# EU Clinical Trials Register

## Clinical trial results:
## Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 in adult and elderly subjects with insomnia disorder

### Summary

| EudraCT number | 2017-004643-20 |
|---|---|
| Trial protocol | BG FI DE SE FR CZ BE HU |
| Global end of trial date | 14 May 2020 |

### Results information

| Result version number | v1 (current) |
|---|---|
| This version publication date | 22 May 2021 |
| First version publication date | 22 May 2021 |

### Trial information

#### Trial identification

| Sponsor protocol code | ID-078A302 |
|---|---|

#### Additional study identifiers

| ISRCTN number | - |
|---|---|
| ClinicalTrials.gov id (NCT number) | NCT03575104 |
| WHO universal trial number (UTN) | - |

Notes:

#### Sponsors

| Sponsor organisation name | Idorsia Pharmaceuticals Ltd |
|---|---|
| Sponsor organisation address | Hegenheimermattweg 91, Allschwil, Switzerland, 4123 |
| Public contact | Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com |
| Scientific contact | Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.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 | 18 June 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 April 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 May 2020 |
| Was the trial ended prematurely? | No |

Notes:


## General information about the trial

Main objective of the trial:

To evaluate the efficacy of 10 mg and 25 mg daridorexant (ACT-541468) on objective and subjective sleep parameters in subjects with insomnia disorder.

Protection of trial subjects:

Prior to the start of the study, each study site consulted an IEC or IRB, i.e., a review panel that was responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation. The protocol and any material provided to the subject (such as a subject information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate IEC or IRB before the study was started.
Sponsor personnel and the investigators were required to conduct the study in full compliance with ICHGCP Guidelines, the principles of the Declaration of Helsinki, and with the laws and regulations of the countries in which the study is conducted.
Both the sponsor and the investigators had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests. The investigators were responsible for maintaining the subjects' identities in strictest confidence.
Written informed consent was required to be obtained from each individual participating in the study prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study. It was made clear to each subject that he or she was completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 29 May 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:


## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 34 |
| Country: Number of subjects enrolled | Korea, Republic of: 6 |
| Country: Number of subjects enrolled | United States: 325 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Sweden: 10 |
| Country: Number of subjects enrolled | Bulgaria: 63 |
| Country: Number of subjects enrolled | Czech Republic: 3 |
| Country: Number of subjects enrolled | Finland: 10 |
| Country: Number of subjects enrolled | France: 2 |

| Country: Number of subjects enrolled | Germany: 436 |
|---|---|
| Country: Number of subjects enrolled | Hungary: 34 |
| Worldwide total number of subjects | 924 |
| EEA total number of subjects | 559 |

Notes:

## Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 561 |
| From 65 to 84 years | 362 |
| 85 years and over | 1 |

# Subject disposition

## Recruitment

Recruitment details:

The study was conducted at 81 sites in 11 countries (Canada, Republic of Korea, United States, Belgium, Sweden, Bulgaria, Czech Republic, Finland, France, Germany, Hungary), of which 61 sites randomized subjects.

## Pre-assignment

Screening details:

Screening details: The screening phase lasted for 20 to 31 days, from signing informed consent at Visit 1 until randomization (Visit 4).

## Period 1

| Period 1 title | DB treatment period (up to EOS) (overall period) |
|---|---|
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

### Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Daridorexant 10 mg |

Arm description: -

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Daridorexant 10 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Daridorexant was supplied as film-coated tablets at the strength of 10 mg for oral use.

| **Arm title** | Daridorexant 25 mg |
|---|---|

Arm description: -

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Daridorexant 25 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Daridorexant was supplied as film-coated tablets at the strength of 25 mg for oral use.

| **Arm title** | Placebo |
|---|---|

Arm description: -

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

Dosage and administration details:

Matching placebo was supplied as film-coated tablets for oral use.

| Number of subjects in period 1 | Daridorexant 10 mg | Daridorexant 25 mg | Placebo |
|---|---|---|---|
| Started | 307 | 309 | 308 |
| Completed | 283 | 280 | 286 |
| Not completed | 24 | 29 | 22 |
|     Consent withdrawn by subject | 13 | 16 | 11 |
|     Adverse event, non-fatal | 4 | 3 | 4 |
|     Other reasons | 6 | 8 | 6 |
|     Lost to follow-up | 1 | 2 | 1 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Daridorexant 10 mg |
|---|---|
| Reporting group description: - | |
| Reporting group title | Daridorexant 25 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |

Reporting group description: -

| Reporting group values | Daridorexant 10 mg | Daridorexant 25 mg | Placebo |
|---|---|---|---|
| Number of subjects | 307 | 309 | 308 |
| Age categorical Units: Subjects | | | |
| From 18-64 years | 186 | 188 | 187 |
| >=65 years | 121 | 121 | 121 |
| Age continuous Units: years | | | |
| arithmetic mean | 57.1 | 56.3 | 56.7 |
| standard deviation | ± 14.0 | ± 14.4 | ± 14.1 |
| Gender categorical Units: Subjects | | | |
| Female | 215 | 218 | 205 |
| Male | 92 | 91 | 103 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 924 | | |
| Age categorical Units: Subjects | | | |
| From 18-64 years | 561 | | |
| >=65 years | 363 | | |
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 638 | | |
| Male | 286 | | |

# End points

## End points reporting groups

| Reporting group title | Daridorexant 10 mg |
|---|---|
| Reporting group description: - | |
| Reporting group title | Daridorexant 25 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

## Primary: Change in WASO from baseline to Month 1 (sleep maintenance)

| End point title | Change in WASO from baseline to Month 1 (sleep maintenance) |
|---|---|
| End point description: | |
| End point type | Primary |
| End point timeframe: | |

Baseline: mean of the 2 PSG nights at Visit 3
Month 1: mean of the 2 PSG nights at Visit 6

| End point values | Daridorexant 10 mg | Daridorexant 25 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 309 | 308 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | -15.31 (-19.531 to -11.087) | -24.19 (-28.466 to -19.911) | -12.57 (-16.817 to -8.323) | |

## Statistical analyses

| Statistical analysis title | Betw.-treatm. for change in WASO to Month 1 |
|---|---|
| Statistical analysis description: | |
| Between-treatment analysis for change in WASO (min) from baseline to Month 1 (daridorexant 10 mg vs placebo) | |
| Comparison groups | Daridorexant 10 mg v Placebo |
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3669 [1] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -2.74 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.693 |
| upper limit | 3.215 |

Notes:

[1] - [1] - Mixed effects model for repeated measures: change in WASO from baseline = baseline WASO + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

| **Statistical analysis title** | Betw.-treatm. for change in WASO to Month 1 |
|---|---|

Statistical analysis description:

Between-treatment analysis for change in WASO (min) from baseline to Month 1 (daridorexant 25 mg vs placebo)

| Comparison groups | Daridorexant 25 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0001 [2] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -11.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.604 |
| upper limit | -5.633 |

Notes:

[2] - [2] - Mixed effects model for repeated measures: change in WASO from baseline = baseline WASO + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

## Primary: Change in WASO from baseline to Month 3

| End point title | Change in WASO from baseline to Month 3 |
|---|---|

End point description:

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

End point timeframe:

Baseline: mean of the 2 PSG nights at Visit 3.
Month 3: mean of the 2 PSG nights at Visit 8.

| **End point values** | Daridorexant 10 mg | Daridorexant 25 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 309 | 308 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | -15.95 (-20.734 to -11.165) | -24.25 (-29.021 to -19.474) | -14.00 (-18.756 to -9.241) | |

## Statistical analyses

| Statistical analysis title | Betw.-treatm. for change in WASO to Month 3 |
|---|---|
| Statistical analysis description: | |
| Between-treatment analysis for change in WASO (min) from baseline to Month 3 (daridorexant 10 mg vs placebo) | |
| Comparison groups | Daridorexant 10 mg v Placebo |
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5686 [3] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS Mean difference to placebo |
| Point estimate | -1.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.666 |
| upper limit | 4.764 |

Notes:

[3] - [3] - Mixed effects model for repeated measures: change in WASO from baseline = baseline WASO + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

| Statistical analysis title | Betw.-treatm. for change in WASO to Month 3 |
|---|---|
| Statistical analysis description: | |
| Between-treatment analysis for change in WASO (min) from baseline to Month 3 (daridorexant 25 mg vs placebo) | |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0028 [4] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS Mean difference to placebo |
| Point estimate | -10.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.95 |
| upper limit | -3.548 |

Notes:

[4] - [4] - Mixed effects model for repeated measures: change in WASO from baseline = baseline WASO +
age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

## Primary: Change in LPS from baseline to Month 1 (sleep onset)

| End point title | Change in LPS from baseline to Month 1 (sleep onset) |
|---|---|
| End point description: | |
| End point type | Primary |
| End point timeframe: | |

Baseline: mean of the 2 PSG nights at Visit 3.
Month 1: mean of the 2 PSG nights at Visit 6.

| End point values | Daridorexant 10 mg | Daridorexant 25 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 309 | 308 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | -22.62 (-26.733 to -18.503) | -26.46 (-30.626 to -22.292) | -20.01 (-24.148 to -15.875) | |

## Statistical analyses

| Statistical analysis title | Betw.-treatm. for change in LPS to Month 1 |
|---|---|
| Statistical analysis description: | |
| Between-treatment analysis for change in LPS (min) from baseline to Month 1 (daridorexant 10 mg vs placebo) | |
| Comparison groups | Daridorexant 10 mg v Placebo |
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3782 [5] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -2.61 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -8.41 |
|     upper limit | 3.197 |

Notes:

[5] - [5] - Mixed effects model for repeated measures: change in LPS from baseline = baseline LPS + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

| Statistical analysis title | Betw.-treatm. for change in LPS to Month 1 |
|---|---|
| Statistical analysis description: | |
| Between-treatment analysis for change in LPS (min) from baseline to Month 1 (daridorexant 25 mg vs placebo) | |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0303 [6] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -6.45 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.282 |
| upper limit | -0.614 |

Notes:

[6] - [6] - Mixed effects model for repeated measures: change in LPS from baseline = baseline LPS + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

## Primary: Change in LPS from baseline to Month 3

| End point title | Change in LPS from baseline to Month 3 |
|---|---|

End point description:

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

End point timeframe:

Baseline: mean of the 2 PSG nights at Visit 3.
Month 3: mean of the 2 PSG nights at Visit 8.

| **End point values** | Daridorexant 10 mg | Daridorexant 25 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 309 | 308 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | -23.09 (-27.600 to -18.571) | -28.91 (-33.413 to -24.399) | -19.89 (-24.384 to -15.405) | |

## Statistical analyses

| **Statistical analysis title** | Betw.-treatm. for change in LPS to Month 3 |
|---|---|

Statistical analysis description:

Between-treatment analysis for change in LPS (min) from baseline to Month 3 (daridorexant 10 mg vs placebo)

| Comparison groups | Daridorexant 10 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3233 [7] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -3.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.528 |
| upper limit | 3.146 |

Notes:

[7] - [7] - Mixed effects model for repeated measures: change in LPS from baseline = baseline LPS + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

| Statistical analysis title | Betw.-treatm. for change in LPS to Month 3 |
|---|---|

Statistical analysis description:

Between-treatment analysis for change in LPS (min) from baseline to Month 3 (daridorexant 25 mg vs placebo)

| Comparison groups | Daridorexant 25 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0053 [8] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -9.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.339 |
| upper limit | -2.684 |

Notes:

[8] - [7] - Mixed effects model for repeated measures: change in LPS from baseline = baseline LPS + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

## Secondary: Change in the subjective Total Sleep Time (sTST) from baseline to Month 1

| End point title | Change in the subjective Total Sleep Time (sTST) from baseline to Month 1 |
|---|---|

End point description:

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

End point timeframe:

"Baseline" is the mean value based on the screening sleep diary in the 7 days preceding the first PSG at Visit 3.
"Month 1" is the mean value based on the sleep diary in the 7 days preceding the first PSG at Visit 6.

| End point values | Daridorexant 10 mg | Daridorexant 25 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 309 | 308 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | 41.01 (35.439 to 46.584) | 43.77 (38.136 to 49.412) | 27.64 (22.015 to 33.274) | |

## Statistical analyses

| Statistical analysis title | Betw.-treatm. for change in sTST to Month 1 |
|---|---|

Statistical analysis description:

Between-treatment analysis for change from baseline in sTST (min) to Month 1 (daridorexant 10 mg vs placebo) Statistical

| Comparison groups | Daridorexant 10 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0009 [9] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | 13.37 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | 5.507 |
|    upper limit | 21.226 |

Notes:

[9] - Mixed effects model for repeated measures: change from baseline in sTST = baseline sTST + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

| **Statistical analysis title** | Betw.-treatm. for change in sTST to Month 1 |
|---|---|

Statistical analysis description:

Between-treatment analysis for change from baseline in sTST (min) to Month 1 (daridorexant 25 mg vs placebo)

| Comparison groups | Daridorexant 25 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 [10] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | 16.13 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | 8.224 |
|    upper limit | 24.035 |

Notes:

[10] - Mixed effects model for repeated measures: change from baseline in sTST = baseline sTST + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

## Secondary: Change in sTST from baseline to Month 3

| End point title | Change in sTST from baseline to Month 3 |
|---|---|

End point description:

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

End point timeframe:

"Baseline" is the mean value based on the screening sleep diary in the 7 days preceding the first PSG at Visit 3.
"Month 3" is the mean value based on the sleep diary in the 7 days preceding the first PSG at Visit 8.

| End point values | Daridorexant 10 mg | Daridorexant 25 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 309 | 308 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | 50.70 (44.398 to 57.008) | 56.18 (49.812 to 62.547) | 37.12 (30.776 to 43.464) | |

## Statistical analyses

| Statistical analysis title | Betw.-treatm. for change in sTST to Month 3 |
|---|---|
| Statistical analysis description: | |
| Between-treatment analysis for change from baseline in sTST (min) to Month 3 (daridorexant 10 mg vs placebo) | |
| Comparison groups | Daridorexant 10 mg v Placebo |
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0028 [11] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | 13.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.691 |
| upper limit | 22.475 |

Notes:

[11] - Mixed effects model for repeated measures: change from baseline in sTST = baseline sTST + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

| Statistical analysis title | Betw.-treatm. for change in sTST to Month 3 |
|---|---|
| Statistical analysis description: | |
| Between-treatment analysis for change from baseline in sTST (min) to Month 3 (daridorexant 25 mg vs placebo) | |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 [12] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | 19.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.125 |
| upper limit | 27.994 |

Notes:

[12] - Mixed effects model for repeated measures: change from baseline in sTST = baseline sTST + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

## Secondary: Change in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score from baseline to Month 1

| End point title | Change in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score from baseline to Month 1 |
|---|---|

End point description:

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

End point timeframe:

"Baseline" is the mean value based on the screening IDSIQ entries in the 7 days preceding the first PSG at Visit 3.
"Month 1" is the mean value based on the IDSIQ entries in the 7 days preceding the first PSG at Visit 6.

| End point values | Daridorexant 10 mg | Daridorexant 25 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 309 | 308 | |
| Units: Score units | | | | |
| least squares mean (confidence interval 95%) | -3.18 (-3.763 to -2.599) | -3.51 (-4.096 to -2.917) | -2.75 (-3.340 to -2.163) | |

### Statistical analyses

| Statistical analysis title | Betw.-treatm. for change in IDSIQ to Month 1 |
|---|---|

Statistical analysis description:

Between-treatment analysis for change in in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score from baseline to Month 1 (daridorexant 10 mg vs placebo)

| Comparison groups | Daridorexant 10 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3048 [13] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -0.43 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -1.251 |
|     upper limit | 0.392 |

Notes:

[13] - Mixed effects model for repeated measures: change from baseline in IDSIQ sleepiness domain score = baseline IDSIQ sleepiness domain score + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

| Statistical analysis title | Betw.-treatm. for change in IDSIQ to Month 1 |
|---|---|

Statistical analysis description:

Between-treatment analysis for change in in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score from baseline to Month 1 (daridorexant 25 mg vs placebo)

| | |
|---|---|
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0733 [14] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.581 |
| upper limit | 0.071 |

Notes:

[14] - Mixed effects model for repeated measures: change from baseline in IDSIQ sleepiness domain score = baseline IDSIQ sleepiness domain score + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

## Secondary: Change in IDSIQ sleepiness domain score from baseline to Month 3

| | |
|---|---|
| End point title | Change in IDSIQ sleepiness domain score from baseline to Month 3 |

End point description:

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

End point timeframe:

"Baseline" is the mean value based on the screening IDSIQ entries in the 7 days preceding the first PSG at Visit 3.
"Month 3" is the mean value based on the IDSIQ entries in the 7 days preceding the first PSG at Visit 8.

| End point values | Daridorexant 10 mg | Daridorexant 25 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 309 | 308 | |
| Units: Score units | | | | |
| least squares mean (confidence interval 95%) | -4.75 (-5.437 to -4.056) | -5.27 (-5.964 to -4.569) | -4.01 (-4.705 to -3.322) | |

## Statistical analyses

| **Statistical analysis title** | Betw.-treatm. for change in IDSIQ to Month 3 |
|---|---|

Statistical analysis description:

Between-treatment analysis for change in in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score from baseline to Month 3 (daridorexant 10 mg vs placebo)

| | |
|---|---|
| Comparison groups | Daridorexant 10 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 615 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1393 |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -0.73 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -1.706 |
|     upper limit | 0.239 |

| | |
|---|---|
| **Statistical analysis title** | Betw.-treatm. for change in IDSIQ to Month 3 |

Statistical analysis description:

Between-treatment analysis for change in in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score from baseline to Month 3 (daridorexant 25 mg vs placebo)

| | |
|---|---|
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 617 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.012 [15] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -1.25 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -2.23 |
|     upper limit | -0.276 |

Notes:

[15] - Mixed effects model for repeated measures: change from baseline in IDSIQ sleepiness domain score = baseline IDSIQ sleepiness domain score + age group (< 65; ≥ 65 years) + treatment + visit + treatment × visit + baseline × visit.

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

TEAEs were AEs that started or worsened on or after DB study treatment start date up to 30 days after DB study treatment end date or the date of enrollment in the ID-078A303 extension study.

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

## Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 22.1 |

## Reporting groups

| Reporting group title | Daridorexant 10 mg |
|---|---|
| Reporting group description: - | |
| Reporting group title | Daridorexant 25 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: Placebo | |

| Serious adverse events | Daridorexant 10 mg | Daridorexant 25 mg | Placebo |
|---|---|---|---|
| **Total subjects affected by serious adverse events** | | | |
| subjects affected / exposed | 3 / 306 (0.98%) | 3 / 308 (0.97%) | 4 / 306 (1.31%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 0 / 308 (0.00%) | 1 / 306 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 0 / 308 (0.00%) | 1 / 306 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 0 / 308 (0.00%) | 1 / 306 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| Microvascular coronary artery disease | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | 0 / 306 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Nervous system disorders** | | | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | 0 / 306 (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 |
| **Ear and labyrinth disorders** | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | 0 / 306 (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 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | 0 / 306 (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 |
| **Psychiatric disorders** | | | |
| Schizophrenia | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 1 / 308 (0.32%) | 0 / 306 (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 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 306 (0.00%) | 0 / 308 (0.00%) | 1 / 306 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Infections and infestations** | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 306 (0.33%) | 0 / 308 (0.00%) | 0 / 306 (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 |

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

| **Non-serious adverse events** | Daridorexant 10 mg | Daridorexant 25 mg | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 49 / 306 (16.01%) | 28 / 308 (9.09%) | 30 / 306 (9.80%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 14 / 306 (4.58%) | 16 / 308 (5.19%) | 11 / 306 (3.59%) |
| occurrences (all) | 19 | 16 | 12 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 38 / 306 (12.42%) | 13 / 308 (4.22%) | 20 / 306 (6.54%) |
| occurrences (all) | 41 | 15 | 22 |

# More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 26 February 2018 | The IDSIQ was updated to add the item 'energetic', in line with FDA requirements. |
| 19 April 2018 | • Inclusion/exclusion criteria:<br>– Exclusion criteria #16 and 17 (concerning treatment with CYP3A4 inhibitors/inducers, and consumption of grapefruit / bitter oranges, respectively), previously assessed at Visit 2, were shifted to be assessed at Visit 1.<br>– Exclusion criterion #3 was updated to clarify the indication for acceptable CBT since it was considered that any CBT could impact the efficacy endpoints.<br>• Safety visit at Month 2 (Visit 7):<br>– A safety visit taking place after 2 months of treatment (Visit 7) was added, as treatment with the study drug had been evaluated for a maximum of 1 month in the Phase 2 studies.<br>• Contraception requirement:<br>– The protocol was aligned with the Heads of Medicines Agencies Clinical Trials Facilitation Group recommendations for the use of an acceptable contraception method.<br>• Forbidden concomitant activities:<br>– The following activity was added: Driving or engaging in activities that require operating vehicles or dangerous machinery within 8 hours following study treatment intake for adult and elderly subjects.<br>• A rationale for the run-in period was added.<br>• The categories of AESIs were modified: the three original categories were placed under 'Narcolepsy-like symptoms' and sub-categories were created.<br>• Exclusion criterion #5 was amended to mention that the subjects with a history of major depressive disorder currently without any symptoms and not requiring treatment were eligible.<br>• Clarification regarding study treatment discontinuation: upon discontinuation of study treatment for any reason, subjects were encouraged to remain in the study and perform the visits and assessments as planned by the protocol (except the run-out period) until the End-of-Study. This would decrease the amount of missing data which was important from a study integrity perspective. |
| 30 July 2018 | Two assessments (PGI-C and PGI-S, both capturing night-time symptoms) were added as requested by the FDA to anchor and better understand the data collected with the SDQ. In addition, the sponsor clarified the use of a back-up device for alcohol tests. |
| 08 November 2018 | The patient preferences sub-study (PAUSe) was implemented at ID-078A302 study sites in Germany and the USA to support the recruitment of at least 360 subjects in these countries. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported