



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
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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
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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
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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
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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
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End point description:

End point type	Primary
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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
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End point description:

End point type	Primary
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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
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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
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End point description:

End point type	Secondary
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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
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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
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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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
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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
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End point description:

End point type	Secondary
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Daridorexant 10 mg
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Reporting group description: -	
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Reporting group title	Daridorexant 25 mg
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Reporting group description: -	
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Reporting group title	Placebo
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Reporting group description:	
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Placebo	
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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	<ul style="list-style-type: none">• Inclusion/exclusion criteria:<ul style="list-style-type: none">– 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.– Exclusion criterion #3 was updated to clarify the indication for acceptable CBT since it was considered that any CBT could impact the efficacy endpoints.• Safety visit at Month 2 (Visit 7):<ul style="list-style-type: none">– 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.• Contraception requirement:<ul style="list-style-type: none">– The protocol was aligned with the Heads of Medicines Agencies Clinical Trials Facilitation Group recommendations for the use of an acceptable contraception method.• Forbidden concomitant activities:<ul style="list-style-type: none">– 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.• A rationale for the run-in period was added.• The categories of AESIs were modified: the three original categories were placed under 'Narcolepsy-like symptoms' and sub-categories were created.• 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.• 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