Clinical trial results:
Multi-center, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, polysomnography dose-response study to assess the efficacy and safety of ACT-541468 in elderly subjects with insomnia disorder

Summary

EudraCT number	2016-000827-16
Trial protocol	DE
Global end of trial date	29 June 2017

Results information

Result version number	v1
This version publication date	08 July 2018
First version publication date	08 July 2018

Trial information

Trial identification

Sponsor protocol code	AC-078A202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02841709
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Hegenheimermattweg 95, 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	17 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2017
Global end of trial reached?	Yes
Global end of trial date	29 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the dose-response of ACT-541468 on the change of Wake After Sleep Onset (WASO) assessed by polysomnography (PSG) on the first two days of each treatment period.

Protection of trial subjects:

The study was conducted 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. Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety and well-being of human subjects involved. 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. Prior to any study procedure, written informed consent was obtained from each participating subject. It was made clear to each subject that he or she was completely free to withdraw from it at any time for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 November 2016
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	Germany: 34
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	58
EEA total number of subjects	34

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)	0
From 65 to 84 years	57
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Conducted at 10 centers in 2 countries (USA and Germany)

Pre-assignment

Screening details:

Screening phase: From signing informed consent to randomization, lasting a maximum of 28 days and comprising a screening period (screening visit + at least 7 days at home) and a run-in period (2 consecutive PSG nights on single-blind placebo treatment, + 5–12 days at home with no treatment; assessments collected were used for baseline).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	ACT-541468 5 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ACT-541468 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

ACT-541468 5 mg orally once daily on the first two evenings of the assigned treatment period.

Arm title	ACT-541468 10 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ACT-541468 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

ACT-541468 10 mg orally once daily on the first two evenings of the assigned treatment period.

Arm title	ACT-541468 25 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ACT-541468 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

ACT-541468 25 mg orally once daily on the first two evenings of the assigned treatment period.

Arm title	ACT-541468 50 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	ACT-541468 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

2 x ACT-541468 25 mg orally once daily on the first two evenings of the assigned treatment period.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Matching placebo orally once daily on the first two evenings of the assigned treatment period.

Number of subjects in period 1	ACT-541468 5 mg	ACT-541468 10 mg	ACT-541468 25 mg
Started	58	58	58
Completed	58	58	58

Number of subjects in period 1	ACT-541468 50 mg	Placebo
Started	58	58
Completed	58	58

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	58	58	
Age categorical Units: Subjects			
From 65-84 years	57	57	
85 years and over	1	1	
Age continuous Units: years			
median	69		
full range (min-max)	65 to 85	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	19	19	
Insomnia Severity Index			
Range 0 - 28			
Units: Index			
median	20		
full range (min-max)	15 to 28	-	

End points

End points reporting groups

Reporting group title	ACT-541468 5 mg
Reporting group description: -	
Reporting group title	ACT-541468 10 mg
Reporting group description: -	
Reporting group title	ACT-541468 25 mg
Reporting group description: -	
Reporting group title	ACT-541468 50 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change in wake after sleep onset (WASO)

End point title	Change in wake after sleep onset (WASO)

End point description:

WASO is the time (min) spent awake after onset of persistent sleep until lights on, as determined by PSG.
The change from baseline to Days 1&2 in WASO (min) was analyzed using the generalized MCP-Mod approach, which combines a Multiple Comparison Procedure (MCP) to assess the efficacy of ACT-541468 versus placebo followed by a modeling (Mod) step to characterize the dose-response relationship (see attachment).
Modified full analysis set.

End point type	Primary

End point timeframe:

Baseline to Days 1&2

End point values	ACT-541468 5 mg	ACT-541468 10 mg	ACT-541468 25 mg	ACT-541468 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	54	55	56
Units: minute				
least squares mean (standard error)	-18.9 (± 4.44)	-32.0 (± 4.50)	-45.1 (± 4.47)	-61.4 (± 4.44)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: minute				
least squares mean (standard error)	-13.6 (± 4.50)			

Attachments (see zip file)	Predicted mean (95% CL) dose-response profile/ACT-541468 -

Statistical analyses

Statistical analysis title	Between treatment - 5 mg vs. placebo
Comparison groups	ACT-541468 5 mg v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.258 [2]
Method	Linear mixed effects model
Parameter estimate	LS mean difference
Point estimate	-5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	4
Variability estimate	Standard error of the mean
Dispersion value	4.73

Notes:

[1] - Number of subjects included in the analysis = 56.

[2] - two-sided

Statistical analysis title	Between treatment - 10 mg vs. placebo
Comparison groups	ACT-541468 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001 [4]
Method	Linear mixed effects model
Parameter estimate	LS mean difference
Point estimate	-18.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.8
upper limit	-9
Variability estimate	Standard error of the mean
Dispersion value	4.76

Notes:

[3] - Number of subjects included in the analysis = 54.

[4] - two-sided

Statistical analysis title	Between treatment - 25 mg vs placebo
Comparison groups	Placebo v ACT-541468 25 mg

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.001 [6]
Method	Linear mixed effects model
Parameter estimate	LS mean difference
Point estimate	-31.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.9
upper limit	-22.2
Variability estimate	Standard error of the mean
Dispersion value	4.74

Notes:

[5] - Number of subjects included in the analysis = 55.

[6] - two-sided

Statistical analysis title	Between treatment - 50 mg vs placebo
Comparison groups	Placebo v ACT-541468 50 mg
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.001 [8]
Method	Linear mixed effects model
Parameter estimate	LS mean difference
Point estimate	-47.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.2
upper limit	-38.5
Variability estimate	Standard error of the mean
Dispersion value	4.74

Notes:

[7] - Number of subjects included in the analysis = 56.

[8] - two-sided

Secondary: Change in latency to persistent sleep (LPS)

End point title	Change in latency to persistent sleep (LPS)

End point description:

LPS (min) is the time from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 min) scored as non-awake, i.e., epochs scored as either sleep stage 1 (S1), sleep stage 2 (S2), sleep stage 3 (slow wave sleep) or REM, as determined by polysomnography (PSG).
Full analysis set.

End point type	Secondary

End point timeframe:

Baseline to Days 1&2

End point values	ACT-541468 5 mg	ACT-541468 10 mg	ACT-541468 25 mg	ACT-541468 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	54	55	56
Units: minute				
arithmetic mean (standard deviation)	-37.92 (± 48.76)	-44.61 (± 41.28)	-44.81 (± 41.56)	-44.88 (± 44.22)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: minute				
arithmetic mean (standard deviation)	-33.88 (± 41.74)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data on adverse events were collected from Screening to Safety Follow-up period.
Below, data are reported for treatment-emergent adverse events.
Safety set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Run-in period

Reporting group description:

Run-in period = 2 consecutive PSG nights on single-blind placebo treatment, followed by 5-12 days at home with no treatment.

Reporting group title	Placebo

Reporting group description: -

Reporting group title	ACT-541468 5 mg

Reporting group description: -

Reporting group title	ACT-541468 10 mg

Reporting group description: -

Reporting group title	ACT-541468 25 mg

Reporting group description: -

Reporting group title	ACT-541468 50 mg

Reporting group description: -

Serious adverse events	Run-in period	Placebo	ACT-541468 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	ACT-541468 10 mg	ACT-541468 25 mg	ACT-541468 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Run-in period	Placebo	ACT-541468 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 58 (12.07%)	11 / 54 (20.37%)	14 / 56 (25.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Thrombophlebitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 58 (0.00%)	2 / 54 (3.70%)	0 / 56 (0.00%)
occurrences (all)	0	2	0
Feeling abnormal			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	1 / 58 (1.72%)	0 / 54 (0.00%)	2 / 56 (3.57%)
occurrences (all)	1	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 58 (1.72%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	2
Nasal oedema			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	2
Delusional disorder, unspecified type			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Hallucination, visual			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Fall			

subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Cerebellar ataxia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	2 / 56 (3.57%)
occurrences (all)	0	0	2
Dysgeusia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	2 / 58 (3.45%)	1 / 54 (1.85%)	2 / 56 (3.57%)
occurrences (all)	2	1	2
Hyporeflexia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	1 / 58 (1.72%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Tension headache			

subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Defaecation urgency			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	1 / 56 (1.79%)
occurrences (all)	0	1	1
Dry mouth			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Frequent bowel movements			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 58 (0.00%)	2 / 54 (3.70%)	0 / 56 (0.00%)
occurrences (all)	0	2	0
Muscle spasms			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 54 (1.85%)	1 / 56 (1.79%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypochloraemia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 54 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	ACT-541468 10 mg	ACT-541468 25 mg	ACT-541468 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 54 (22.22%)	10 / 55 (18.18%)	16 / 56 (28.57%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	1	1	0
Thrombophlebitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	4 / 56 (7.14%)
occurrences (all)	1	0	4
Feeling abnormal			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1

Gait disturbance			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	1 / 56 (1.79%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Nasal oedema			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Delusional disorder, unspecified type			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Hallucination, visual			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Blood pressure systolic increased			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0

Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Ventricular extrasystoles			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Nervous system disorders			
Cerebellar ataxia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			

subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	1 / 56 (1.79%)
occurrences (all)	0	1	1
Hyporeflexia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Tension headache			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Defaecation urgency			

subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	1	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0

Rash pruritic			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	2 / 56 (3.57%)
occurrences (all)	1	0	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypochloraemia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2016	One global amendment was issued to the original AC-078A202 protocol (dated 15 June 2016); this amendment (Global Amendment 1) was issued before enrolment of the first subject. Hence, all subjects were enrolled and treated under Global Protocol Version 2. Some changes: • The list of forbidden concomitant medications was modified (e.g. CYP3A4 substrates, inhibitors and inducers were added) • The list of inclusion/exclusion criteria was modified (e.g. subjects with severe renal impairment were not to be included) • The study-specific criteria for premature discontinuation of double-blind study treatment were defined • The sleep diary questionnaire was amended by two additional questions

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported