



## Clinical trial results:

### Interventional, Open-Label, Flexible-Dose Study of Vortioxetine on Emotional Functioning in Patients With Major Depressive Disorder With Inadequate Response to SSRI/SNRI Treatment

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2017-004829-33   |
| Trial protocol           | FR ES LT IT      |
| Global end of trial date | 21 February 2020 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 07 March 2021 |
| First version publication date | 07 March 2021 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 17797A |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03835715 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | H. Lundbeck A/S  |
| Sponsor organisation address | Otillavej 9, Valby, Denmark, 2500  |
| Public contact               | LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, 0045 36301311, LundbeckClinicalTrials@lundbeck.com |
| Scientific contact           | LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, 0045 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                       | 21 February 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 21 February 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 February 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effectiveness of 10-20 milligrams (mg) flexible-dose vortioxetine after 8 weeks of treatment on emotional functioning in participants with major depressive disorder (MDD) with inadequate response to selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) treatment who were candidates for a switch and had a desire to change medication.

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                          | 05 February 2019 |
| 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 | Spain: 68     |
| Country: Number of subjects enrolled | France: 49    |
| Country: Number of subjects enrolled | Italy: 14     |
| Country: Number of subjects enrolled | Lithuania: 20 |
| Worldwide total number of subjects   | 151           |
| EEA total number of subjects         | 151           |

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) | 147 |
| From 65 to 84 years  | 4   |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants who met each of the inclusion and none of the exclusion criteria were eligible to participate in the study. A total of 151 participants were enrolled, out of which 150 participants were treated.

### Period 1

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

### Arms

|           |              |
|-----------|--------------|
| Arm title | Vortioxetine |
|-----------|--------------|

Arm description:

Participants received vortioxetine 10 mg tablet orally once daily. After the first week of treatment, the dose of vortioxetine could be adjusted (to 10 or 20 mg/day) up to Week 8. Participants were treated for 8 weeks.

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

Dosage and administration details:

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

| Number of subjects in period 1 <sup>[1]</sup> | Vortioxetine |
|---|--------------|
| Started                                       | 150          |
| Received at least 1 dose of study drug        | 150          |
| Completed                                     | 131          |
| Not completed                                 | 19           |
| Consent withdrawn by subject                  | 1            |
| Adverse event, non-fatal                      | 6            |
| Other than specified                          | 1            |
| Lost to follow-up                             | 6            |
| Lack of efficacy                              | 2            |
| Protocol deviation                            | 3            |

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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: The number of participants reported in the baseline period are the participants who were enrolled and treated.

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Participants received vortioxetine 10 mg tablet orally once daily. After the first week of treatment, the dose of vortioxetine could be adjusted (to 10 or 20 mg/day) up to Week 8. Participants were treated for 8 weeks.

| Reporting group values  | Vortioxetine    | Total |  |
|---|-----------------|-------|--|
| Number of subjects  | 150             | 150   |  |
| Age categorical<br>Units: Subjects                                      |                 |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 47.1<br>± 12.02 | -     |  |
| Gender categorical<br>Units: Subjects                                   |                 |       |  |
| Female  | 105             | 105   |  |
| Male  | 45              | 45    |  |

## End points

### End points reporting groups

|  |              |
|--|--------------|
| Reporting group title  | Vortioxetine |
| Reporting group description:   |              |
| Participants received vortioxetine 10 mg tablet orally once daily. After the first week of treatment, the dose of vortioxetine could be adjusted (to 10 or 20 mg/day) up to Week 8. Participants were treated for 8 weeks. |              |

### Primary: Change From Baseline in Oxford Depression Questionnaire (ODQ) Total Score at Week 8

|  |  |
|--|--|
| End point title  | Change From Baseline in Oxford Depression Questionnaire (ODQ) Total Score at Week 8 <sup>[1]</sup> |
| End point description:   |  |
| ODQ: self-reported, 26-item questionnaire assessing 5 dimensions of emotional functioning (not caring[NC]; emotional detachment[ED]; positive reduction[PR]; general reduction[GR]; antidepressant as cause[AC]), comprised of 3 sections: Section 1(12 items) evaluated respondents' experiences during past week; Section 2(8 items) compared respondents' experiences during past week to the experience before their depression; Section 3(6 items) assessed participant's perception of a relationship between current antidepressant and emotional functioning. Each item rated on a 5-point likert scale:1 (disagree) to 5 (agree), summed into scores for each dimension and total score (range:26-130). Higher values=higher levels of emotional blunting. Full analysis set (FAS): all participants who received at least 1 dose of study drug, had a valid baseline assessment and at least 1 valid postbaseline assessment of ODQ total score. 'Number of participants analysed'=participants evaluable for this endpoint. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Baseline, Week 8   |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis could not be presented for this single arm.

|                                  |                      |  |  |  |
|----------------------------------|----------------------|--|--|--|
| <b>End point values</b>          | Vortioxetine         |  |  |  |
| Subject group type               | Reporting group      |  |  |  |
| Number of subjects analysed      | 131                  |  |  |  |
| Units: units on a scale          |                      |  |  |  |
| arithmetic mean (standard error) | -29.84 ( $\pm$ 1.91) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Motivation and Energy Inventory (MEI) Total Score and Subscale Scores (Mental or Cognitive Energy, Social Motivation, and Physical Energy) at Week 8

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Motivation and Energy Inventory (MEI) Total Score and Subscale Scores (Mental or Cognitive Energy, Social Motivation, and Physical Energy) at Week 8 |
|-----------------|--|

End point description:

The MEI is a 27-item, participant-rated scale initially developed and validated to evaluate interventions

to improve motivation and energy in participants with depression. The MEI is designed to assess 3 domains: mental or cognitive energy, social motivation, and physical energy. Respondents used scales ranging from 0 (indicating that the behaviour was never present) to 5 or 6 (a behaviour or feeling that was present very frequently or all of the time). All items used either a 5- or 7-point likert scale. Total score = sum of each item score (range: 0-144). Items 3-11, 13-15, 17, and 18 were reverse-scored to ensure that higher scores indicate greater levels of motivation and energy. FAS: all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score. Number of participants analysed' = participants evaluable for this endpoint. 'n' = participants evaluable for specified categories.

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

End point timeframe:

Baseline, Week 8

| End point values                           | Vortioxetine    |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                         | Reporting group |  |  |  |
| Number of subjects analysed                | 131             |  |  |  |
| Units: units on a scale                    |                 |  |  |  |
| arithmetic mean (standard error)           |                 |  |  |  |
| Total Score (n = 130)                      | 34.28 (± 2.75)  |  |  |  |
| Mental or Cognitive Energy Score (n = 130) | 14.98 (± 1.23)  |  |  |  |
| Social Motivation Score (n = 131)          | 9.55 (± 0.92)   |  |  |  |
| Physical Energy Score (n = 131)            | 10.30 (± 0.88)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in ODQ Domain Scores (NC, ED, PR, GR, AC, PR-NC, and GR-ED) and ODQ Total Score (Calculated Only From Sections 1 and 2 of the Questionnaire [Excluding Items Related to the Antidepressants as Cause Domain]) at Week 8

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in ODQ Domain Scores (NC, ED, PR, GR, AC, PR-NC, and GR-ED) and ODQ Total Score (Calculated Only From Sections 1 and 2 of the Questionnaire [Excluding Items Related to the Antidepressants as Cause Domain]) at Week 8 |
|-----------------|--|

End point description:

ODQ: self-reported, 26-item questionnaire assessing 5 dimensions of emotional functioning (NC; ED; PR; GR; AC), comprised of 3 sections: Section 1 (12 items) evaluated respondents' experiences during past week; Section 2 (8 items) compared respondents' experiences during past week to the experience before their depression; and Section 3 (6 items) assessed participant's perception of a relationship between current antidepressant and emotional functioning. Each item rated on a 5-point likert scale: 1 (disagree) to 5 (agree) and summed into scores for each dimension and a total score (range: 26-130). Total score, calculated only from Sections 1 and 2 are reported in this endpoint. Higher values reflected higher levels of emotional blunting. FAS: all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score. 'Number of participants analysed'=participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 8



|                                  |                 |  |  |  |
|----------------------------------|-----------------|--|--|--|
| <b>End point values</b>          | Vortioxetine    |  |  |  |
| Subject group type               | Reporting group |  |  |  |
| Number of subjects analysed      | 131             |  |  |  |
| Units: units on a scale          |                 |  |  |  |
| arithmetic mean (standard error) |                 |  |  |  |
| ODQ NC Score                     | -5.98 (± 0.52)  |  |  |  |
| ODQ ED Score                     | -4.72 (± 0.46)  |  |  |  |
| ODQ PR Score                     | -7.81 (± 0.55)  |  |  |  |
| ODQ GR Score                     | -6.56 (± 0.44)  |  |  |  |
| ODQ AC Score                     | -5.08 (± 0.50)  |  |  |  |
| ODQ PR-NC Score                  | -13.65 (± 1.01) |  |  |  |
| ODQ GR-ED Score                  | -11.20 (± 0.74) |  |  |  |
| ODQ Section 1+2 Score            | -24.73 (± 1.62) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants who Responded "No" (Absence of Emotional Effects) to Screening Question on Emotional Functioning

|  |   |
|--|---|
| End point title  | Percentage of Participants who Responded "No" (Absence of Emotional Effects) to Screening Question on Emotional Functioning |
| End point description:   |   |
| The participants were asked the following screening question on emotional functioning: Emotional effects vary, but may include, for example, feeling emotionally "numbed" or "blunted" in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or "just not caring" about things that you used to care about. Have you experienced such emotional effects during the last 6 weeks? FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score. Here, 'Number of participants analysed' signifies participants evaluable for this endpoint. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Week 8   |   |

|                                   |                     |  |  |  |
|-----------------------------------|---------------------|--|--|--|
| <b>End point values</b>           | Vortioxetine        |  |  |  |
| Subject group type                | Reporting group     |  |  |  |
| Number of subjects analysed       | 138                 |  |  |  |
| Units: percentage of participants |                     |  |  |  |
| number (confidence interval 95%)  | 49.3 (40.9 to 57.6) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Disability Scale (SDS) Total and Individual Item Scores (Family Life/Home Responsibilities, Social Life, and Work/School) at Week 8

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Disability Scale (SDS) Total and Individual Item Scores (Family Life/Home Responsibilities, Social Life, and Work/School) at Week 8 |
|-----------------|---|

#### End point description:

The SDS is a series of participant self-rated, 10-point visual analogue scales designed to measure the extent to which the participant's life is impaired by panic, anxiety, phobic, or depressive symptoms. The participant rated the extent to which his or her work, social life or leisure activities, and home life or family responsibilities were impaired by his or her symptoms. The sum of the 3 SDS items yielded a total score (possible range 0-30), with higher scores indicating worse functioning. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score. Here, 'Number of participants analysed' signifies participants evaluable for this endpoint. 'n' signifies participants evaluable for specified categories.

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

| End point values                                  | Vortioxetine    |  |  |  |
|---|-----------------|--|--|--|
| Subject group type                                | Reporting group |  |  |  |
| Number of subjects analysed                       | 131             |  |  |  |
| Units: units on a scale                           |                 |  |  |  |
| arithmetic mean (standard error)                  |                 |  |  |  |
| Total Score (n = 131)                             | -7.73 (± 0.91)  |  |  |  |
| Family Life/Home Responsibilities Score (n = 131) | -2.54 (± 0.32)  |  |  |  |
| Social Life Score (n = 131)                       | -2.42 (± 0.30)  |  |  |  |
| Work/School Score (n = 90)                        | -3.19 (± 0.40)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Days Lost and Days Underproductive at Week 8 as Collected in the SDS Questionnaire

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Days Lost and Days Underproductive at Week 8 as Collected in the SDS Questionnaire |
|-----------------|--|

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**End point description:**

The number of days lost and the number of underproductive days lost from work due to the symptoms were also captured in SDS questionnaire. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score. Here, 'Number of participants analysed' signifies participants evaluable for this endpoint.

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

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End point timeframe:

Baseline, Week 8

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| End point values                 | Vortioxetine    |  |  |  |
|----------------------------------|-----------------|--|--|--|
| Subject group type               | Reporting group |  |  |  |
| Number of subjects analysed      | 131             |  |  |  |
| Units: days                      |                 |  |  |  |
| arithmetic mean (standard error) |                 |  |  |  |
| Days Lost                        | -1.86 (± 0.21)  |  |  |  |
| Days Underproductive             | -2.21 (± 0.28)  |  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change From Baseline in Clinical Global Impression – Severity of Illness (CGI-S) Score at Week 8**

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

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End point description:

CGI provides an overall clinician-determined summary measure of the severity of a participant's clinical condition and improvement or worsening that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behaviour, and impact of symptoms on participant's ability to function. CGI consists of 2 clinician-rated subscales: CGI-S and CGI-I. The CGI-S provides clinician's impression of the participant's current state of mental illness. Clinician rated the severity of 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). Higher scores indicated worsened condition. FAS: all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid postbaseline assessment of the ODQ total score. Here, 'Number of participants analysed' signifies participants evaluable for this endpoint.

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

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End point timeframe:

Baseline, Week 8

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|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Vortioxetine        |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 131                 |  |  |  |
| Units: units on a scale          |                     |  |  |  |
| arithmetic mean (standard error) | -1.83 ( $\pm$ 0.10) |  |  |  |

## 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 provides an overall clinician-determined summary measure of the severity of a participant's clinical condition and improvement or worsening that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behaviour, and impact of symptoms on participant's ability to function. CGI consists of 2 clinician-rated subscales: CGI-S and CGI-I. The CGI-I provides clinician's impression of the participant's improvement or worsening. Clinician assessed the participant's condition relative to baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Higher scores indicated worsened condition. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid postbaseline assessment of the ODQ total score. Here, 'Number of participants analysed' signifies participants evaluable for this endpoint.

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

End point timeframe:

Week 8

|                                  |                    |  |  |  |
|----------------------------------|--------------------|--|--|--|
| <b>End point values</b>          | Vortioxetine       |  |  |  |
| Subject group type               | Reporting group    |  |  |  |
| Number of subjects analysed      | 131                |  |  |  |
| Units: units on a scale          |                    |  |  |  |
| arithmetic mean (standard error) | 2.01 ( $\pm$ 0.10) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Response Based on the CGI-I at Week 8

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Response Based on the CGI-I at Week 8 |
|-----------------|---|

End point description:

Response was defined as a CGI-I score of 1 or 2. The CGI provides an overall clinician-determined summary measure of the severity of a participant's clinical condition and improvement or worsening that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behaviour, and impact of symptoms on participant's ability to

function. CGI consists of 2 clinician-rated subscales: CGI-S and CGI-I. The CGI-I provides clinician's impression of the participant's improvement or worsening. Clinician assessed the participant's condition relative to baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Higher scores indicated worsened condition. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score.

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

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Vortioxetine    |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 143             |  |  |  |
| Units: participants         | 96              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Remission Based on the CGI-S at Week 8

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Remission Based on the CGI-S at Week 8 |
|-----------------|--|

End point description:

Remission was defined as a CGI-S score of 1 or 2. The CGI provides an overall clinician-determined summary measure of the severity of a participant's clinical condition and improvement or worsening that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behaviour, and impact of symptoms on participant's ability to function. CGI consists of 2 clinician-rated subscales: CGI-S and CGI-I. The CGI-S provides clinician's impression of the participant's current state of mental illness. Clinician rated the severity of 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). Higher scores indicated worsened condition. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score.

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

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Vortioxetine    |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 143             |  |  |  |
| Units: participants         | 63              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Digit-Symbol Substitution Test (DSST) Total Score at Week 8

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Digit-Symbol Substitution Test (DSST) Total Score at 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 was counted. The total score was the number of correct symbols and the total score ranged from 0 (less than normal functioning) to 133 (greater than normal functioning), higher scores indicating better cognitive performance. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score. Here, 'Number of participants analysed' signifies participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 8

|                                  |                    |  |  |  |
|----------------------------------|--------------------|--|--|--|
| <b>End point values</b>          | Vortioxetine       |  |  |  |
| Subject group type               | Reporting group    |  |  |  |
| Number of subjects analysed      | 130                |  |  |  |
| Units: units on a scale          |                    |  |  |  |
| arithmetic mean (standard error) | 7.83 ( $\pm$ 0.92) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Montgomery and Åsberg Depression Rating Scale (MADRS) Total Score at Week 8

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

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. The items in the scale are designed to assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Symptoms were rated on a 7-point scale from 0 (no symptoms) to 6 (severe symptom). The total score of the 10 items ranges from 0 to 60 with higher scores indicating worse symptom severity. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score. Here, 'Number of participants analysed' signifies participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 8

|                                  |                      |  |  |  |
|----------------------------------|----------------------|--|--|--|
| <b>End point values</b>          | Vortioxetine         |  |  |  |
| Subject group type               | Reporting group      |  |  |  |
| Number of subjects analysed      | 131                  |  |  |  |
| Units: units on a scale          |                      |  |  |  |
| arithmetic mean (standard error) | -13.77 ( $\pm$ 0.68) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in MADRS Anhedonia Factor Score at Week 8

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in MADRS Anhedonia Factor Score at Week 8 |
|-----------------|--|

End point description:

The 5-item MADRS anhedonia subscale score was based on the following MADRS items: 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel). Symptoms were rated on a 7-point scale from 0 (no symptoms) to 6 (severe symptom). The total score of the 5 items ranges from 0 to 30 with higher scores indicating worse symptom severity. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score. Here, 'Number of participants analysed' signifies participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 8

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Vortioxetine        |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 131                 |  |  |  |
| Units: units on a scale          |                     |  |  |  |
| arithmetic mean (standard error) | -8.86 ( $\pm$ 0.44) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Response Based on the MADRS at Week 8

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Response Based on the MADRS at Week 8 |
|-----------------|---|

End point description:

Response was defined as a  $\geq 50\%$  reduction in MADRS total score compared to 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. The items in the scale are designed to assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Symptoms were rated on a 7-point scale from 0 (no symptoms) to 6 (severe symptom). The total score of the 10 items ranges from 0 to 60 with higher scores indicating worse symptom severity. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score.

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

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Vortioxetine    |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 143             |  |  |  |
| Units: participants         | 81              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Remission Based on the MADRS at Week 8

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Remission Based on the MADRS at Week 8 |
|-----------------|--|

End point description:

Remission was defined as a MADRS total score of  $\leq 10$ . 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. The items in the scale are designed to assess apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Symptoms were rated on a 7-point scale from 0 (no symptoms) to 6 (severe symptom). The total score of the 10 items ranges from 0 to 60 with higher scores indicating worse symptom severity. FAS included all participants who received at least 1 dose of study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the ODQ total score.

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

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Vortioxetine    |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 143             |  |  |  |
| Units: participants         | 61              |  |  |  |

## Statistical analyses





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 12

Adverse event reporting additional description:

All-patients-treated set (APTS) included all enrolled participants who took at least 1 dose of study drug.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants received vortioxetine 10 mg tablet orally once daily. After the first week of treatment, the dose of vortioxetine could be adjusted (to 10 or 20 mg/day) up to Week 8. Participants were treated for 8 weeks.

| Serious adverse events                            | Vortioxetine    |  |  |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 1 / 150 (0.67%) |  |  |
| number of deaths (all causes)                     | 0               |  |  |
| number of deaths resulting from adverse events    | 0               |  |  |
| Pregnancy, puerperium and perinatal conditions    |                 |  |  |
| Abortion missed                                   |                 |  |  |
| subjects affected / exposed                       | 1 / 150 (0.67%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |

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

| Non-serious adverse events                            | Vortioxetine      |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 45 / 150 (30.00%) |  |  |
| Nervous system disorders                              |                   |  |  |
| Dizziness   |                   |  |  |
| subjects affected / exposed                           | 10 / 150 (6.67%)  |  |  |
| occurrences (all)                                     | 10                |  |  |
| Headache  |                   |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 12 / 150 (8.00%)<br>13 |  |  |
| Gastrointestinal disorders                       |                        |  |  |
| Diarrhoea  |                        |  |  |
| subjects affected / exposed                      | 9 / 150 (6.00%)        |  |  |
| occurrences (all)                                | 10                     |  |  |
| Nausea   |                        |  |  |
| subjects affected / exposed                      | 31 / 150 (20.67%)      |  |  |
| occurrences (all)                                | 38                     |  |  |
| Vomiting   |                        |  |  |
| subjects affected / exposed                      | 10 / 150 (6.67%)       |  |  |
| occurrences (all)                                | 11                     |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 10 July 2019 | It included the following changes: - Inclusion criterion 5: sertraline added to list of allowed selective serotonin reuptake inhibitors (SSRIs) taken prior to the study. - Updated: Recent and Concomitant Medication, Disallowed or Allowed with restrictions to better reflect the participant population's medical treatment needs.  |
| 15 July 2019 | It included the following changes: - Added: exploratory objective, endpoint, and assessment to explore the association between digital biomarkers/phenotypes and clinical features using the phone application discovery by Mindstrong. This amendment was never effectuated as no participant consented to using the phone application. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported