



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 | 2017-004642-20 |
| Trial protocol | DK DE ES IT |
| Global end of trial date | 25 February 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 11 March 2021 |
| First version publication date | 11 March 2021 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | ID-078A301 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03545191 |
| 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 | 31 March 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 January 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 February 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 25 mg and 50 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 ICH-GCP 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 | 04 June 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| 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 | Poland: 14 |
| Country: Number of subjects enrolled | Spain: 91 |
| Country: Number of subjects enrolled | Denmark: 63 |
| Country: Number of subjects enrolled | Germany: 444 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Switzerland: 5 |
| Country: Number of subjects enrolled | United States: 300 |
| Worldwide total number of subjects | 930 |
| EEA total number of subjects | 612 |

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) | 566 |
| From 65 to 84 years | 361 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 75 sites in 10 countries (Australia, Canada, Denmark, Germany, Italy, Poland, Serbia, Spain, Switzerland, and the USA), of which 51 sites in 7 countries (Canada, Denmark, Germany, Poland, Spain, Switzerland, and the USA) randomized subjects.

Pre-assignment

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

| | |
|------------------|--------------------|
| Arm title | Daridorexant 50 mg |
|------------------|--------------------|

Arm description: -

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Daridorexant 50 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Daridorexant 50 mg was supplied as film-coated tablets at the strength of 50 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 25 mg | Daridorexant 50 mg | Placebo |
|---------------------------------------|--------------------|--------------------|---------|
| Started | 310 | 310 | 310 |
| Completed | 288 | 285 | 280 |
| Not completed | 22 | 25 | 30 |
| Adverse event, serious fatal | 1 | - | - |
| Consent withdrawn by subject | 13 | 10 | 12 |
| Adverse event, non-fatal | 4 | 2 | 7 |
| Other reasons | 3 | 11 | 8 |
| Lost to follow-up | 1 | 2 | 3 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|--------------------|
| Reporting group title | Daridorexant 25 mg |
| Reporting group description: - | |
| Reporting group title | Daridorexant 50 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | Daridorexant 25 mg | Daridorexant 50 mg | Placebo |
|---------------------------------------|--------------------|--------------------|---------|
| Number of subjects | 310 | 310 | 310 |
| Age categorical Units: Subjects | | | |
| From 18-64 years | 189 | 189 | 188 |
| >=65 year | 121 | 121 | 122 |
| Age continuous Units: years | | | |
| arithmetic mean | 55.8 | 55.5 | 55.1 |
| standard deviation | ± 15.3 | ± 15.3 | ± 15.4 |
| Gender categorical Units: Subjects | | | |
| Female | 215 | 199 | 210 |
| Male | 95 | 111 | 100 |

| Reporting group values | Total | | |
|---------------------------------------|-------|--|--|
| Number of subjects | 930 | | |
| Age categorical Units: Subjects | | | |
| From 18-64 years | 566 | | |
| >=65 year | 364 | | |
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 624 | | |
| Male | 306 | | |

End points

End points reporting groups

| | |
|--------------------------------|--------------------|
| Reporting group title | Daridorexant 25 mg |
| Reporting group description: - | |
| Reporting group title | Daridorexant 50 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

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

| | |
|---|---|
| End point title | Change in WASO (sleep maintenance) from baseline to Month 1 |
| 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 25 mg | Daridorexant 50 mg | Placebo | |
|--|-----------------------------|-----------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 310 | 310 | 310 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | -18.40 (-22.126 to -14.674) | -28.98 (-32.668 to -25.299) | -6.20 (-9.928 to -2.475) | |

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 25 mg vs placebo) | |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 ^[1] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -12.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.435 |
| upper limit | -6.961 |

Notes:

[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 50 mg vs placebo)

| | |
|---|---|
| Comparison groups | Daridorexant 50 mg v Placebo |
| Number of subjects included in analysis | 620 |
| 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 | -22.78 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -27.996 |
| upper limit | -17.567 |

Notes:

[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 25 mg | Daridorexant 50 mg | Placebo | |
|--|-----------------------------|-----------------------------|----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 310 | 310 | 310 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | -22.97 (-26.955 to -18.988) | -29.41 (-33.399 to -25.427) | -11.11 (-15.131 to -7.088) | |

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 25 mg vs placebo) | |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 ^[3] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS Mean difference to placebo |
| Point estimate | -11.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.494 |
| upper limit | -6.23 |

Notes:

[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 50 mg vs placebo) | |
| Comparison groups | Daridorexant 50 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 ^[4] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS Mean difference to placebo |
| Point estimate | -18.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.945 |
| upper limit | -12.661 |

Notes:

[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 (sleep onset) from baseline to Month 1

| | |
|--|--|
| End point title | Change in LPS (sleep onset) from baseline to Month 1 |
| 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 25 mg | Daridorexant 50 mg | Placebo | |
|--|-----------------------------|-----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 310 | 310 | 310 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | -28.17 (-31.509 to -24.827) | -31.20 (-34.506 to -27.896) | -19.85 (-23.177 to -16.515) | |

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 25 mg vs placebo) | |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0005 ^[5] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -8.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.014 |
| upper limit | -3.629 |

Notes:

[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 50 mg vs placebo) | |
| Comparison groups | Daridorexant 50 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 ^[6] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -11.35 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.022 |
| upper limit | -6.687 |

Notes:

[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 25 mg | Daridorexant 50 mg | Placebo | |
|--|-----------------------------|-----------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 310 | 310 | 310 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | -30.73 (-34.037 to -27.417) | -34.80 (-38.118 to -31.490) | -23.13 (-26.464 to -19.803) | |

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 25 mg vs placebo)

| | |
|---|---|
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0015 ^[7] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -7.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.265 |
| upper limit | -2.923 |

Notes:

[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 50 mg vs placebo) | |
| Comparison groups | Daridorexant 50 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 ^[8] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -11.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.348 |
| upper limit | -6.994 |

Notes:

[8] - 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 entries in the 7 days preceding the first PSG at Visit 6.

| End point values | Daridorexant 25 mg | Daridorexant 50 mg | Placebo | |
|--|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 310 | 310 | 310 | |
| Units: minute | | | | |
| least squares mean (confidence interval 95%) | 34.18 (28.718 to 39.645) | 43.62 (38.173 to 49.063) | 21.56 (16.101 to 27.022) | |

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 25 mg vs placebo) | |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0013 ^[9] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | 12.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.953 |
| upper limit | 20.288 |

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 50 mg vs placebo) | |
| Comparison groups | Daridorexant 50 mg v Placebo |
| Number of subjects included in analysis | 620 |
| 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 | 22.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.405 |
| upper limit | 29.708 |

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 25 mg | Daridorexant 50 mg | Placebo | |
|--|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 310 | 310 | 310 | |
| Units: minutes | | | | |
| least squares mean (confidence interval 95%) | 47.83 (41.333 to 54.328) | 57.67 (51.171 to 64.168) | 37.90 (31.393 to 44.404) | |

Statistical analyses

| Statistical analysis title | Betw.-treatm. for change in sTST to Month 3 |
|--|---|
| Statistical analysis description: | |
| Between-treatment analysis for change in sTST (min) from baseline to Month 3 (daridorexant 25 mg vs placebo) | |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0334 ^[11] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | 9.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.782 |
| upper limit | 19.082 |

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 in sTST (min) from baseline to Month 3 (daridorexant 50 mg vs placebo) | |
| Comparison groups | Daridorexant 50 mg v Placebo |
| Number of subjects included in analysis | 620 |
| 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 | 19.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.623 |
| upper limit | 28.918 |

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 25 mg | Daridorexant 50 mg | Placebo | |
|--|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 310 | 310 | 310 | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | -2.77 (-3.316 to -2.225) | -3.77 (-4.309 to -3.224) | -2.02 (-2.566 to -1.476) | |

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 25 mg vs placebo)

| | |
|---|---|
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0547 ^[13] |
| 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 | -1.515 |
| upper limit | 0.015 |

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 50 mg vs placebo)

| | |
|---|---|
| Comparison groups | Daridorexant 50 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 ^[14] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -1.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.508 |
| upper limit | -0.983 |

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 25 mg | Daridorexant 50 mg | Placebo | |
|--|--------------------------|--------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 310 | 310 | 310 | |
| Units: score | | | | |
| least squares mean (confidence interval 95%) | -4.78 (-5.491 to -4.067) | -5.70 (-6.405 to -4.987) | -3.79 (-4.503 to -3.080) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Betw.-treatm. for change in IDSIQ to Month 3 |
| Comparison groups | Daridorexant 25 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0534 ^[15] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.99 |
| upper limit | 0.014 |

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.

| | |
|---|--|
| Statistical analysis title | Betw.-treatm. for change in IDSIQ to Month 3 |
| Comparison groups | Daridorexant 50 mg v Placebo |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0002 ^[16] |
| Method | Mixed effects model (repeated measures) |
| Parameter estimate | LS mean difference to placebo |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.905 |
| upper limit | -0.905 |

Notes:

[16] - 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 25 mg |
|-----------------------|--------------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| | |
|-----------------------|--------------------|
| Reporting group title | Daridorexant 50 mg |
|-----------------------|--------------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
|--------------------------------|--|

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

| | |
|------------------------------|--|
| Reporting group description: | |
|------------------------------|--|

| | |
|---------|--|
| Placebo | |
|---------|--|

| Serious adverse events | Daridorexant 25 mg | Daridorexant 50 mg | Placebo |
|---|--------------------|--------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 310 (0.65%) | 3 / 308 (0.97%) | 7 / 309 (2.27%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | 1 | 0 | 0 |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 308 (0.32%) | 0 / 309 (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 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 308 (0.32%) | 0 / 309 (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 |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 308 (0.32%) | 0 / 309 (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 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 308 (0.00%) | 1 / 309 (0.32%) |
| 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 | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 310 (0.32%) | 0 / 308 (0.00%) | 0 / 309 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 308 (0.32%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 310 (0.32%) | 0 / 308 (0.00%) | 0 / 309 (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 |
| Renal and urinary disorders | | | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 308 (0.32%) | 0 / 309 (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 | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 308 (0.00%) | 2 / 309 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Panic attack | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 308 (0.00%) | 1 / 309 (0.32%) |
| 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 | | | |
| Anal abscess | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 308 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 308 (0.00%) | 1 / 309 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 25 mg | Daridorexant 50 mg | Placebo |
|---|--------------------|--------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 44 / 310 (14.19%) | 41 / 308 (13.31%) | 35 / 309 (11.33%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 17 / 310 (5.48%) | 20 / 308 (6.49%) | 12 / 309 (3.88%) |
| occurrences (all) | 24 | 27 | 18 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 28 / 310 (9.03%) | 24 / 308 (7.79%) | 24 / 309 (7.77%) |
| occurrences (all) | 28 | 26 | 29 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 19 April 2018 | Changes were made regarding inclusion/exclusion criteria, safety visit at Month 2 (Visit 7), contraception requirement, forbidden concomitant activities, and categories of AESIs. |
| 30 July 2018 | Two assessments (PGI-C and PGI-S, both capturing night-time symptoms) were added to anchor and better understand the data collected with the SDQ. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported