|
| End point title  | Percentage of MADRS Responders at Week 8 |
| End point description:   |  |
| Response was defined as a $\geq 50\%$ decrease in MADRS total score from baseline. The MADRS is a 10-item rating scale designed to assess the severity of the symptoms in depressive illness and to be sensitive to treatment effects. Items in the scale assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The total score of the 10 items ranges from 0 (no symptoms) to 60 (severe symptoms), with higher scores indicating more severe symptoms. |  |
| Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.   |  |
| End point type   | Secondary                                |
| End point timeframe:   |  |
| Week 8   |  |

|                                   |                 |                 |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>           | Vortioxetine    | Desvenlafaxine  |  |  |
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 295             | 286             |  |  |
| Units: Percentage of participants |                 |                 |  |  |
| number (not applicable)           | 43.4            | 36.7            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With MADRS Remission at Week 8

|  |   |
|--|---|
| End point title  | Percentage of Participants With MADRS Remission at Week 8 |
| End point description:   |   |
| Remission was defined as a MADRS total score $\leq 10$ . The MADRS is a 10-item rating scale designed to assess the severity of the symptoms in depressive illness and to be sensitive to treatment effects. Items in the scale assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The total score of the 10 items ranges from 0 (no symptoms) to 60 (severe symptoms), with higher scores indicating more severe symptoms. |   |
| Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Week 8   |   |

|                                   |                 |                 |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>           | Vortioxetine    | Desvenlafaxine  |  |  |
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 295             | 286             |  |  |
| Units: Percentage of participants |                 |                 |  |  |
| number (not applicable)           | 18.0            | 20.3            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline to Week 8 in MADRS Anhedonia Factor Score

|  |  |
|--|--|
| End point title  | Change from Baseline to Week 8 in MADRS Anhedonia Factor Score |
| End point description:   |  |
| The MADRS is a 10-item rating scale designed to assess the severity of the symptoms in depressive illness and to be sensitive to treatment effects. Items in the scale assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The anhedonia factor score is based on 5 items (apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel) and ranges from 0 to 30 with higher scores representing more severe symptoms. |  |
| Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.   |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline, Week 8   |  |

| End point values                    | Vortioxetine        | Desvenlafaxine      |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 295                 | 286                 |  |  |
| Units: Score on a scale             |                     |                     |  |  |
| least squares mean (standard error) | -8.11 ( $\pm$ 0.32) | -7.80 ( $\pm$ 0.33) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical Global Impression – Global Improvement (CGI-I) Score at Week 8

|                 |   |
|-----------------|---|
| End point title | Clinical Global Impression – Global Improvement (CGI-I) Score at Week 8 |
|-----------------|---|

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). In all cases, the assessment was made independent of whether the rater believed the improvement was drug-related.

Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 8

| End point values                    | Vortioxetine       | Desvenlafaxine     |  |  |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed         | 295                | 286                |  |  |
| Units: Score on a scale             |                    |                    |  |  |
| least squares mean (standard error) | 2.31 ( $\pm$ 0.07) | 2.40 ( $\pm$ 0.07) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline to Week 8 in Clinical Global Impression – Severity of Illness (CGI-S) Score

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to Week 8 in Clinical Global Impression – Severity of Illness (CGI-S) Score |
|-----------------|--|

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).

Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 8     |           |

| End point values                    | Vortioxetine        | Desvenlafaxine      |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 295                 | 286                 |  |  |
| Units: Score on a scale             |                     |                     |  |  |
| least squares mean (standard error) | -1.54 ( $\pm$ 0.06) | -1.41 ( $\pm$ 0.07) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Digital Symbol Substitution Test (DSST) Total Score to Week 8

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Digital Symbol Substitution Test (DSST) Total Score to Week 8 |
|-----------------|---|

End point description:

The DSST is a cognitive test designed to assess psychomotor speed of performance requiring visual perception, spatial decision-making, and motor skills. The DSST is sensitive to cognitive impairments affecting attention, processing speed, and executive function (including working memory). The DSST consists of 133 digits and requires the participant to substitute each digit with a simple symbol in a 90-second period. Each correct symbol is counted, and the total score ranges from 0 (less than normal functioning) to 133 (greater than normal functioning).

Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 8     |           |

| End point values                    | Vortioxetine       | Desvenlafaxine     |  |  |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed         | 295                | 285                |  |  |
| Units: Score on a scale             |                    |                    |  |  |
| least squares mean (standard error) | 9.72 ( $\pm$ 0.89) | 9.53 ( $\pm$ 0.91) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Participant's Probability of Choosing Hard Task For Each Effort Expenditure for Rewards Task (EEfRT) Trial at Week 8

|                 |  |
|-----------------|--|
| End point title | Participant's Probability of Choosing Hard Task For Each Effort Expenditure for Rewards Task (EEfRT) Trial at Week 8 |
|-----------------|--|

End point description:

The EEfRT is a neuropsychological task to assess willingness to make efforts to obtain a monetary reward under different conditions of reward probability and magnitude. The participant is given an opportunity to choose between two tasks with different levels of difficulty: a "hard task" and an "easy task" option, which require different amounts of repeated manual button pressing. For easy-task choices, the participant is eligible to win a fixed amount of monetary reward on each trial if he/she successfully completes the task. For hard-task choices, the participant is eligible to win higher amounts that vary per trial within a range ("reward magnitude").

Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 8               |           |

| End point values            | Vortioxetine    | Desvenlafaxine  |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 284             | 276             |  |  |
| Units: Probability          |                 |                 |  |  |
| number (not applicable)     | 0.31            | 0.32            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: EEfRT: Proportion of Hard Choice Tasks at Week 8

|                 |  |
|-----------------|--|
| End point title | EEfRT: Proportion of Hard Choice Tasks at Week 8 |
|-----------------|--|

End point description:

The EEfRT is a neuropsychological task to assess willingness to make efforts to obtain a monetary reward under different conditions of reward probability and magnitude. The participant is given an opportunity to choose between two tasks with different levels of difficulty: a "hard task" and an "easy task" option, which require different amounts of repeated manual button pressing. For easy-task choices, the participant is eligible to win a fixed amount of monetary reward on each trial if he/she successfully completes the task. For hard-task choices, the participant is eligible to win higher amounts that vary per trial within a range ("reward magnitude").

Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 8               |           |

| End point values                 | Vortioxetine       | Desvenlafaxine     |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 284                | 276                |  |  |
| Units: Proportion                |                    |                    |  |  |
| arithmetic mean (standard error) | 0.33 ( $\pm$ 0.01) | 0.34 ( $\pm$ 0.01) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 8 in Functioning Assessment Short Test (FAST) Total Score

|                 |  |
|-----------------|--|
| End point title | Change From Baseline to Week 8 in Functioning Assessment Short Test (FAST) Total Score |
|-----------------|--|

End point description:

The FAST is a clinician-rated clinical outcome assessment tool designed to assess difficulty in functioning. The FAST consists of 24 items in 6 specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, leisure time. Each item is rated on a 4-point scale from 0 (no difficulty) to 3 (severe difficulty). The items are summed to yield a total score ranging from 0 (no difficulty) to 72 (severe difficulty), with higher scores reflecting more serious difficulties.

Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 8

| End point values                    | Vortioxetine         | Desvenlafaxine       |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed         | 296                  | 288                  |  |  |
| Units: Score on a scale             |                      |                      |  |  |
| least squares mean (standard error) | -15.79 ( $\pm$ 0.85) | -14.15 ( $\pm$ 0.85) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline to Week 8 in FAST Sub-domain Scores

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to Week 8 in FAST Sub-domain Scores |
|-----------------|--|

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**End point description:**

The FAST is a clinician-rated clinical outcome assessment tool designed to assess difficulty in functioning. The FAST consists of 24 items in 6 specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, leisure time. Each item is rated on a 4-point scale from 0 (no difficulty) to 3 (severe difficulty).

Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint.

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|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 8     |           |

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| End point values                          | Vortioxetine    | Desvenlafaxine  |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                        | Reporting group | Reporting group |  |  |
| Number of subjects analysed               | 301             | 290             |  |  |
| Units: Score on a scale                   |                 |                 |  |  |
| least squares mean (standard error)       |                 |                 |  |  |
| Autonomy (n= 300, 290)                    | -2.52 (± 0.23)  | -2.05 (± 0.24)  |  |  |
| Occupational Functioning (n= 295, 288)    | -2.91 (± 0.25)  | -2.49 (± 0.25)  |  |  |
| Cognitive Functioning (n= 301, 290)       | -3.17 (± 0.32)  | -2.74 (± 0.33)  |  |  |
| Financial Issues (n= 301, 290)            | -0.61 (± 0.13)  | -0.60 (± 0.14)  |  |  |
| Interpersonal Relationships (n= 301, 290) | -3.77 (± 0.36)  | -3.22 (± 0.37)  |  |  |
| Leisure Time (n= 301, 290)                | -1.40 (± 0.17)  | -1.47 (± 0.17)  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change From Baseline to Week 8 in the Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q) Long Form Subscales**

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|                 |  |
|-----------------|--|
| End point title | Change From Baseline to Week 8 in the Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q) Long Form Subscales |
|-----------------|--|

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**End point description:**

The Q-LES-Q Long Form is a participant self-rated scale designed to measure the degree of enjoyment and satisfaction experienced by participants in various areas of daily life. It consists of 93 items to measure: physical health, feelings, work, household duties, school, leisure time activities, social relations, and general activities. Each item is rated on a 5-point scale ranging from 1 (very poor) to 5 (very good). Raw scores for each category are converted to a 1 to 100 scale with higher scores representing higher quality of life.

Analysis was performed on the FAS – all randomized participants who took at least 1 dose of double-blind study drug and had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable (MADRS). Here, 'number of subjects analyzed' signifies participants evaluable for this endpoint. 'n' signifies participants evaluable for specified category.

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|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 8     |           |

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| <b>End point values</b>                            | Vortioxetine    | Desvenlafaxine  |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed                        | 301             | 290             |  |  |
| Units: Score on a scale                            |                 |                 |  |  |
| least squares mean (standard error)                |                 |                 |  |  |
| Work (n= 195, 195)                                 | 17.70 (± 1.81)  | 16.83 (± 1.84)  |  |  |
| Household Duties (n= 287, 276)                     | 14.29 (± 1.84)  | 14.22 (± 1.89)  |  |  |
| School (n= 33, 36)                                 | 11.12 (± 6.41)  | 18.73 (± 5.84)  |  |  |
| Leisure Time (n= 301, 290)                         | 20.78 (± 2.05)  | 20.92 (± 2.10)  |  |  |
| Social Relations (n= 301, 290)                     | 16.10 (± 1.69)  | 15.56 (± 1.73)  |  |  |
| Physical Health (n= 301, 290)                      | 17.79 (± 1.70)  | 16.63 (± 1.74)  |  |  |
| Feelings (n= 301, 289)                             | 17.20 (± 1.73)  | 16.46 (± 1.78)  |  |  |
| General Activities (n= 301, 290)                   | 17.99 (± 1.57)  | 17.12 (± 1.61)  |  |  |
| Satisfaction with Medication (n= 246, 222)         | 27.46 (± 1.66)  | 23.81 (± 1.72)  |  |  |
| Overall Satisfaction and Contentment (n= 301, 290) | 24.96 (± 2.24)  | 23.63 (± 2.30)  |  |  |

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug (Day 1) up to Week 12. Adverse Events were not reported after Day 56 (Visit 5) unless they were Serious Adverse Events.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Desvenlafaxine |
|-----------------------|----------------|

Reporting group description:

Participants received a fixed dose of 50mg once daily during the treatment period. In order to maintain the blind, a dose adjustment could have been requested based on the participant's response and the investigator's clinical judgement, however, the dose of desvenlafaxine remained fixed. From Week 8, participants received 50mg desvenlafaxine or placebo every other day for one week.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Vortioxetine |
|-----------------------|--------------|

Reporting group description:

Participants received 10 milligrams (mg) vortioxetine once daily for the first week. At the end of Week 1 (Day 7), the dose was increased to 20mg/day. The dose may have been adjusted (10 or 20mg/day) at unscheduled visits or at the end of Week 4 (Day 28) (only once) based on the participant's response and the investigator's clinical judgement. No dose changes were permitted after Week 4. The dose remained fixed until the end of the treatment period (Week 8, Day 56). From Week 8, participants received placebo once daily for one week.

| Serious adverse events                            | Desvenlafaxine  | Vortioxetine    |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 1 / 293 (0.34%) | 0 / 310 (0.00%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    | 0               | 0               |  |
| Gastrointestinal disorders                        |                 |                 |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                       | 1 / 293 (0.34%) | 0 / 310 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |

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

| Non-serious adverse events                            | Desvenlafaxine    | Vortioxetine      |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 61 / 293 (20.82%) | 85 / 310 (27.42%) |  |
| Nervous system disorders                              |                   |                   |  |

|                             |                  |                   |  |
|-----------------------------|------------------|-------------------|--|
| Headache                    |                  |                   |  |
| subjects affected / exposed | 25 / 293 (8.53%) | 30 / 310 (9.68%)  |  |
| occurrences (all)           | 29               | 34                |  |
| Dizziness                   |                  |                   |  |
| subjects affected / exposed | 16 / 293 (5.46%) | 16 / 310 (5.16%)  |  |
| occurrences (all)           | 18               | 16                |  |
| Gastrointestinal disorders  |                  |                   |  |
| Nausea                      |                  |                   |  |
| subjects affected / exposed | 27 / 293 (9.22%) | 62 / 310 (20.00%) |  |
| occurrences (all)           | 29               | 75                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported