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