



## Clinical trial results:

**A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Seltorexant 20 mg as Adjunctive Therapy to Antidepressants in Adult and Elderly Patients with Major Depressive Disorder with Insomnia Symptoms Who Have Responded Inadequately to Antidepressant Therapy and an Open-labeled Long-term Safety Extension Treatment with Seltorexant.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2020-000337-40 |
| Trial protocol           | CZ BG          |
| Global end of trial date | 30 April 2024  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 16 May 2025  |
| First version publication date | 16 May 2025  |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | CR108804 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04533529 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Janssen Research & Development, LLC  |
| Sponsor organisation address | 920 Route 202 South, Raritan, New Jersey, United States, 08869                             |
| Public contact               | Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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                       | 30 April 2024 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 April 2024 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the efficacy of seltorexant 20 milligrams compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in subjects with major depressive disorder with insomnia symptoms (MDDIS) who had an inadequate response to current antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy:

Selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI)

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 18 September 2020 |
| 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: 77           |
| Country: Number of subjects enrolled | Czechia: 78            |
| Country: Number of subjects enrolled | Spain: 26              |
| Country: Number of subjects enrolled | Sweden: 70             |
| Country: Number of subjects enrolled | Brazil: 89             |
| Country: Number of subjects enrolled | Colombia: 41           |
| Country: Number of subjects enrolled | Mexico: 30             |
| Country: Number of subjects enrolled | Russian Federation: 21 |
| Country: Number of subjects enrolled | South Africa: 18       |
| Country: Number of subjects enrolled | Taiwan: 19             |
| Country: Number of subjects enrolled | United States: 117     |
| Worldwide total number of subjects   | 586                    |
| EEA total number of subjects         | 251                    |

Notes:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| 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)                      | 535 |
| From 65 to 84 years                       | 51  |
| 85 years and over                         | 0   |

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## Subject disposition

### Recruitment

Recruitment details:

A total of 588 subjects were enrolled and randomised, 586 were treated with either seltorexant or matching placebo (2 randomised subjects didn't meet enrollment criteria and were withdrawn before treatment).

### Pre-assignment

Screening details:

Out of 586 treated subjects, 540 completed the double-blind (DB) phase, 522 entered the open-label (OL) phase, and 360 completed OL phase.

### Period 1

|                              |                                      |
|------------------------------|--------------------------------------|
| Period 1 title               | DB Treatment phase (Day 1 to Day 43) |
| 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>             | Double -blind Phase (DB): Placebo |

Arm description:

During DB phase, subjects with major depressive disorder (MDD) with or without insomnia symptoms (IS) who had an inadequate response to an ongoing antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were randomised to receive placebo (matching to seltorexant) once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

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

Dosage and administration details:

Subjects received placebo matching to seltorexant tablet orally once daily from Day 1 to Day 42.

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | DB: Seltorexant 20 mg |
|------------------|-----------------------|

Arm description:

During DB phase, subjects with MDD with or without IS who had an inadequate response to an ongoing antidepressant therapy with a SSRI or SNRI were randomised to receive seltorexant 20 milligrams (mg) tablet orally once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Seltorexant  |
| Investigational medicinal product code | JNJ-42847922 |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects received seltorexant 20 mg tablet orally once daily from Day 1 to Day 42.

| <b>Number of subjects in period 1</b>      | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg |
|--|-----------------------------------|-----------------------|
| Started                                    | 303                               | 283                   |
| Completed                                  | 277                               | 263                   |
| Not completed                              | 26                                | 20                    |
| Consent withdrawn by subject               | 11                                | 6                     |
| Physician decision                         | -                                 | 2                     |
| Adverse event, non-fatal                   | 5                                 | 5                     |
| Initiated prohibited medication            | 1                                 | -                     |
| Non-Compliance with primary antidepressant | 2                                 | -                     |
| Pregnancy                                  | -                                 | 1                     |
| Non-Compliance with study drug             | 3                                 | 3                     |
| Lost to follow-up                          | 2                                 | 1                     |
| Lack of efficacy                           | 1                                 | -                     |
| Protocol deviation                         | 1                                 | 2                     |

## Period 2

|                              |                                       |
|------------------------------|---------------------------------------|
| Period 2 title               | OL Treatment Phase (Day 43 to 1 year) |
| Is this the baseline period? | No                                    |
| Allocation method            | Not applicable                        |
| Blinding used                | Not blinded                           |

## Arms

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | OL Treatment Phase: Seltorexant 20 mg |
|------------------|---------------------------------------|

### Arm description:

Subjects who received placebo or seltorexant 20 mg tablet in the DB treatment phase entered OL phase and received seltorexant 20 mg tablet orally, once daily from Day 43 up to 1 year as an adjunctive therapy to ongoing SSRI/SNRI antidepressant therapy.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Seltorexant  |
| Investigational medicinal product code | JNJ-42847922 |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

### Dosage and administration details:

Subjects received seltorexant 20 mg tablet orally, once daily from Day 43 up to 1 year.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | OL Treatment Phase: Seltorexant 20 mg |
|---|---------------------------------------|
| Started   | 522                                   |
| Completed   | 360                                   |
| Not completed                                       | 162                                   |
| Adverse event, serious fatal                        | 1                                     |
| Consent withdrawn by subject                        | 64                                    |
| Physician decision                                  | 1                                     |
| Adverse event, non-fatal                            | 33                                    |
| Initiated prohibited medication                     | 6                                     |
| Non-Compliance with primary antidepressant          | 3                                     |
| Site terminated by sponsor                          | 3                                     |
| Non-Compliance with study drug                      | 11                                    |
| Unspecified   | 2                                     |
| Lost to follow-up                                   | 13                                    |
| Lack of efficacy                                    | 22                                    |
| Protocol deviation                                  | 3                                     |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only reported subjects were eligible to include in the current period.

### Period 3

|                              |                          |
|------------------------------|--------------------------|
| Period 3 title               | DB FU (Day 44 to Day 57) |
| Is this the baseline period? | No                       |
| Allocation method            | Not applicable           |
| Blinding used                | Not blinded              |

### Arms

|                              |                                  |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes                              |
| <b>Arm title</b>             | DB Follow-up (FU) Phase: Placebo |

Arm description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

|          |                 |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | DB FU Phase: Seltorexant 20 mg |
|------------------|--------------------------------|

Arm description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

|          |                 |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

| Number of subjects in period 3 <sup>[2]</sup> | DB Follow-up (FU) Phase: Placebo | DB FU Phase: Seltorexant 20 mg |
|---|----------------------------------|--------------------------------|
|   | Started                          | 22                             |
| Completed                                     | 18                               | 15                             |
| Not completed                                 | 4                                | 7                              |
| Consent withdrawn by subject                  | 2                                | 4                              |
| Adverse event, non-fatal                      | -                                | 2                              |
| Unspecified                                   | 1                                | 1                              |
| Lost to follow-up                             | 1                                | -                              |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only reported subjects were eligible to include in the current period.

#### Period 4

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 4 title               | OL FU (1 year to 1 year, 2 weeks) |
| Is this the baseline period? | No                                |
| Allocation method            | Not applicable                    |
| Blinding used                | Not blinded                       |

#### Arms

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | OL FU Phase: Seltorexant 20 mg |
|------------------|--------------------------------|

Arm description:

After completion of OL treatment phase, subjects were followed up for safety up to 7 to 14 days from 1 year up to 1 year 2 weeks.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| Number of subjects in period 4 | OL FU Phase: Seltorexant 20 mg |
|--------------------------------|--------------------------------|
| Started                        | 453                            |
| Completed                      | 425                            |
| Not completed                  | 28                             |
| Consent withdrawn by subject   | 16                             |
| Adverse event, non-fatal       | 4                              |
| Site terminated by sponsor     | 1                              |
| Unspecified                    | 2                              |
| Lost to follow-up              | 5                              |

## Baseline characteristics

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Double -blind Phase (DB): Placebo |
|-----------------------|-----------------------------------|

Reporting group description:

During DB phase, subjects with major depressive disorder (MDD) with or without insomnia symptoms (IS) who had an inadequate response to an ongoing antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were randomised to receive placebo (matching to seltorexant) once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | DB: Seltorexant 20 mg |
|-----------------------|-----------------------|

Reporting group description:

During DB phase, subjects with MDD with or without IS who had an inadequate response to an ongoing antidepressant therapy with a SSRI or SNRI were randomised to receive seltorexant 20 milligrams (mg) tablet orally once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

| Reporting group values  | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg | Total |
|---|-----------------------------------|-----------------------|-------|
| Number of subjects  | 303                               | 283                   | 586   |
| Age Categorical<br>Units: Subjects                                      |                                   |                       |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 45.9<br>± 14.28                   | 44.3<br>± 13.99       | -     |
| Gender categorical<br>Units: Subjects                                   |                                   |                       |       |
| Male  | 71                                | 66                    | 137   |
| Female  | 232                               | 217                   | 449   |

## End points

### End points reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | Double -blind Phase (DB): Placebo     |
| Reporting group description:<br>During DB phase, subjects with major depressive disorder (MDD) with or without insomnia symptoms (IS) who had an inadequate response to an ongoing antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were randomised to receive placebo (matching to seltorexant) once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy. |                                       |
| Reporting group title   | DB: Seltorexant 20 mg                 |
| Reporting group description:<br>During DB phase, subjects with MDD with or without IS who had an inadequate response to an ongoing antidepressant therapy with a SSRI or SNRI were randomised to receive seltorexant 20 milligrams (mg) tablet orally once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.   |                                       |
| Reporting group title   | OL Treatment Phase: Seltorexant 20 mg |
| Reporting group description:<br>Subjects who received placebo or seltorexant 20 mg tablet in the DB treatment phase entered OL phase and received seltorexant 20 mg tablet orally, once daily from Day 43 up to 1 year as an adjunctive therapy to ongoing SSRI/SNRI antidepressant therapy.  |                                       |
| Reporting group title   | DB Follow-up (FU) Phase: Placebo      |
| Reporting group description:<br>After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.   |                                       |
| Reporting group title   | DB FU Phase: Seltorexant 20 mg        |
| Reporting group description:<br>After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.   |                                       |
| Reporting group title   | OL FU Phase: Seltorexant 20 mg        |
| Reporting group description:<br>After completion of OL treatment phase, subjects were followed up for safety up to 7 to 14 days from 1 year up to 1 year 2 weeks.   |                                       |

### Primary: Double-blind (DB) Phase: Change From Baseline to Day 43 in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score : Estimand 2

|   |   |
|---|---|
| End point title   | Double-blind (DB) Phase: Change From Baseline to Day 43 in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score : Estimand 2 |
| End point description:<br>MADRS, clinician-rated scale designed to measure depression severity and detected changes due to antidepressant intervention. Scale consisted of 10 items, each of which was scored from 0 (not present or normal) to 6 (severe or continuous presence of symptoms). MADRS evaluated reported sadness, apparent sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts. MADRS total score was sum of scores from individual question items, which ranged from 0-60. Higher scores represented a more severe condition. Negative changes in MADRS total score indicated improvement. Full analysis set 2 (FAS2) included all randomised subjects with major depressive disorder with insomnia symptoms (MDDIS) per interactive web response system (IWRS) who received at least 1 dose of study intervention in DB phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint. |   |
| End point type  | Primary   |
| End point timeframe:<br>DB: Baseline (Day 1), Day 43  |   |

|                                      |                                   |                       |  |  |
|--------------------------------------|-----------------------------------|-----------------------|--|--|
| <b>End point values</b>              | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg |  |  |
| Subject group type                   | Reporting group                   | Reporting group       |  |  |
| Number of subjects analysed          | 207                               | 201                   |  |  |
| Units: Units on a scale              |                                   |                       |  |  |
| arithmetic mean (standard deviation) | -10.2 (± 10.20)                   | -12.9 (± 9.53)        |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Statistical Analysis set -1                               |
| Comparison groups                       | DB: Seltorexant 20 mg v Double -blind Phase (DB): Placebo |
| Number of subjects included in analysis | 408   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.007   |
| Method                                  | mixed model repeated measures (MMRM)                      |
| Parameter estimate                      | Least square (LS) difference                              |
| Point estimate                          | -2.5  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -4.35   |
| upper limit                             | -0.68   |
| Variability estimate                    | Standard error of the mean                                |
| Dispersion value                        | 0.94  |

## Primary: Open Label (OL) Treatment Phase: Number of Subjects with Treatment Emergent Adverse Events (TEAEs)

|                        |   |
|------------------------|---|
| End point title        | Open Label (OL) Treatment Phase: Number of Subjects with Treatment Emergent Adverse Events (TEAEs) <sup>[1]</sup>   |
| End point description: | An AE was defined as any untoward medical occurrence in a clinical investigation subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the study drug. Treatment emergent AEs was defined as any AE occurred at or after the initial administration of study intervention through the day of last dose plus 2 days. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. |
| End point type         | Primary   |
| End point timeframe:   | From start of the treatment in OL phase (Day 1 [Day 43 from study baseline]) up to 2 days after last dose (up to 52 weeks of the OL phase)  |

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: Only descriptive data was planned to be reported for this endpoint.

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type          | Reporting group                          |  |  |  |
| Number of subjects analysed | 522                                      |  |  |  |
| Units: Subjects             | 330                                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Blood Pressure

|                 |  |
|-----------------|--|
| End point title | OL Treatment Phase: Change From Baseline in Vital Signs: Blood Pressure <sup>[2]</sup> |
|-----------------|--|

End point description:

Change from baseline in vital signs of systolic/diastolic blood pressure (SBP/DBP) were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[2] - 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: Only descriptive data was planned to be reported for this endpoint.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 359                                      |  |  |  |
| Units: millimetre of mercury (mmHg)  |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| DBP: Week 52                         | 0.5 (± 8.30)                             |  |  |  |
| SBP: Week 52                         | 0.0 (± 10.85)                            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Number of Subjects with Treatment-emergent Adverse Events of Special Interest (AESI)

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Number of Subjects with Treatment-emergent Adverse Events of Special Interest (AESI) <sup>[3]</sup> |
|-----------------|---|

End point description:

The AEs considered to be of special interest: cataplexy, sleep paralysis, complex, sleep-related behaviors/parasomnias such as confusional arousals, somnambulism, sleep terrors, bruxism, sleep sex, sleep-related eating disorder, and catathrenia, fall, motor vehicle accident. Treatment emergent AEs was defined as any AE occurred at or after the initial administration of study intervention through the day of last dose plus 2 days. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase.

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

End point timeframe:

From start of the treatment in OL phase (Day 1 [Day 43 from study baseline]) up to 2 days after last dose (up to 52 weeks of the OL phase)

Notes:

[3] - 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: Only descriptive data was planned to be reported for this endpoint.

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type          | Reporting group                          |  |  |  |
| Number of subjects analysed | 522                                      |  |  |  |
| Units: Subjects             | 18                                       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Pulse Rate

|                 |  |
|-----------------|--|
| End point title | OL Treatment Phase: Change From Baseline in Vital Signs: Pulse Rate <sup>[4]</sup> |
|-----------------|--|

End point description:

Change from baseline in vital signs of pulse rate were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[4] - 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: Only descriptive data was planned to be reported for this endpoint.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 359                                      |  |  |  |
| Units: Beats per minute              |  |  |  |  |
| arithmetic mean (standard deviation) | 0.3 (± 8.81)                             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Body Mass Index (BMI)

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Change From Baseline in Vital Signs: Body Mass Index (BMI) <sup>[5]</sup> |
|-----------------|---|

End point description:

Change from baseline in vital signs of BMI were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[5] - 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: Only descriptive data was planned to be reported for this endpoint.

|  |                                       |  |  |  |
|--|---------------------------------------|--|--|--|
| <b>End point values</b>                                | OL Treatment Phase: Seltorexant 20 mg |  |  |  |
| Subject group type                                     | Reporting group                       |  |  |  |
| Number of subjects analysed                            | 365                                   |  |  |  |
| Units: Kilograms per square meter (kg/m <sup>2</sup> ) |                                       |  |  |  |
| arithmetic mean (standard deviation)                   | 0.55 (± 1.634)                        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Waist Circumference

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Change From Baseline in Vital Signs: Waist Circumference <sup>[6]</sup> |
|-----------------|---|

End point description:

Change from baseline in vital signs of waist circumference were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[6] - 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: Only descriptive data was planned to be reported for this endpoint.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 362                                      |  |  |  |
| Units: Centimeters                   |  |  |  |  |
| arithmetic mean (standard deviation) | 0.6 (± 5.94)                             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Temperature

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Change From Baseline in Vital Signs: Temperature <sup>[7]</sup> |
|-----------------|---|

End point description:

Change from baseline in vital signs of temperature were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[7] - 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: Only descriptive data was planned to be reported for this endpoint.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 359                                      |  |  |  |
| Units: Centigrade                    |  |  |  |  |
| arithmetic mean (standard deviation) | -0.01 (± 0.306)                          |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Change From Baseline in Vital Signs: Weight

|                 |  |
|-----------------|--|
| End point title | OL Treatment Phase: Change From Baseline in Vital Signs: Weight <sup>[8]</sup> |
|-----------------|--|

End point description:

Change from baseline in vital signs of weight were reported. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, 'N' (overall number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type Primary

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[8] - 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: Only descriptive data was planned to be reported for this endpoint.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 365                                      |  |  |  |
| Units: Kilograms                     |  |  |  |  |
| arithmetic mean (standard deviation) | 1.54 (± 4.442)                           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: OL Treatment Phase: Number of Subjects with New Suicidal Ideation and Behavior Using the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title OL Treatment Phase: Number of Subjects with New Suicidal Ideation and Behavior Using the Columbia Suicide Severity Rating Scale (C-SSRS)<sup>[9]</sup>

End point description:

C-SSRS is a clinician-rated instrument that reports severity and frequency of suicide-related ideation and behaviors. Suicidal ideation was classified on a 5-item scale: 1 (wish to be dead), 2 (non-specific active suicidal thoughts), 3 (suicidal ideation without plan and intent), 4 (suicidal ideation intent to act without plan), and 5 (suicidal ideation with plan and intent), Suicidal behavior is classified on a 5-item scale: 6 (preparatory acts or behavior), 7 (aborted attempt), 8 (interrupted attempt), 9 (actual attempt), and 10 (suicide). Minimum total score 0, maximum total score 10; higher total scores indicate more suicidal ideation and/or suicidal behavior. If no events qualify for scores of 1 to 10, score of 0 was assigned (0= "no event that can be assessed on the basis of C-SSRS"). The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Higher scores indicated greater severity.

End point type Primary

End point timeframe:

From DB Baseline up to week 52 of OL phase

Notes:

[9] - 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: Only descriptive data was planned to be reported for this endpoint.

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type          | Reporting group                          |  |  |  |
| Number of subjects analysed | 522                                      |  |  |  |
| Units: Subjects             |  |  |  |  |
| Suicidal ideation           | 87                                       |  |  |  |
| Suicidal behavior           | 7  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Physician Withdrawal Checklist (PWC-20) Total Scores

|                 |  |
|-----------------|--|
| End point title | OL Treatment Phase: Physician Withdrawal Checklist (PWC-20) Total Scores <sup>[10]</sup> |
|-----------------|--|

End point description:

Potential withdrawal effects were assessed by the clinician using the PWC-20. The PWC-20 was a reliable and sensitive instrument for the assessment of discontinuation symptoms. The assessment has 20 items evaluated to detect withdrawal symptoms. Symptoms are rated on a scale of 0-3. Symptoms rated on a scale of 0 =not present, 1=mild, 2 =moderate, and 3 =severe. The total PWC-20 score was the sum of 20 item scores and ranged between 0 and 60. The higher score indicates more frequent/severe symptoms. Follow-up analysis set included all randomised subjects who entered the follow-up phase after OL. Here, "N" (overall number of subjects analysed): subjects who were evaluable and "n" (number analysed): number of subjects evaluable for each arm at specified time points.

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

End point timeframe:

End of OL (Week 52 of OL phase), follow-up 1 (1 day after end of OL phase), and follow-up 2 (2 weeks after end of OL phase)

Notes:

[10] - 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: Only descriptive data was planned to be reported for this endpoint.

|                                      |                                   |  |  |  |
|--------------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>              | OL FU Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type                   | Reporting group                   |  |  |  |
| Number of subjects analysed          | 443                               |  |  |  |
| Units: Units on a scale              |                                   |  |  |  |
| arithmetic mean (standard deviation) |                                   |  |  |  |
| End of OL (Week 59) (n=443)          | 7.6 (± 8.37)                      |  |  |  |
| followup 1 (n=435)                   | 5.8 (± 7.34)                      |  |  |  |
| followup 2 (n=401)                   | 6.7 (± 7.42)                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: OL Treatment Phase: Number of Subjects with Clinical Laboratory Abnormalities

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Number of Subjects with Clinical Laboratory Abnormalities <sup>[11]</sup> |
|-----------------|---|

End point description:

Laboratory parameters: hematology (platelet count, red blood cell [RBC] count, hemoglobin, hematocrit, neutrophils (Segmented/Leukocytes), lymphocytes, monocytes, eosinophils/leukocytes [Eos/Leu], basophils, Reticulocytes/ Erythrocytes [Reti/Ery]); chemistry (sodium, potassium, chloride, bicarbonate, creatinine, glucose, aspartate transaminase [AST], alanine transaminase [ALT], gamma-glutamyl transferase [GGT], alkaline phosphatase, total, bilirubin, phosphate, albumin, total protein, total cholesterol); urine (specific gravity, pH, glucose, blood, bilirubin, urobilinogen, RBC). Clinically significant abnormalities (low/high) were determined at the investigator's discretion. Only those categories in which at least one subject had data were reported in this endpoint. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Here, n (number analysed) signifies number of subjects evaluable for specified categories.

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

End point timeframe:

From OL Baseline (Day 1 [Day 43 from study baseline]) to Week 52 of OL phase

Notes:

[11] - 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: Only descriptive data was planned to be reported for this endpoint.

| End point values                        | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
|---|--|--|--|--|
| Subject group type                      | Reporting group                          |  |  |  |
| Number of subjects analysed             | 522                                      |  |  |  |
| Units: Subjects                         |  |  |  |  |
| ALT High (n=516)                        | 3  |  |  |  |
| AST High (n=519)                        | 1  |  |  |  |
| Bicarbonate Low (n=507)                 | 1  |  |  |  |
| Chloride Low (n=520)                    | 1  |  |  |  |
| Cholesterol High (n=520)                | 18                                       |  |  |  |
| Creatine Kinase High (n=519)            | 10                                       |  |  |  |
| GGT High (n=516)                        | 1  |  |  |  |
| Glucose High (n=518)                    | 1  |  |  |  |
| HDL Cholesterol low (n=520)             | 43                                       |  |  |  |
| Hemoglobin A1C/ Hemoglobin High (n=518) | 5  |  |  |  |
| LDL Cholesterol Low (n=520)             | 85                                       |  |  |  |
| LDL Cholesterol High (n=520)            | 90                                       |  |  |  |
| Phosphate low (n=520)                   | 8  |  |  |  |
| Potassium Low (n=517)                   | 2  |  |  |  |
| Potassium High (n=517)                  | 3  |  |  |  |
| Triglycerides High (n=520)              | 1  |  |  |  |
| Eos/Leu High (n=518)                    | 5  |  |  |  |
| Erythrocytes High(n=516)                | 5  |  |  |  |
| Hematocrit High (n=514)                 | 8  |  |  |  |
| Leukocytes Low (n=516)                  | 1  |  |  |  |
| Leukocytes High (n=516)                 | 4  |  |  |  |
| Lymphocytes/Leukocytes High (n=518)     | 2  |  |  |  |
| Lymphocytes/Leukocytes Low (n=518)      | 6  |  |  |  |
| Neutrophils low (n=518)                 | 5  |  |  |  |
| Neutrophils High (n=518)                | 1  |  |  |  |

|                               |     |  |  |  |
|-------------------------------|-----|--|--|--|
| Platelets Low (n=516)         | 1   |  |  |  |
| Platelets High (n=516)        | 2   |  |  |  |
| Reti/Ery Low (n=518)          | 6   |  |  |  |
| Reti/Ery High (n=518)         | 136 |  |  |  |
| Specific Gravity High (n=522) | 47  |  |  |  |
| Urine pH High (n=522)         | 56  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Number of Subjects with Electrocardiogram (ECG) Abnormalities

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Number of Subjects with Electrocardiogram (ECG) Abnormalities <sup>[12]</sup> |
|-----------------|---|

End point description:

The ECG parameters that were analysed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazetts formula (QTcB), Fridericias formula (QTcF). The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. Only those categories in which at least one subject had data were reported in this endpoint. Here, n (number analysed) signifies number of subjects evaluable for specified time points. Here B: denotes baseline.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[12] - 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: Only descriptive data was planned to be reported for this endpoint.

| End point values                      | OL Treatment Phase: Seltorexant 20 mg |  |  |  |
|---------------------------------------|---------------------------------------|--|--|--|
| Subject group type                    | Reporting group                       |  |  |  |
| Number of subjects analysed           | 522                                   |  |  |  |
| Units: Subjects                       |                                       |  |  |  |
| B: ECG Mean Heart Rate <=50 (n=522)   | 11                                    |  |  |  |
| B: ECG Mean Heart Rate >=100 (n=522)  | 4                                     |  |  |  |
| B: PR Interval <=120 (n=522)          | 10                                    |  |  |  |
| B: PR Interval >=200 (n=522)          | 6                                     |  |  |  |
| B: RR Interval <=600 (n=522)          | 4                                     |  |  |  |
| B: RR Interval >=1200 (n=522)         | 10                                    |  |  |  |
| B: QRS Duration >=120 (n=522)         | 3                                     |  |  |  |
| B: QT Interval >= 500 (n=522)         | 1                                     |  |  |  |
| W52: ECG Mean Heart Rate <=50 (n=358) | 3                                     |  |  |  |
| W52:ECG Mean Heart Rate >=100 (n=358) | 4                                     |  |  |  |
| W52:PR Interval <=120 (n=358)         | 6                                     |  |  |  |
| W52: PR Interval >=200 (n=358)        | 5                                     |  |  |  |
| W52: RR Interval <=600 (n=358)        | 4                                     |  |  |  |

|                                 |   |  |  |  |
|---------------------------------|---|--|--|--|
| W52: RR Interval >=1200 (n=358) | 3 |  |  |  |
| W52: QRS Duration >=120 (n=358) | 4 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: OL Treatment Phase: Number of Subjects With Sexual Dysfunction as Determined by Arizona Sexual Experiences Scale (ASEX) Score

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Number of Subjects With Sexual Dysfunction as Determined by Arizona Sexual Experiences Scale (ASEX) Score <sup>[13]</sup> |
|-----------------|---|

End point description:

ASEX is a five-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Each of the 5 items is rated on a 6-point Likert scale, ranging from 1 to 6. The 5 items are summed to create a total score, ranging from 5 to 30, with the higher scores indicating more sexual dysfunction. Sexual dysfunction is defined as an ASEX total score of 19 or greater, or a score of 5 or greater on any item, or a score of 4 or greater on any 3 items. The safety (OL) analysis set included all randomised subjects who received at least 1 dose of study intervention in the OL phase. . Here, "N" (overall number of subjects analysed): subjects who were evaluable and "n" (number analysed): number of subjects evaluable for each arm at specified time points.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]) and OL Week 52

Notes:

[13] - 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: Only descriptive data was planned to be reported for this endpoint.

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
| Subject group type          | Reporting group                          |  |  |  |
| Number of subjects analysed | 512                                      |  |  |  |
| Units: Subjects             |  |  |  |  |
| Baseline (OL) (n=512)       | 391                                      |  |  |  |
| Week 52 (n=365)             | 235                                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DB Phase: Change from Baseline to Day 43 in the MADRS Without Sleep Item (MADRS-WOSI) Total Score- Estimand 2

|                 |   |
|-----------------|---|
| End point title | DB Phase: Change from Baseline to Day 43 in the MADRS Without Sleep Item (MADRS-WOSI) Total Score- Estimand 2 |
|-----------------|---|

End point description:

The MADRS was a clinician-rated scale designed to measure depression severity and detected changes due to antidepressant treatment. MADRS-WOSI was defined as the full MADRS without the sleep item.

The MADRS-WOSI scale consisted of 9 items, each of which was scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms). MADRS-WOSI total score was the sum of scores from individual question items, which ranged from 0 to 54, higher scores represented a more severe condition. The MADRS-WOSI evaluated apparent sadness, reported sadness, inner tension, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Negative change in MADRS total score indicated improvement. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint.

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| DB: Baseline (Day 1), Day 43 |           |

|                                      |                                   |                       |  |  |
|--------------------------------------|-----------------------------------|-----------------------|--|--|
| <b>End point values</b>              | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg |  |  |
| Subject group type                   | Reporting group                   | Reporting group       |  |  |
| Number of subjects analysed          | 207                               | 201                   |  |  |
| Units: Units on a scale              |                                   |                       |  |  |
| arithmetic mean (standard deviation) | -9.2 (± 9.31)                     | -11.3 (± 8.68)        |  |  |

## Statistical analyses

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis set -2 |
|-----------------------------------|-----------------------------|

Statistical analysis description:

In accordance with protocol predefined testing sequence, statistical significance of the primary endpoint and first key secondary endpoint was required before testing the secondary endpoint (MADRS-WOSI) and thus, a formal statistical testing was performed.

|   |   |
|---|---|
| Comparison groups                       | DB: Seltorexant 20 mg v Double -blind Phase (DB): Placebo |
| Number of subjects included in analysis | 408   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.024   |
| Method                                  | MMRM  |
| Parameter estimate                      | LS mean difference  |
| Point estimate                          | -1.9  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -3.61   |
| upper limit                             | -0.26   |
| Variability estimate                    | Standard error of the mean                                |
| Dispersion value                        | 0.85  |

## Secondary: DB Phase: Change from Baseline to Day 43 in Sleep Disturbance Using the Patient Reported Outcome Measurement Information System-Sleep Disturbance (PROMIS-SD) Short Form (8a) T-score: Estimand 2

|                 |  |
|-----------------|--|
| End point title | DB Phase: Change from Baseline to Day 43 in Sleep Disturbance Using the Patient Reported Outcome Measurement |
|-----------------|--|

End point description:

PROMIS-SD Short Form 8a: static 8-item questionnaire, assessed self-perceptions of sleep initiation (2 items), quality of sleep (3 items), early morning feelings (2 items), worrying about sleep (1 item). Each question, 5 options ranged 1 to 5. Direction of responses was not same, sometimes "not at all" =more sleep disturbance; "not at all" =less sleep disturbance. Total raw score for short form with all questions answered was sum of values of response to each question, total score ranged 8 - 40. Lower scores=less sleep disturbance. Total raw score converted into T-score. T-score rescaled the raw score into standardized score with mean-50; SD-10. Negative changes in scores=improvement. Higher values represent more severe sleep disturbance. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase. N (number of subjects analysed) signifies subjects evaluable.

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

End point timeframe:

DB: Baseline (Day 1), Day 43

| End point values                     | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg |  |  |
|--------------------------------------|-----------------------------------|-----------------------|--|--|
| Subject group type                   | Reporting group                   | Reporting group       |  |  |
| Number of subjects analysed          | 207                               | 201                   |  |  |
| Units: T-score                       |                                   |                       |  |  |
| arithmetic mean (standard deviation) | -7.1 (± 10.44)                    | -10.9 (± 9.10)        |  |  |

**Statistical analyses**

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | Statistical analysis set -3 |
|-----------------------------------|-----------------------------|

Statistical analysis description:

In accordance with protocol predefined testing sequence, statistical significance of the primary endpoint was required before testing the secondary endpoint (PROMIS-SD; Short Form 8a) and thus, a formal statistical testing was performed.

|   |   |
|---|---|
| Comparison groups                       | DB: Seltorexant 20 mg v Double -blind Phase (DB): Placebo |
| Number of subjects included in analysis | 408   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.001   |
| Method                                  | MMRM  |
| Parameter estimate                      | LS mean difference  |
| Point estimate                          | -3.6  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5.25   |
| upper limit                             | -1.85   |
| Variability estimate                    | Standard error of the mean                                |
| Dispersion value                        | 0.87  |

**Secondary: DB Phase: Change from Baseline to Day 43 in the MADRS-6 Total Score**

|                 |   |
|-----------------|---|
| End point title | DB Phase: Change from Baseline to Day 43 in the MADRS-6 Total Score |
|-----------------|---|

End point description:

The 6-item MADRS was a clinician-administered scale designed to measure the core symptoms of depression severity and detected changes due to antidepressant intervention. It is a subset of MADRS (10-item). The MADRS-6 subscale score was the sum of scores for the following MADRS items: apparent sadness, reported sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts. Each item is scored from 0 (item not present or normal) to 6 (most severe or continuous presence of symptoms); the overall score ranges from 0 to 36, higher scores represented a more severe condition. Negative change in score indicates improvement. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint.

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

End point timeframe:

DB: Baseline (Day 1), Day 43

| End point values                     | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg |  |  |
|--------------------------------------|-----------------------------------|-----------------------|--|--|
| Subject group type                   | Reporting group                   | Reporting group       |  |  |
| Number of subjects analysed          | 207                               | 201                   |  |  |
| Units: Units on a scale              |                                   |                       |  |  |
| arithmetic mean (standard deviation) | -6.9 ( $\pm$ 7.02)                | -8.4 ( $\pm$ 6.73)    |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: DB Phase: Percentage of Subjects with Response on Depressive Symptoms Scale Based on MADRS at Day 43**

|                 |  |
|-----------------|--|
| End point title | DB Phase: Percentage of Subjects with Response on Depressive Symptoms Scale Based on MADRS at Day 43 |
|-----------------|--|

End point description:

Responders, defined as subjects with a  $\geq$ 50 percent (%) improvement in the MADRS total score from baseline to a given timepoint. The MADRS was a clinician-rated scale designed to measure depression severity and detected changes due to antidepressant treatment. Scale consisted of 10 items, each of which was scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms). MADRS total score was sum of scores from individual question items, which ranged from 0 to 60, higher scores represented a more severe condition. The MADRS evaluated apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts. Negative change in MADRS total score indicated improvement. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase.

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

End point timeframe:

At Day 43

|                               |                                   |                       |  |  |
|-------------------------------|-----------------------------------|-----------------------|--|--|
| <b>End point values</b>       | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg |  |  |
| Subject group type            | Reporting group                   | Reporting group       |  |  |
| Number of subjects analysed   | 223                               | 213                   |  |  |
| Units: Percentage of subjects |                                   |                       |  |  |
| number (not applicable)       | 22.9                              | 36.2                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DB Phase: Change From Baseline to Day 43 in Patient Health Questionnaire 9-item (PHQ-9) Total Score

|                 |   |
|-----------------|---|
| End point title | DB Phase: Change From Baseline to Day 43 in Patient Health Questionnaire 9-item (PHQ-9) Total Score |
|-----------------|---|

End point description:

The PHQ-9 was a 9-item, subject reported endpoint to assess depressive symptoms. The scale scores each of the 9 symptom domains of the diagnostic and statistical manual of mental disorders-5th edition (DSM-5) major depressive disorder (MDD) criteria. Each item was rated on a 4 points scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The subject's item responses were summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: none-minimal (0-4), mild (5-9), moderate (10-14), moderately Severe (15-19) and severe (20-27). Negative changes in PHQ-9 total score indicated improvement. FAS2 included all randomised subjects with MDDIS per IWRS who received at least 1 dose of study intervention in DB phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint.

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

End point timeframe:

DB: Baseline (Day 1), Day 43

|                                      |                                   |                       |  |  |
|--------------------------------------|-----------------------------------|-----------------------|--|--|
| <b>End point values</b>              | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg |  |  |
| Subject group type                   | Reporting group                   | Reporting group       |  |  |
| Number of subjects analysed          | 207                               | 201                   |  |  |
| Units: Units on a scale              |                                   |                       |  |  |
| arithmetic mean (standard deviation) | -5.5 (± 6.63)                     | -7.6 (± 5.98)         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: OL Treatment Phase: Change From Baseline Over Time in MADRS Total Score

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Change From Baseline Over Time in MADRS Total Score |
|-----------------|---|

**End point description:**

MADRS was a clinician-administered scale designed to measure depression severity and detected changes due to antidepressant treatment. The MADRS evaluates the following 10 items: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), total score was sum of scores from individual question items, which ranged from 0-60. Higher scores represented a more severe condition. Negative change in MADRS total score indicated improvement. FAS2 (OL) included all FAS2 subjects who received at least 1 dose of study intervention in the OL phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and n (number analysed) signifies number of subjects evaluable for specified time points.

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

**End point timeframe:**

OL Baseline (Day 1 [Day 43 from study baseline]), OL Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| <b>End point values</b>              | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 381                                      |  |  |  |
| Units: Units on a scale              |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Week 4 (n=381)                       | -5.0 (± 8.27)                            |  |  |  |
| Week 8 (n=366)                       | -6.2 (± 9.53)                            |  |  |  |
| Week 12 (n=345)                      | -6.8 (± 9.88)                            |  |  |  |
| Week 16 (n=339)                      | -7.7 (± 10.41)                           |  |  |  |
| Week 20 (n=327)                      | -8.6 (± 10.53)                           |  |  |  |
| Week 24 (n=311)                      | -8.0 (± 10.93)                           |  |  |  |
| Week 28 (n=296)                      | -8.8 (± 11.03)                           |  |  |  |
| Week 32 (n=291)                      | -9.5 (± 11.20)                           |  |  |  |
| Week 36 (n=289)                      | -9.3 (± 11.32)                           |  |  |  |
| Week 40 (n=280)                      | -10.2 (± 11.45)                          |  |  |  |
| Week 44 (n=274)                      | -11.0 (± 10.93)                          |  |  |  |
| Week 48 (n=274)                      | -11.2 (± 10.62)                          |  |  |  |
| Week 52 (n=273)                      | -11.4 (± 10.43)                          |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

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**Secondary: OL Treatment Phase: Change From Baseline Over Time in the Clinical Global Impression-Severity (CGI S) Score**


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|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Change From Baseline Over Time in the Clinical Global Impression-Severity (CGI S) Score |
|-----------------|---|

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**End point description:**

The CGI-S (depression) provided an overall clinician-determined summary measure of severity of the subject's illness that considers all available information, included knowledge of subject's history, psychosocial circumstances, symptoms, behavior, impact of symptoms on subject's ability to function. CGI-S evaluated severity of psychopathology on a scale of 1 to 7. The CGI-S was 7-point global assessment scale that measures clinician's impression of severity of illness, rating: 1=normal (not at all ill), 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill subjects, with higher scores indicate worsening. Negative changes in CGI-S score indicate improvement. FAS2 (OL) included all FAS2 subjects who received at least 1 dose of study intervention in the OL phase. Here, N (number of subjects analysed) signifies subjects evaluable, n signifies number of subjects evaluable for specified time points.

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

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**End point timeframe:**

OL Baseline (Day 1 [Day 43 from study baseline]), OL Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

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| <b>End point values</b>              | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 381                                      |  |  |  |
| Units: Units on a scale              |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Week 4 (n=381)                       | -0.6 (± 0.99)                            |  |  |  |
| Week 8 (n=366)                       | -0.8 (± 1.12)                            |  |  |  |
| Week 12 (n=345)                      | -0.8 (± 1.21)                            |  |  |  |
| Week 16 (n=339)                      | -1.0 (± 1.34)                            |  |  |  |
| Week 20 (n=327)                      | -1.0 (± 1.35)                            |  |  |  |
| Week 24 (n=311)                      | -1.1 (± 1.39)                            |  |  |  |
| Week 28 (n=296)                      | -1.1 (± 1.40)                            |  |  |  |
| Week 32 (n=291)                      | -1.3 (± 1.35)                            |  |  |  |
| Week 36 (n=289)                      | -1.2 (± 1.47)                            |  |  |  |
| Week 40 (n=280)                      | -1.3 (± 1.45)                            |  |  |  |
| Week 44 (n=274)                      | -1.5 (± 1.42)                            |  |  |  |
| Week 48 (n=274)                      | -1.5 (± 1.39)                            |  |  |  |
| Week 52 (n=273)                      | -1.6 (± 1.37)                            |  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: OL Treatment Phase: Change from Baseline Over Time in the MADRS-WOSI Total Score**

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|                 |  |
|-----------------|--|
| End point title | OL Treatment Phase: Change from Baseline Over Time in the MADRS-WOSI Total Score |
|-----------------|--|

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**End point description:**

MADRS was a clinician-administered scale designed to measure depression severity and detected changes due to antidepressant treatment. The MADRS evaluates the following 10 items: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), total score was sum of

scores from individual question items, which ranged from 0-60. Higher scores represented a more severe condition. Negative change in MADRS total score indicated improvement. FAS2 (OL) included all FAS2 subjects who received at least 1 dose of study intervention in the OL phase. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and n (number analysed) signifies number of subjects evaluable for specified time points.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]), OL Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| End point values                     | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 381                                      |  |  |  |
| Units: Units on a scale              |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Week 4 (n=381)                       | -4.2 (± 7.47)                            |  |  |  |
| Week 8 (n=366)                       | -5.3 (± 8.56)                            |  |  |  |
| Week 12 (n=345)                      | -5.9 (± 8.91)                            |  |  |  |
| Week 16 (n= 339)                     | -6.7 (± 9.41)                            |  |  |  |
| Week 20 (n=327)                      | -7.5 (± 9.50)                            |  |  |  |
| Week 24 (n= 311)                     | -7.0 (± 9.95)                            |  |  |  |
| Week 28 (n=296)                      | -7.7 (± 10.03)                           |  |  |  |
| Week 32 (n= 291)                     | -8.3 (± 10.25)                           |  |  |  |
| Week 36 (n=289)                      | -8.1 (± 10.19)                           |  |  |  |
| Week 40 (n=280)                      | -8.8 (± 10.44)                           |  |  |  |
| Week 44 (n= 274)                     | -9.6 (± 9.87)                            |  |  |  |
| Week 48 (n= 274)                     | -9.9 (± 9.62)                            |  |  |  |
| Week 52 (n= 273)                     | -9.8 (± 9.34)                            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: OL Treatment Phase: Change From Baseline Over Time in Sleep Disturbance Using the PROMIS SD Short Form 8a T-score

|                 |   |
|-----------------|---|
| End point title | OL Treatment Phase: Change From Baseline Over Time in Sleep Disturbance Using the PROMIS SD Short Form 8a T-score |
|-----------------|---|

End point description:

PROMIS-SD Short Form 8a: static 8-item questionnaire, assessed self-perceptions of sleep initiation (2 items), quality of sleep (3 items), early morning feelings (2 items), worrying about sleep (1item). Each question, 5 options ranged 1- 5. Direction of responses was not same, sometimes "not at all" =more sleep disturbance; "not at all" =less sleep disturbance. Total raw score for short form with all questions answered was sum of values of response to each question, total score ranged 8 - 40. Lower scores=less sleep disturbance. Total raw score converted into T-score. T-score rescaled raw score into standardized score with mean-50; SD-10. Negative changes in scores=improvement. Higher values represent more severe sleep disturbance. FAS2 (OL) included all FAS2 subjects who received at least 1 dose of study intervention in OL phase. Here, N (number of subjects analysed) signifies subjects evaluable, n (number analysed) signifies number of subjects evaluable for specified time points.

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

End point timeframe:

OL Baseline (Day 1 [Day 43 from study baseline]), OL Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| <b>End point values</b>              | OL Treatment Phase:<br>Seltorexant 20 mg |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                          |  |  |  |
| Number of subjects analysed          | 380                                      |  |  |  |
| Units: T-score                       |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Week 4 (n=380)                       | -4.9 (± 8.57)                            |  |  |  |
| Week 8 (n=366)                       | -5.3 (± 9.21)                            |  |  |  |
| Week 12 (n=344)                      | -6.3 (± 9.48)                            |  |  |  |
| Week 16 (n=339)                      | -6.4 (± 10.24)                           |  |  |  |
| Week 20 (n=326)                      | -6.8 (± 10.29)                           |  |  |  |
| Week 24 (n=311)                      | -6.7 (± 9.99)                            |  |  |  |
| Week 28 (n=296)                      | -7.1 (± 10.09)                           |  |  |  |
| Week 32 (n=291)                      | -7.2 (± 10.32)                           |  |  |  |
| Week 36 (n= 289)                     | -7.6 (± 10.66)                           |  |  |  |
| Week 40 (n=280)                      | -8.2 (± 10.46)                           |  |  |  |
| Week 44 (n=274)                      | -9.1 (± 10.56)                           |  |  |  |
| Week 48 (n=274)                      | -8.6 (± 10.42)                           |  |  |  |
| Week 52 (n=273)                      | -9.6 (± 10.44)                           |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs/other AEs: DB: Day (D) 1 to 2 days after last dose (D44); DB FU: D44 to D57; OL: D1 [D43 study BL] to 2 days after last dose (Week [W] 52); OL FU: W 52 to 2 Weeks after end of OL phase (W61); Death: DB: D1 to D43, OL: D43 to 1 year 2 weeks

Adverse event reporting additional description:

DB phase: The safety analysis included all randomised subjects who received at least 1 dose of study intervention in the DB phase. OL Phase: The safety analysis included all randomised subjects who received at least 1 dose of study intervention in the OL phase.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 26.1   |

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Double -blind Phase (DB): Placebo |
|-----------------------|-----------------------------------|

Reporting group description:

During DB phase, subjects with major depressive disorder (MDD) with or without insomnia symptoms (IS) who had an inadequate response to an ongoing antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) were randomised to receive placebo (matching to seltorexant) once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | DB: Seltorexant 20 mg |
|-----------------------|-----------------------|

Reporting group description:

During DB phase, subjects with MDD with or without IS who had an inadequate response to an ongoing antidepressant therapy with a SSRI or SNRI were randomised to receive seltorexant 20 milligrams (mg) tablet orally once daily from Day 1 to Day 42 as an adjunctive therapy to SSRI/SNRI antidepressant therapy.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | OL Treatment Phase: Seltorexant 20 mg |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects who received placebo or seltorexant 20 mg tablet in the DB treatment phase entered OL phase and received seltorexant 20 mg tablet orally, once daily from Day 43 up to 1 year as an adjunctive therapy to ongoing SSRI/SNRI antidepressant therapy.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | DB Follow-up (FU) Phase: Placebo |
|-----------------------|----------------------------------|

Reporting group description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | DB FU Phase: Seltorexant 20 mg |
|-----------------------|--------------------------------|

Reporting group description:

After completion or discontinuation from the DB treatment, subjects who did not enter the OL phase entered DB follow up phase and were followed up for safety up to 14 days from Day 43 up to Day 57.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | OL FU Phase: Seltorexant 20 mg |
|-----------------------|--------------------------------|

Reporting group description:

After completion of OL treatment phase, subjects were followed up for safety up to 7 to 14 days from 1 year up to 1 year 2 weeks.

| <b>Serious adverse events</b>                     | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg | OL Treatment Phase: Seltorexant 20 mg |
|---|-----------------------------------|-----------------------|---------------------------------------|
| Total subjects affected by serious adverse events |                                   |                       |                                       |
| subjects affected / exposed                       | 1 / 303 (0.33%)                   | 1 / 283 (0.35%)       | 29 / 522 (5.56%)                      |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| number of deaths (all causes)  | 0               | 0               | 1               |
| number of deaths resulting from adverse events                             | 0               | 0               | 0               |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                 |                 |                 |
| <b>Neurogenic Tumour</b>   |                 |                 |                 |
| subjects affected / exposed  | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Parathyroid Tumour Benign</b>   |                 |                 |                 |
| subjects affected / exposed  | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Vascular disorders</b>  |                 |                 |                 |
| <b>Deep Vein Thrombosis</b>  |                 |                 |                 |
| subjects affected / exposed  | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 1           |
| <b>Hypertension</b>  |                 |                 |                 |
| subjects affected / exposed  | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>General disorders and administration site conditions</b>                |                 |                 |                 |
| <b>Chest Pain</b>  |                 |                 |                 |
| subjects affected / exposed  | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Fatigue</b>   |                 |                 |                 |
| subjects affected / exposed  | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Psychiatric disorders</b>   |                 |                 |                 |
| <b>Depression</b>  |                 |                 |                 |
| subjects affected / exposed  | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 2 / 522 (0.38%) |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Suicidal Ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 2 / 522 (0.38%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicide Attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 7 / 522 (1.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Transaminases Increased                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight Increased                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Concussion                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 303 (0.33%) | 0 / 283 (0.00%) | 0 / 522 (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           |
| Skin Laceration                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal Compression Fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 303 (0.33%) | 0 / 283 (0.00%) | 0 / 522 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cardiac disorders                               |                 |                 |                 |
| Tachycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral Infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic Stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient Ischaemic Attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Iron Deficiency Anaemia                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 1 / 283 (0.35%) | 0 / 522 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Optic Nerve Sheath Haemorrhage                  |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                            | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastrointestinal disorders</b>                      |                 |                 |                 |
| Lower Gastrointestinal Haemorrhage                     |                 |                 |                 |
| subjects affected / exposed                            | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |                 |                 |
| Intervertebral Disc Protrusion                         |                 |                 |                 |
| subjects affected / exposed                            | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal Stenosis  |                 |                 |                 |
| subjects affected / exposed                            | 1 / 303 (0.33%) | 0 / 283 (0.00%) | 0 / 522 (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           |
| Rotator Cuff Syndrome                                  |                 |                 |                 |
| subjects affected / exposed                            | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Infections and infestations</b>                     |                 |                 |                 |
| Pneumonia  |                 |                 |                 |
| subjects affected / exposed                            | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia Aspiration                                   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 1           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Septic Shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vestibular Neuritis                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 303 (0.00%) | 0 / 283 (0.00%) | 1 / 522 (0.19%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                                       | DB Follow-up (FU)<br>Phase: Placebo | DB FU Phase:<br>Seltorexant 20 mg | OL FU Phase:<br>Seltorexant 20 mg |
|---|-------------------------------------|-----------------------------------|-----------------------------------|
| Total subjects affected by serious adverse events                   |                                     |                                   |                                   |
| subjects affected / exposed   | 0 / 22 (0.00%)                      | 0 / 22 (0.00%)                    | 0 / 453 (0.00%)                   |
| number of deaths (all causes)                                       | 0                                   | 0                                 | 0                                 |
| number of deaths resulting from adverse events                      | 0                                   | 0                                 | 0                                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                     |                                   |                                   |
| Neurogenic Tumour   |                                     |                                   |                                   |
| subjects affected / exposed   | 0 / 22 (0.00%)                      | 0 / 22 (0.00%)                    | 0 / 453 (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                             |
| Parathyroid Tumour Benign   |                                     |                                   |                                   |
| subjects affected / exposed   | 0 / 22 (0.00%)                      | 0 / 22 (0.00%)                    | 0 / 453 (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                             |
| Vascular disorders  |                                     |                                   |                                   |
| Deep Vein Thrombosis  |                                     |                                   |                                   |
| subjects affected / exposed   | 0 / 22 (0.00%)                      | 0 / 22 (0.00%)                    | 0 / 453 (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                             |
| Hypertension  |                                     |                                   |                                   |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                                 | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>General disorders and administration site conditions</b> |                |                |                 |
| <b>Chest Pain</b>   |                |                |                 |
| subjects affected / exposed                                 | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Fatigue</b>  |                |                |                 |
| subjects affected / exposed                                 | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Psychiatric disorders</b>                                |                |                |                 |
| <b>Depression</b>   |                |                |                 |
| subjects affected / exposed                                 | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Suicidal Ideation</b>                                    |                |                |                 |
| subjects affected / exposed                                 | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Suicide Attempt</b>                                      |                |                |                 |
| subjects affected / exposed                                 | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Investigations</b>                                       |                |                |                 |
| <b>Transaminases Increased</b>                              |                |                |                 |
| subjects affected / exposed                                 | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Weight Increased</b>                                     |                |                |                 |
| subjects affected / exposed                                 | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Injury, poisoning and procedural complications  |                |                |                 |
| Concussion                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| Fall  |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| Skin Laceration                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| Spinal Compression Fracture                     |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiac disorders                               |                |                |                 |
| Tachycardia                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| Nervous system disorders                        |                |                |                 |
| Dizziness                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| Cerebral Infarction                             |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| Ischaemic Stroke                                |                |                |                 |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| subjects affected / exposed                            | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Syncope</b>   |                |                |                 |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Transient Ischaemic Attack</b>                      |                |                |                 |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Blood and lymphatic system disorders</b>            |                |                |                 |
| <b>Iron Deficiency Anaemia</b>                         |                |                |                 |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Eye disorders</b>                                   |                |                |                 |
| <b>Optic Nerve Sheath Haemorrhage</b>                  |                |                |                 |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Gastrointestinal disorders</b>                      |                |                |                 |
| <b>Lower Gastrointestinal Haemorrhage</b>              |                |                |                 |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |                 |
| <b>Intervertebral Disc Protrusion</b>                  |                |                |                 |
| subjects affected / exposed                            | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Spinal Stenosis</b>                                 |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Rotator Cuff Syndrome</b>                    |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Infections and infestations</b>              |                |                |                 |
| <b>Pneumonia</b>                                |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Pneumonia Aspiration</b>                     |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Sepsis</b>                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Septic Shock</b>                             |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Urosepsis</b>                                |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |
| <b>Vestibular Neuronitis</b>                    |                |                |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 0 / 453 (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           |

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

| <b>Non-serious adverse events</b>   | Double -blind Phase (DB): Placebo | DB: Seltorexant 20 mg  | OL Treatment Phase: Seltorexant 20 mg |
|---|-----------------------------------|------------------------|---------------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed        | 35 / 303 (11.55%)                 | 41 / 283 (14.49%)      | 162 / 522 (31.03%)                    |
| Investigations<br>Weight Increased<br>subjects affected / exposed<br>occurrences (all)      | 4 / 303 (1.32%)<br>4              | 5 / 283 (1.77%)<br>5   | 34 / 522 (6.51%)<br>34                |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)    | 27 / 303 (8.91%)<br>33            | 25 / 283 (8.83%)<br>38 | 62 / 522 (11.88%)<br>117              |
| Infections and infestations<br>Covid-19<br>subjects affected / exposed<br>occurrences (all) | 5 / 303 (1.65%)<br>5              | 9 / 283 (3.18%)<br>10  | 46 / 522 (8.81%)<br>47                |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 303 (1.32%)<br>4              | 4 / 283 (1.41%)<br>4   | 44 / 522 (8.43%)<br>56                |

| <b>Non-serious adverse events</b>   | DB Follow-up (FU) Phase: Placebo | DB FU Phase: Seltorexant 20 mg | OL FU Phase: Seltorexant 20 mg |
|---|----------------------------------|--------------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed        | 1 / 22 (4.55%)                   | 0 / 22 (0.00%)                 | 10 / 453 (2.21%)               |
| Investigations<br>Weight Increased<br>subjects affected / exposed<br>occurrences (all)      | 0 / 22 (0.00%)<br>0              | 0 / 22 (0.00%)<br>0            | 0 / 453 (0.00%)<br>0           |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)    | 0 / 22 (0.00%)<br>0              | 0 / 22 (0.00%)<br>0            | 6 / 453 (1.32%)<br>6           |
| Infections and infestations<br>Covid-19<br>subjects affected / exposed<br>occurrences (all) | 1 / 22 (4.55%)<br>1              | 0 / 22 (0.00%)<br>0            | 3 / 453 (0.66%)<br>3           |
| Nasopharyngitis   |                                  |                                |                                |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 22 (0.00%) | 1 / 453 (0.22%) |
| occurrences (all)           | 0              | 0              | 1               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 29 October 2020 | The purpose of this amendment was to address health authority feedback in regards to the assumption of treatment difference and increase in sample size determination, the addition of the Montgomery-Asberg Depression Rating Scale without Sleep Item (MADRS-WOSI) as a key secondary endpoint, European Union (EU)-specific statistical analyses, use of approved selective serotonin reuptake inhibitor (SSRI)/ serotonin-norepinephrine reuptake inhibitor (SNRI) as a background antidepressant in the participating country, language of restrictions on driving and alcohol use, disallowed concomitant medications, addition of brief neurological examinations, and adjustment of concomitant therapy following study drug stoppage, and study discontinuation for subjects.  |
| 25 June 2021    | The purpose of this amendment was to clarify and modify eligibility criteria based on early enrolment experiences and made the following changes at screening: lower the initial screening assessment of the Hamilton Depression Rating Scale (HDRS), 17 items total score from 22 to 20 and greater than or equal to ( $\geq$ )18 at end of screening; increase the maximum duration of stable antidepressant therapy from 12 months to 18 months; increase the length of the current depressive episode to less than or equal to ( $\leq$ )24 months ( $\leq$ 18 months); revise the upper limit of body mass index (BMI) eligibility range to kilogram per square meter ( $\text{kg}/\text{m}^2$ ) 40 $\text{kg}/\text{m}^2$ (from 37 $\text{kg}/\text{m}^2$ ); extend the screening period for up to 2 weeks if approved by the medical monitor and clarify use of concomitant medications in the OL phase. This amendment also included changes to laboratory tests to remove evaluation of prothrombin time (PT) and clarify follicle stimulating hormone (FSH) testing; added text to specify that locally approved (including under emergency use authorization Coronavirus disease 2019 (COVID-19) vaccination may be used during the trial with the recommendation that vaccination occurs at least 5 days prior to the start of dosing, or once randomized, at least 5 days prior to the next scheduled visit. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported