



Clinical trial results:

Multi-center, double-blind, randomized, placebo-controlled, active reference, parallel-group, polysomnography dose response study to assess the efficacy and safety of ACT-541468 in adult subjects with insomnia disorder

Summary

EudraCT number	2016-000826-21
Trial protocol	DE SE HU ES
Global end of trial date	20 June 2017

Results information

Result version number	v1
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	AC-078A201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02839200
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	13 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2017
Global end of trial reached?	Yes
Global end of trial date	20 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 was to evaluate the dose-response of ACT-541468 on the change of WASO [Wake After Sleep Onset] assessed by Polysomnography [PSG] after treatment on Days 1 and 2.

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	29 September 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	Spain: 26
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Germany: 199
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	United States: 101
Worldwide total number of subjects	360
EEA total number of subjects	256

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	360
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Conducted at 38 sites in 6 countries (Germany, Hungary, Israel, Spain, Sweden, and the USA)

Pre-assignment

Screening details:

Screening phase: screening period (screening visit followed by at least 7 days at home) and a run-in period (2 PSG nights on single-blind placebo, followed by 5–12 days with no treatment), and lasting a max. of 28 days. N = 360 subjects were randomized; N = 359 subjects were treated; N = 1 subject discontinued due to "randomization error."

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?	Yes
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Arm title	ACT-541468 5 mg
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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.

Arm title	ACT-541468 10 mg
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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.

Arm title	ACT-541468 25 mg
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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.

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.	
Arm title	Zolpidem 10 mg
Arm description: -	
Arm type	Active reference
Investigational medicinal product name	Zolpidem 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
Over-encapsulated tablets of commercially available Stilnox® for oral administration once daily.	
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:	
Placebo (2 types of placebo: one matching ACT-541468, one matching zolpidem) administered orally once daily during the treatment period.	
Placebo was also administered during the run-in period and during the run-out period.	

Number of subjects in period 1^[1]	ACT-541468 5 mg	ACT-541468 10 mg	ACT-541468 25 mg
Started	60	58	60
Completed	56	58	59
Not completed	4	0	1
Consent withdrawn by subject	2	-	1
Adverse event, non-fatal	-	-	-
Lost to follow-up	2	-	-

Number of subjects in period 1^[1]	ACT-541468 50 mg	Zolpidem 10 mg	Placebo
Started	61	60	60
Completed	61	58	59
Not completed	0	2	1

Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	1	-
Lost to follow-up	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects number enrolled in the trial includes all subjects who were randomized (N= 360).

The number of subjects reported to be in the baseline period includes all subjects who were randomized and received at least 1 dose of treatment (N = 359). N = 1 discontinued due to randomization error.

Baseline characteristics

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	Zolpidem 10 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	ACT-541468 5 mg	ACT-541468 10 mg	ACT-541468 25 mg
Number of subjects	60	58	60
Age categorical Units: Subjects			
Adults (18-64 years)	60	58	60
Age continuous Units: years			
median	41	48	48
full range (min-max)	22 to 64	21 to 63	18 to 64
Gender categorical Units: Subjects			
Female	38	38	39
Male	22	20	21

Reporting group values	ACT-541468 50 mg	Zolpidem 10 mg	Placebo
Number of subjects	61	60	60
Age categorical Units: Subjects			
Adults (18-64 years)	61	60	60
Age continuous Units: years			
median	46	43	48
full range (min-max)	18 to 63	23 to 61	23 to 64
Gender categorical Units: Subjects			
Female	39	38	38
Male	22	22	22

Reporting group values	Total		
Number of subjects	359		

Age categorical			
Units: Subjects			
Adults (18-64 years)	359		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	230		
Male	129		

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	Zolpidem 10 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change in WASO from baseline to Days 1&2

End point title	Change in WASO from baseline to Days 1&2
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 with the MCP-Mod method (see attachment for dose-response relationship).	
Modified full analysis set.	
End point type	Primary
End point timeframe:	
From 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	60	58	60	61
Units: minutes				
least squares mean (standard error)	-28.4 (± 4.24)	-32.3 (± 4.32)	-37.7 (± 4.25)	-47.1 (± 4.21)

End point values	Zolpidem 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: minutes				
least squares mean (standard error)	-29.9 (± 4.30)	-21.4 (± 4.24)		

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

Statistical analysis title	Between treatment - change in WASO - 5 mg
Comparison groups	Placebo v ACT-541468 5 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.241
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.7
upper limit	4.7
Variability estimate	Standard error of the mean
Dispersion value	5.95

Statistical analysis title	Between treatment - change in WASO - 10 mg
Comparison groups	ACT-541468 10 mg v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.072
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-10.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.6
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	6

Statistical analysis title	Between treatment - change in WASO - 25 mg
Comparison groups	ACT-541468 25 mg v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-16.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.9
upper limit	-4.5
Variability estimate	Standard error of the mean
Dispersion value	5.95

Statistical analysis title	Between treatment - change in WASO - 50 mg
Comparison groups	ACT-541468 50 mg v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-25.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.3
upper limit	-13.9
Variability estimate	Standard error of the mean
Dispersion value	5.92

Statistical analysis title	Between treatment - change in WASO - Zolpidem 10mg
Comparison groups	Placebo v Zolpidem 10 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.155
Method	ANCOVA
Parameter estimate	LS mean
Point estimate	-8.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.4
upper limit	3.3

Variability estimate	Standard error of the mean
Dispersion value	5.97

Notes:

[1] - Separate ANCOVA model.

Secondary: Change in latency to persistent sleep (LPS) to Days 1&2

End point title	Change in latency to persistent sleep (LPS) to Days 1&2
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: From 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	60	58	60	61
Units: minutes				
arithmetic mean (standard deviation)	-26.88 (± 45.42)	-29.31 (± 26.79)	-36.14 (± 34.34)	-36.41 (± 26.71)

End point values	Zolpidem 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: minutes				
arithmetic mean (standard deviation)	-45.12 (± 32.82)	-22.02 (± 46.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in subjective latency to sleep onset (sLSO) to Week 4

End point title	Change in subjective latency to sleep onset (sLSO) to Week 4
End point description: Full analysis set.	
End point type	Secondary
End point timeframe: From baseline to Week 4.	

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	58	52	56	57
Units: minutes				
arithmetic mean (standard deviation)	-13.38 ($\pm$ 27.79)	-21.07 ($\pm$ 24.26)	-15.5 ($\pm$ 25.51)	-23.65 ($\pm$ 24.12)

End point values	Zolpidem 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: minutes				
arithmetic mean (standard deviation)	-19.98 ($\pm$ 19.28)	-16.32 ($\pm$ 21.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in subjective WASO (sWASO) to Week 4

End point title	Change in subjective WASO (sWASO) to Week 4
End point description:	
Full analysis set.	
End point type	Secondary
End point timeframe:	
From baseline to Week 4.	

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	51	45	53	49
Units: minutes				
arithmetic mean (standard deviation)	-31.32 ($\pm$ 33.32)	-24.35 ($\pm$ 33.4)	-29.8 ($\pm$ 39.88)	-35.45 ($\pm$ 37.53)

End point values	Zolpidem 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	50		

Units: minutes				
arithmetic mean (standard deviation)	-29.08 (± 27.28)	-23.61 (± 32.62)		

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 (TEAEs).

Adverse event reporting additional description:

Safety set.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	PLACEBO
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Reporting group description:

PLACEBO

Reporting group title	ACT-541468 5mg
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Reporting group description:

ACT-541468 5mg

Reporting group title	ACT-541468 10mg
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Reporting group description:

ACT-541468 10mg

Reporting group title	ACT-541468 25mg
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Reporting group description:

ACT-541468 25mg

Reporting group title	ACT-541468 50mg
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Reporting group description:

ACT-541468 50mg

Reporting group title	ZOLPIDEM 10mg
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Reporting group description:

ZOLPIDEM 10mg

Serious adverse events	PLACEBO	ACT-541468 5mg	ACT-541468 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Accident at work			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
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			
Myocardial infarction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (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	ACT-541468 25mg	ACT-541468 50mg	ZOLPIDEM 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Accident at work			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (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
Craniocerebral injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (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	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (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
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (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

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

Non-serious adverse events	PLACEBO	ACT-541468 5mg	ACT-541468 10mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 60 (30.00%)	21 / 60 (35.00%)	21 / 58 (36.21%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Coronary arterial stent insertion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 60 (3.33%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	2	2	1
Feeling hot			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Gait disturbance			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Medical device site erythema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0

Medical device site inflammation subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Medical device site irritation subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Medical device site pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Pyrexia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Nasal congestion subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Pharyngeal erythema subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0

Productive cough subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Psychiatric disorders			
Abnormal dreams subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Nervousness subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Nightmare subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Stress subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Bilirubin conjugated increased subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Blood calcium decreased			

subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 60 (1.67%)	2 / 60 (3.33%)	1 / 58 (1.72%)
occurrences (all)	1	2	2
ECG signs of myocardial infarction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Hand fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Joint injury			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Atrial tachycardia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Atrioventricular block first degree			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Defect conduction intraventricular			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Cervicobrachial syndrome			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	2 / 58 (3.45%)
occurrences (all)	1	1	4
Dizziness postural			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Dysarthria			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 60 (1.67%)	6 / 60 (10.00%)	5 / 58 (8.62%)
occurrences (all)	1	7	5
Hypersomnia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	3 / 60 (5.00%)	3 / 60 (5.00%)	3 / 58 (5.17%)
occurrences (all)	3	4	3
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Paraesthesia ear			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Chromatopsia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Abdominal distension			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	3	0	1
Constipation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 60 (3.33%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	2	1	0
Dry mouth			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Faeces pale			

subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Flatulence subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	2 / 60 (3.33%) 2	0 / 58 (0.00%) 0
Photosensitivity reaction subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Pruritus generalised subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Renal and urinary disorders			

Bladder discomfort subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Nocturia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Renal pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Back pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Muscle tightness subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 2
Neck pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	1 / 58 (1.72%) 1
Infections and infestations			
Acute sinusitis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Gastroenteritis			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Helicobacter infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	4 / 60 (6.67%)	2 / 60 (3.33%)	2 / 58 (3.45%)
occurrences (all)	4	2	2
Pharyngitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0

Hypocalcaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	ACT-541468 25mg	ACT-541468 50mg	ZOLPIDEM 10mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 60 (38.33%)	21 / 61 (34.43%)	24 / 60 (40.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Coronary arterial stent insertion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	3 / 60 (5.00%)	0 / 61 (0.00%)	4 / 60 (6.67%)
occurrences (all)	3	0	5
Feeling hot			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Influenza like illness			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Medical device site erythema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1

Medical device site inflammation subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Medical device site irritation subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Medical device site pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	1 / 60 (1.67%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 2	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Nasal congestion subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Pharyngeal erythema subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0

Productive cough subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Psychiatric disorders			
Abnormal dreams subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Insomnia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	1 / 60 (1.67%) 1
Nervousness subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Nightmare subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Stress subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Bilirubin conjugated increased subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Blood calcium decreased			

subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	1	1	0
ECG signs of myocardial infarction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	2	0	0
Weight increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Hand fracture			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Joint injury			

subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Atrial tachycardia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Atrioventricular block first degree			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Defect conduction intraventricular			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Ventricular extrasystoles			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Cervicobrachial syndrome			

subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	4
Dizziness postural			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dysarthria			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	5 / 60 (8.33%)	5 / 61 (8.20%)	6 / 60 (10.00%)
occurrences (all)	5	6	8
Hypersomnia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	4 / 60 (6.67%)	4 / 61 (6.56%)	3 / 60 (5.00%)
occurrences (all)	5	5	3
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Paraesthesia ear			

subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Vertigo subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Eye disorders			
Chromatopsia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	4 / 60 (6.67%) 5
Constipation subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	1 / 60 (1.67%) 1
Diarrhoea subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Dry mouth subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Faeces pale			

subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 61 (0.00%) 0	1 / 60 (1.67%) 1
Nausea subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	1 / 61 (1.64%) 1	4 / 60 (6.67%) 5
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Photosensitivity reaction subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	2 / 61 (3.28%) 2	0 / 60 (0.00%) 0
Pruritus generalised subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Renal and urinary disorders			

Bladder discomfort subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Nocturia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Renal pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Muscle tightness subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Neck pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	1 / 61 (1.64%) 1	0 / 60 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Infections and infestations			
Acute sinusitis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0	0 / 60 (0.00%) 0
Gastroenteritis			

subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Helicobacter infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 60 (0.00%)	2 / 61 (3.28%)	5 / 60 (8.33%)
occurrences (all)	0	2	5
Pharyngitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0

Hypocalcaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2016	Two global amendments were issued to the original AC-078A201 protocol (dated 3 May 2016). Global Amendment 1 was issued before enrolment of the first subject. Hence, all subjects were enrolled and treated under Global Protocol Versions 2 and 3. Some changes of Amendment 1: • The list of forbidden concomitant medications was expanded (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 sleep diary questionnaire was amended by two additional questions
16 December 2016	Two global amendments were issued to the original AC-078A201 protocol (dated 3 May 2016). Global Amendment 1 was issued before enrolment of the first subject. Hence, all subjects were enrolled and treated under Global Protocol Versions 2 and 3. Some changes of Amendment 2: • The list of forbidden concomitant medications was expanded (e.g., ethinylestradiol was removed) • The sleep diary questionnaire was improved

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported