Clinical trial results:
A prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group, 12-week study to evaluate the safety and tolerability of macitentan in subjects with combined pre- and post-capillary pulmonary hypertension (CpcPH) due to left ventricular dysfunction

Summary

EudraCT number	2013-003822-96
Trial protocol	IT CZ AT BE ES
Global end of trial date	15 November 2015

Results information

Result version number	v1 (current)
This version publication date	25 February 2017
First version publication date	25 February 2017

Trial information

Trial identification

Sponsor protocol code	AC-055G201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02070991
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.com
Scientific contact	Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.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	16 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of macitentan 10 mg in subjects with CpcPH

Protection of trial subjects:

The study was conducted in 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 country in which the research was conducted. Subjects with LVD and severely reduced ejection fraction (<30%) were not included in the study for safety reasons, since they are more likely to develop complications due to fluid retention. Subjects were required to return to the site for a safety visit after 1 week.

Background therapy:

All subjects were required to be on oral diuretic therapy, and they were allowed to continue their usual heart failure therapy. The dose of diuretic(s) (and other heart failure therapy, if applicable) was required to be stable for at least 1 week prior to baseline RHC and up to Randomization

Evidence for comparator: -

Actual start date of recruitment	05 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	63
EEA total number of subjects	46

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)	8
From 65 to 84 years	54
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 88 patients were screened from 28 sites across Europe and North America in 11 countries. Of these, 63 were randomized.

Pre-assignment

Screening details:

The screening period had to take place within 30 days prior to enrollment into the study.

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	Investigator, Subject, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Macitentan

Arm description:

Patients were administered macitentan oral tablet, 10 mg once daily

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet containing 10mg macitentan, once daily

Arm title	Placebo

Arm description:

Patients were administered matching placebo once daily

Arm type	Placebo
Investigational medicinal product name	Matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet identical to the macitentan tablet, once daily

Number of subjects in period 1	Macitentan	Placebo
Started	31	32
Completed	28	32
Not completed	3	0
Adverse event, serious fatal	2	-
Withdrawal by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan
Reporting group description:	
Patients were administered macitentan oral tablet, 10 mg once daily	
Reporting group title	Placebo
Reporting group description:	
Patients were administered matching placebo once daily	

Reporting group values	Macitentan	Placebo	Total
Number of subjects	31	32	63
Age categorical Units: Subjects			
Adults (18-64 years)	5	3	8
From 65-84 years	26	28	54
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	70	71.5	
standard deviation	± 5.19	± 7.77	-
Gender categorical Units:			
Male	6	16	22
Female	25	16	41
Race Units: Subjects			
Black or African American	0	1	1
American Indian or Alaska	1	0	1
White	30	30	60
Other	0	1	1
NYHA Functional Class at Baseline Units: Subjects			
Class II	5	10	15
Class III	26	22	48
Left Ventricular Ejection Fraction at Baseline as Measured by Investigator Units: Subjects			
< 50%	6	9	15
>= 50%	25	23	48
# of subjects with Atrial Fibrillation at baseline Units: Subjects			
Yes	22	24	46
No	9	8	17
# of subjects with Systemic Hypertension] Units: Subjects			
Yes	30	27	57
No	1	5	6

# of subjects with Diabetes Mellitus Type II Units: Subjects			
Yes	14	13	27
No	17	19	36
# of subjects with Right Ventricular Failure Units: Subjects			
Yes	7	11	18
No	24	21	45
# of subjects with Chronic Kidney Disease Units: Subjects			
Yes	8	6	14
No	23	26	49
# of subjects with Obesity - BMI > 30kg/m2 Units: Subjects			
Yes	20	20	40
No	11	12	23
Time from Left Ventricular Dysfunction diagnosis Units: Years			
arithmetic mean	4.6	3.3	
standard deviation	± 8.9	± 6.5	-
6MWD at baseline Units: Meters			
arithmetic mean	317.2	299.6	
standard deviation	± 104.3	± 107.4	-
PVR at baseline Units: dyn.sec/cm5			
arithmetic mean	491.2	549.3	
standard deviation	± 235.5	± 239.6	-

End points

End points reporting groups

Reporting group title	Macitentan
Reporting group description:	
Patients were administered macitentan oral tablet, 10 mg once daily	
Reporting group title	Placebo
Reporting group description:	
Patients were administered matching placebo once daily	
Subject analysis set title	Full analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Full analysis set included all subjects from the Screened analysis set allocated to a randomized study treatment	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety analysis set included all subjects from the Full analysis set who received at least one dose of study treatment, based on the actual treatment received	

Primary: Proportion of subjects experiencing significant fluid retention or worsening in NYHA functional class up to end-of-treatment

End point title	Proportion of subjects experiencing significant fluid retention or worsening in NYHA functional class up to end-of-treatment
End point description:	
Composite endpoint of significant fluid retention (defined as an increase in body weight due to fluid overload by ≥ 5kg or ≥ 5%, or parenteral administration of diuretics) or a worsening of NYHA functional class from baseline. Subject could have met more than 1 component of the main safety endpoint	
End point type	Primary
End point timeframe:	
From randomization up to End of Study: treatment period up to Week 12	

End point values	Macitentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: Number of subjects				
Subjects with at least one condition	7	4		
Subjects with significant fluid retention	7	3		
Worsening in NYHA Functional Class from baseline	1	2		

Statistical analyses

Statistical analysis title	Treatment difference between macitentan & placebo
Statistical analysis description:	
Difference in % of subjects with at least 1 condition	
Comparison groups	Macitentan v Placebo

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.337
Method	Fisher exact
Parameter estimate	Difference in proportion
Point estimate	10.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.07
upper limit	33.26

Other pre-specified: NT-Pro-BNP at Week 12 Expressed As Percent of Baseline

End point title	NT-Pro-BNP at Week 12 Expressed As Percent of Baseline

End point description:

End point type	Other pre-specified

End point timeframe:

From randomization up to end of treatment period (Week 12)

End point values	Macitentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: % ratio				
geometric mean (confidence interval 95%)	91.56 (72.37 to 115.83)	118.9 (92.53 to 152.78)		

Statistical analyses

Statistical analysis title	Treatment effect

Statistical analysis description:

Ratio of Geometric Means (Macitentan/Placebo)

Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Ratio of geometric means
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.08

Other pre-specified: PVR at rest at Week 12 expressed as percent of Baseline PVR at rest

End point title	PVR at rest at Week 12 expressed as percent of Baseline PVR at rest

End point description:

PVR was assessed at rest by right heart catheterization

End point type	Other pre-specified

End point timeframe:

From randomization up to end of treatment period (Week 12)

End point values	Macitentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	24		
Units: % ratio				
geometric mean (confidence interval 95%)	66.31 (56.15 to 78.3)	71.23 (51.35 to 98.81)		

Statistical analyses

Statistical analysis title	Treatment effect

Statistical analysis description:

Ratio of Geometric Means (Macitentan/Placebo)

Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Ratio of geometric means
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.36

Other pre-specified: Mean Pulmonary Arterial Pressure - Absolute change from Baseline to Week 12

End point title	Mean Pulmonary Arterial Pressure - Absolute change from Baseline to Week 12

End point description:

End point type	Other pre-specified

End point timeframe:

From randomization up to end of treatment period (Week 12)

End point values	Macitentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	25		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-3.5 (-6.1 to -0.9)	-3.8 (-7.5 to -0.1)		

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	4.9

Other pre-specified: Mean Right Atrial Pressure - Absolute change from baseline to week 12

End point title	Mean Right Atrial Pressure - Absolute change from baseline to week 12

End point description:

End point type	Other pre-specified

End point timeframe:

From randomization up to end of treatment period (Week 12)

End point values	Macitentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	25		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-0.9 (-3.5 to 1.7)	-1.6 (-3.3 to 0)		

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	3.6

Other pre-specified: Pulmonary Artery Wedge Pressure - Absolute change from Baseline to Week 12

End point title	Pulmonary Artery Wedge Pressure - Absolute change from Baseline to Week 12

End point description:

End point type	Other pre-specified

End point timeframe:

From randomization up to end of treatment period (Week 12)

End point values	Macitentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	24		
Units: mmHg				
arithmetic mean (confidence interval 95%)	0.8 (-2.3 to 3.9)	1.1 (-1.6 to 3.8)		

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	Macitentan v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	3.7

Other pre-specified: Cardiac Index - Absolute change from Baseline to Week 12

End point title	Cardiac Index - Absolute change from Baseline to Week 12

End point description:

End point type	Other pre-specified

End point timeframe:

From randomization up to end of treatment period (Week 12)

End point values	Macitentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	24		
Units: L/min/m2				
arithmetic mean (confidence interval 95%)	0.37 (0.14 to 0.6)	-0.03 (-0.22 to 0.16)		

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.68

Other pre-specified: Diastolic Pulmonary V. Pressure Gradient - Absolute change from Baseline to Week 12

End point title	Diastolic Pulmonary V. Pressure Gradient - Absolute change from Baseline to Week 12

End point description:

End point type	Other pre-specified

End point timeframe:

From randomization up to end of treatment period (Week 12)

End point values	Macitentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	24		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-4.8 (-7.2 to -2.3)	-4.3 (-7.5 to -1.1)		

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	3.6

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From study treatment initiation up to 30 days after study treatment discontinuation	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo once daily for at least 8.0 weeks to a maximum duration of 14.1 weeks	
Reporting group title	Macitentan_10mg
Reporting group description:	
Subjects received macitentan oral tablet, 10 mg once daily for at least 0.3 week to a maximum duration of 14.9 weeks	

Serious adverse events	Placebo	Macitentan_10mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 32 (18.75%)	11 / 31 (35.48%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure acute			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic respiratory failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Macitentan_10mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 32 (46.88%)	16 / 31 (51.61%)	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Walking distance test abnormal			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	2 / 32 (6.25%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Mitral valve incompetence			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	3 / 32 (9.38%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	2 / 32 (6.25%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 32 (6.25%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Dyspnoea			
subjects affected / exposed	4 / 32 (12.50%)	3 / 31 (9.68%)	
occurrences (all)	5	4	
Pleural effusion			

subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	3	
Hypokalaemia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported