Clinical trial results:
A multicenter, randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ACT-334441 in subjects with systemic lupus erythematosus.

Summary

EudraCT number	2014-002984-14
Trial protocol	BG
Global end of trial date	28 February 2017

Results information

Result version number	v1
This version publication date	16 March 2018
First version publication date	16 March 2018

Trial information

Trial identification

Sponsor protocol code	AC-064A201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02472795
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals
Sponsor organisation address	Gewerbestrasse 16, Allschwil , Switzerland,
Public contact	Global Clinical Study Disclosure, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com
Scientific contact	Global Clinical Study Disclosure, Actelion 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	12 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the pharmacodynamics of ACT-334441, its safety and tolerability profile in adult systemic lupus erythematosus (SLE) subjects.

Protection of trial subjects:

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 in a clinical investigation. The sponsor and the investigators ensured that the study was conducted in full compliance with International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) Guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the countries in which the research was conducted.

Background therapy:

Standard of care therapies for SLE were allowed

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
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	Bulgaria: 19
Country: Number of subjects enrolled	Belarus: 7
Country: Number of subjects enrolled	Georgia: 6
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Ukraine: 9
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	67
EEA total number of subjects	19

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)	67
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 18 sites in 6 countries (BLR, BGR, GEO, RUS, UKR, and USA) from 1 Jun 2015 to 28 Feb 2017 (First subject, first visit to last subject, last visit)

Pre-assignment

Screening details:

The screening period started at the time the ICF was signed (up to 30 days before Randomization), and ended with subject randomization. The period included Visit 1 (Screening) and the pre-randomization (pre-dose) assessments at Visit 2 (Day 1).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ACT-334441 - 0.5 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ACT-334441
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of cenerimod was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

Arm title	ACT-334441 - 1.0 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ACT-334441
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of cenerimod was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

Arm title	ACT-334441 - 2.0 mg

Arm description: -

Arm type	Experimental

Investigational medicinal product name	ACT-334441
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of cenerimod was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

Arm title	ACT-334441 - 4.0 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ACT-334441
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of cenerimod was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of placebo was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

Number of subjects in period 1	ACT-334441 - 0.5 mg	ACT-334441 - 1.0 mg	ACT-334441 - 2.0 mg
Started	12	12	13
Completed	12	11	13
Not completed	0	1	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	1	-

Number of subjects in period 1	ACT-334441 - 4.0 mg	Placebo
Started	13	17
Completed	13	14
Not completed	0	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2

Baseline characteristics

Reporting groups	
Reporting group title	ACT-334441 - 0.5 mg
Reporting group description: -	
Reporting group title	ACT-334441 - 1.0 mg
Reporting group description: -	
Reporting group title	ACT-334441 - 2.0 mg
Reporting group description: -	
Reporting group title	ACT-334441 - 4.0 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	ACT-334441 - 0.5 mg	ACT-334441 - 1.0 mg	ACT-334441 - 2.0 mg
Number of subjects	12	12	13
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	13
Age continuous Units: years			
arithmetic mean	41.4	37.0	39.2
standard deviation	± 13.2	± 6.4	± 11.8
Gender categorical Units: Subjects			
Female	11	12	12
Male	1	0	1
Race Units: Subjects			
Black or African American	0	0	0
White	12	12	13
Body mass index Units: kg/m2			
arithmetic mean	25.2	27.4	26.0
standard deviation	± 5.1	± 8.0	± 5.1

Reporting group values	ACT-334441 - 4.0 mg	Placebo	Total
Number of subjects	13	17	67
Age categorical Units: Subjects			
Adults (18-64 years)	13	17	67
Age continuous Units: years			
arithmetic mean	41.7	41.0	
standard deviation	± 8.1	± 9.5	-

Gender categorical Units: Subjects			
Female	10	16	61
Male	3	1	6
Race Units: Subjects			
Black or African American	0	2	2
White	13	15	65
Body mass index Units: kg/m2			
arithmetic mean	27.5	25.4	
standard deviation	± 4.7	± 6.8	-

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full analysis set included all subjects randomized to a study treatment.

Subject analysis set title	Pharmacodynamics set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PD set included all subjects who received at least 21 days of study treatment, with lymphocyte count measurements at baseline and post-baseline

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety set included all subjects who received at least one dose of study treatment. Unless otherwise stated, any analysis using the Safety set used all available safety data up to EOS

Reporting group values	Full analysis set	Pharmacodynamics set	Safety set
Number of subjects	67	64	67
Age categorical Units: Subjects			
Adults (18-64 years)	67	64	67
Age continuous Units: years			
arithmetic mean	40.1	40.6	40.1
standard deviation	± 9.9	± 9.8	± 9.9
Gender categorical Units: Subjects			
Female	61	59	61
Male	6	5	6
Race Units: Subjects			
Black or African American	2	2	2
White	65	62	65
Body mass index Units: kg/m2			
arithmetic mean	26.2	26.5	26.2
standard deviation	± 6.0	± 6.0	± 6.0

End points

End points reporting groups	
Reporting group title	ACT-334441 - 0.5 mg
Reporting group description: -	
Reporting group title	ACT-334441 - 1.0 mg
Reporting group description: -	
Reporting group title	ACT-334441 - 2.0 mg
Reporting group description: -	
Reporting group title	ACT-334441 - 4.0 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full analysis set included all subjects randomized to a study treatment.	
Subject analysis set title	Pharmacodynamics set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PD set included all subjects who received at least 21 days of study treatment, with lymphocyte count measurements at baseline and post-baseline	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety set included all subjects who received at least one dose of study treatment. Unless otherwise stated, any analysis using the Safety set used all available safety data up to EOS	

Primary: Total lymphocyte count, absolute change from baseline to EOT	
End point title	Total lymphocyte count, absolute change from baseline to EOT
End point description:	
End point type	Primary
End point timeframe:	
From baseline to End of Treatment	

End point values	ACT-334441 - 0.5 mg	ACT-334441 - 1.0 mg	ACT-334441 - 2.0 mg	ACT-334441 - 4.0 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	10	13	13
Units: 10^9/L				
arithmetic mean (standard deviation)	-0.26 (± 0.48)	-0.96 (± 0.68)	-0.86 (± 0.61)	-0.87 (± 1.24)

End point values	Placebo			

Subject group type	Reporting group			
Number of subjects analysed	16			
Units: 10^9/L				
arithmetic mean (standard deviation)	-0.33 (± 0.72)			

Statistical analyses

Statistical analysis title	Lymphocyte count analysis 0.5 mg vs placebo
Comparison groups	ACT-334441 - 0.5 mg v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Lymphocyte count analysis 1 mg vs placebo
Comparison groups	ACT-334441 - 1.0 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Lymphocyte count analysis 2 mg vs placebo
Comparison groups	ACT-334441 - 2.0 mg v Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	0.19

Statistical analysis title	Lymphocyte count analysis 4 mg vs placebo
Comparison groups	ACT-334441 - 4.0 mg v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.19

Primary: Total lymphocyte count, absolute change from baseline to each post-baseline analysis visit

End point title	Total lymphocyte count, absolute change from baseline to each post-baseline analysis visit[1]

End point description:

End point type	Primary

End point timeframe:

From baseline to End of Treatment

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: Statistical analysis already provided for first endpoint "Total lymphocyte count, absolute change from baseline to EOT "

End point values	ACT-334441 - 0.5 mg	ACT-334441 - 1.0 mg	ACT-334441 - 2.0 mg	ACT-334441 - 4.0 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	13	13
Units: 10^9/L				
arithmetic mean (standard deviation)				
Baseline	1.37 (± 0.52)	1.71 (± 0.82)	1.62 (± 0.75)	1.88 (± 0.77)
Week 2	-0.13 (± 0.56)	-0.48 (± 0.56)	-0.52 (± 1.03)	-1.09 (± 0.65)
Week 4	-0.28 (± 0.42)	-0.69 (± 0.76)	-0.86 (± 0.63)	-0.68 (± 1.32)
Week 8	-0.28 (± 0.60)	-0.92 (± 0.60)	-0.89 (± 0.68)	-1.03 (± 1.12)
Week 12	-0.26 (± 0.48)	-0.72 (± 1.03)	-0.86 (± 0.61)	-0.87 (± 1.24)
End of Treatment	-0.26 (± 0.48)	-0.72 (± 1.03)	-0.86 (± 0.61)	-0.87 (± 1.24)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: 10^9/L				
arithmetic mean (standard deviation)				
Baseline	1.65 (± 0.88)			
Week 2	-0.16 (± 0.75)			
Week 4	-0.33 (± 0.69)			
Week 8	-0.09 (± 0.82)			
Week 12	-0.29 (± 0.73)			
End of Treatment	-0.30 (± 0.71)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Enter description here	
Adverse event reporting additional description:	
Enter description here	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	ACT-334441 0.5 mg
Reporting group description:	
ACT-334441 0.5 mg	
Reporting group title	ACT-334441 1.0 mg
Reporting group description:	
ACT-334441 1.0 mg	
Reporting group title	ACT-334441 2.0 mg
Reporting group description:	
ACT-334441 2.0 mg	
Reporting group title	ACT-334441 4.0 mg
Reporting group description:	
ACT-334441 4.0 mg	

Serious adverse events	Placebo	ACT-334441 0.5 mg	ACT-334441 1.0 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Pancreatitis chronic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (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
Hepatobiliary disorders			
Cholecystitis chronic			

subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (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
Post cholecystectomy syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (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

Serious adverse events	ACT-334441 2.0 mg	ACT-334441 4.0 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Pancreatitis chronic			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post cholecystectomy syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	ACT-334441 0.5 mg	ACT-334441 1.0 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 17 (52.94%)	5 / 12 (41.67%)	5 / 12 (41.67%)
Surgical and medical procedures			

Tooth extraction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Pneumonitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood fibrinogen decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram T wave amplitude			

decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Intraocular pressure increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Laboratory test abnormal			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 17 (5.88%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dry age-related macular			

degeneration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Abdominal pain lower			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastroduodenitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hepatobiliary disorders			
Chronic hepatitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nail dystrophy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			

Nitrituria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Erysipelas			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 17 (11.76%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Periodontitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tracheobronchitis			

subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	ACT-334441 2.0 mg	ACT-334441 4.0 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	5 / 13 (38.46%)	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Pneumonitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Bilirubin conjugated increased			

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood fibrinogen decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Blood potassium decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram T wave amplitude decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Intraocular pressure increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Laboratory test abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Lymphopenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Cataract			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dry age-related macular degeneration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Abdominal pain lower			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Gastroduodenitis			

subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Chronic hepatitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Nail dystrophy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Nitrituria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Proteinuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Joint swelling			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Erysipelas			

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Periodontitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Tracheobronchitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2015	Summary of most relevant changes: • Study-specific stopping rules per FDA recommendations were introduced, • ECG discharge criteria from hospital on Day 1 and on the first day of re-initiation following treatment interruption were clarified, • Respiratory system criteria for interruption / premature discontinuation of study treatment per FDA recommendations were revised, • The safety endpoint/variable Occurrence of treatment-emergent decrease of FEV1 or FVC was modified, • Analysis of pulmonary safety events was to include treatment-emergent decrease of FEV1 or FVC to < 85% of baseline values instead of < 80% of baseline values, • Since at Visit 3 and re-initiation visits, study drug was not to be allocated by the IRT system, the compliance could not be calculated automatically in the eCRF. During these visits, a compliance review based on study drug accountability was to be performed by the investigator (or delegate) and recorded in the eCRF, • In case of no medical justification available for study treatment interruption, compliance < 80% was to be reported as a protocol deviation, • Clarifications were added in the laboratory sections, • In order to shorten the time window between assessments during the follow-up period (at 6 and 16 weeks after last dose of study treatment intake), a follow-up assessment via telephone was added at 11 weeks after last dose of study treatment intake to collect SAEs and pregnancy test results, • Informed Consent Form was amended to reflect the changes introduced by the amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported