Clinical trial results:
Multi-center, double-blind, parallel-group, randomized, placebo-controlled, three doses, 40-week extension to studies ID-078A301 and ID-078A302 to assess the long term safety and tolerability of ACT-541468 in adult and elderly subjects with insomnia disorder

Summary

EudraCT number	2017-004644-38
Trial protocol	DK FI SE DE CZ FR HU ES BG BE IT
Global end of trial date	22 February 2021

Results information

Result version number	v1 (current)
This version publication date	27 January 2022
First version publication date	27 January 2022

Trial information

Trial identification

Sponsor protocol code	ID-078A303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03679884
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Idorsia Pharmaceuticals Ltd
Sponsor organisation address	Hegenheimermattweg 91, Allschwil, Switzerland, 4123
Public contact	Clinical Trials Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com
Scientific contact	Clinical Trials 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	22 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2021
Global end of trial reached?	Yes
Global end of trial date	22 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this extension study was to assess the long-term safety and tolerability of 10, 25 and 50 mg ACT–541468 (daridorexant).

Protection of trial subjects:

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 was conducted.
Both the sponsor and the investigator had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests. The investigator was responsible for maintaining the subjects' identities in strictest confidence.
Written informed consent was 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.
An Independent Data Monitoring Committee (IDMC) had overall responsibility for safeguarding the interests of subjects by monitoring, in an unblinded manner, safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study was conducted to the highest scientific and ethical standards.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 46
Country: Number of subjects enrolled	Denmark: 32
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 353
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Canada: 26

Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 257
Worldwide total number of subjects	804
EEA total number of subjects	513

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)	469
From 65 to 84 years	334
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Ninety-four sites in 14 countries (Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, Hungary, South Korea, Poland, Spain, Sweden, Switzerland, and the US) enrolled and randomized subjects.
Note: Subjects' demographic and baseline characteristics were collected in the respective confirmatory study (ID-078A301 or 302).

Pre-assignment

Screening details:

Subjects assigned to the daridorexant arms in Study ID-078A301 and 302 received the same dose in the ID-078A303 extension study. Subjects assigned to the placebo arm in Study ID-078A301 and 302 were re-randomized to receive either placebo or 25 mg daridorexant in a 1:1 ratio, with treatment allocation stratified by age into two categories.

Period 1

Period 1 title	DB treatment phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Carer, 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 administered during the DB treatment phase as film-coated tablets, taken orally once daily at bedtime at a dose of 10 mg.

Arm title	Daridorexant 25 mg

Arm description: -

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

Dosage and administration details:

Daridorexant was administered during the DB treatment phase as film-coated tablets, taken orally once daily at bedtime at a dose of 25 mg.

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 was administered during the DB treatment phase as film-coated tablets, taken orally once daily at bedtime at a dose of 50 mg.

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 administered during the DB treatment phase as film-coated tablets, taken orally once daily at bedtime.

Arm title	Ex-Placebo/Daridorexant 25 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ex-Placebo/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 administered during the DB treatment phase as film-coated tablets, taken orally once daily at bedtime at a dose of 25 mg.

Number of subjects in period 1	Daridorexant 10 mg	Daridorexant 25 mg	Daridorexant 50 mg
Started	142	270	137
Completed	99	190	93
Not completed	43	80	44
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	12	23	8
Adverse event, non-fatal	2	10	9
Other	12	12	12
Withdrawal prior to receiving DB treatment	-	2	-
Lost to follow-up	1	4	2
Lack of efficacy	15	29	13

Number of subjects in period 1	Placebo	Ex-Placebo/Daridorexant 25 mg

Started	128	127
Completed	78	90
Not completed	50	37
Adverse event, serious fatal	-	-
Consent withdrawn by subject	8	9
Adverse event, non-fatal	6	6
Other	7	8
Withdrawal prior to receiving DB treatment	-	1
Lost to follow-up	-	3
Lack of efficacy	29	10

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	Daridorexant 50 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Ex-Placebo/Daridorexant 25 mg
Reporting group description: -	

Reporting group values	Daridorexant 10 mg	Daridorexant 25 mg	Daridorexant 50 mg
Number of subjects	142	270	137
Age categorical Units: Subjects			
Adults (18-64 years)	80	166	83
>=65 years	62	104	54
Age continuous Units: years			
arithmetic mean	58.6	57.6	56.9
standard deviation	± 12.8	± 14.1	± 13.6
Gender categorical Units: Subjects			
Female	103	199	98
Male	39	71	39

Reporting group values	Placebo	Ex-Placebo/Daridorexant 25 mg	Total
Number of subjects	128	127	804
Age categorical Units: Subjects			
Adults (18-64 years)	70	70	469
>=65 years	58	57	335
Age continuous Units: years			
arithmetic mean	59.2	56.5	
standard deviation	± 12.6	± 15.5	-
Gender categorical Units: Subjects			
Female	92	83	575
Male	36	44	229

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	Daridorexant 50 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Ex-Placebo/Daridorexant 25 mg
Reporting group description: -	

Primary: Total no. of subjects with at least one TEAE

End point title	Total no. of subjects with at least one TEAE[1]

End point description:

The primary objective of the study was to assess the long-term safety and tolerability of 10, 25 and 50 mg daridorexant.
The total no. of subjects with at least one TEAE is presented here; no statistical analysis was conducted.
The full set of safety data is available in the Section "Adverse events".

End point type	Primary

End point timeframe:

TEAEs (AEs that started or worsened during the double-blind study period up to 30 days after double-blind study treatment end date) are reported.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary objective of the study was to assess the long-term safety and tolerability of 10, 25 and 50 mg daridorexant. The full set of safety data is available in the Section "Adverse events". No statistical analysis was conducted.

End point values	Daridorexant 10 mg	Daridorexant 25 mg	Daridorexant 50 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	142	268	137	128
Units: Subjects with at least one event	53	103	55	45

End point values	Ex-Placebo/Daridorexant 25 mg			
Subject group type	Reporting group			
Number of subjects analysed	126			
Units: Subjects with at least one event	48			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All treatment-emergent SAEs and AEs are reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Daridorexant 10 mg
Reporting group description: -	
Reporting group title	Daridorexant 25 mg
Reporting group description: -	
Reporting group title	Daridorexant 50 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Ex-Placebo/Daridorexant 25 mg
Reporting group description: -	

Serious adverse events	Daridorexant 10 mg	Daridorexant 25 mg	Daridorexant 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 142 (3.52%)	12 / 268 (4.48%)	7 / 137 (5.11%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Breast cancer			
subjects affected / exposed	2 / 142 (1.41%)	0 / 268 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Chest discomfort			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary mass			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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			
Confusional state			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Depression			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 142 (0.70%)	1 / 268 (0.37%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Bundle branch block left			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Aortic valve disease mixed			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Orthostatic intolerance			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 142 (0.70%)	0 / 268 (0.00%)	0 / 137 (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
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Vomiting			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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

Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 142 (0.70%)	0 / 268 (0.00%)	0 / 137 (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
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 142 (0.00%)	2 / 268 (0.75%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 268 (0.37%)	0 / 137 (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
Appendicitis			

subjects affected / exposed	0 / 142 (0.00%)	0 / 268 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo	Ex-Placebo/Daridorexant 25 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 128 (1.56%)	4 / 126 (3.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary mass			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aortic valve disease mixed			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone disorder			

subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Daridorexant 10 mg	Daridorexant 25 mg	Daridorexant 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 142 (4.93%)	15 / 268 (5.60%)	12 / 137 (8.76%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 142 (4.93%)	15 / 268 (5.60%)	12 / 137 (8.76%)
occurrences (all)	10	16	13

Non-serious adverse events	Placebo	Ex-Placebo/Daridorexant 25 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 128 (4.69%)	11 / 126 (8.73%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 128 (4.69%)	11 / 126 (8.73%)	
occurrences (all)	6	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2018	It was clarified that subjects randomized to the placebo arm in ID-078A301 or ID-078A302 would be re-randomized to either placebo or daridorexant 25 mg in the ID-078A303 study in a 1:1 ratio, with treatment allocation stratified by age into two categories (< 65 and ≥ 65 years, as per the age entered at the screening visit in the ID-078A301 or ID-078A302 study).
17 February 2020	- The sponsor added an interim analysis for safety and efficacy to support regulatory filings, and an optional second interim analysis of safety if needed to fulfill health authority requirements. - It was clarified that, to maintain the integrity of the study after the interim analysis/analyses, participating subjects as well as investigators would remain blinded for the entire duration of the study. The sponsor personnel involved in data collection and medical monitoring of the extension study would also remain blinded until the end of the study. The sponsor made the following clarifications to endpoints: - Endpoints added for ESS, PGI-C and PGA-S. - Endpoint for subjective sleep efficiency removed. - C-SSRS© to be additionally analyzed for the placebo run-out period. - Rebound insomnia to be assessed with sTST only (sWASO and sLSO removed). - VAS scores for daytime alertness and daily ability to function to be analyzed as exploratory efficacy -endpoints instead of safety. - Endpoint added assessing the number (%) of subjects with ≥ 6 point decrease in ISI© total score from baseline.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported