Clinical trial results:
A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Prospective Study to Assess Efficacy of Riociguat in Patients With Operable CTEPH Prior to Pulmonary Endarterectomy With High Preoperative Pulmonary Vascular Resistance

Summary

EudraCT number	2017-001121-40
Trial protocol	GB DE FR
Global end of trial date	05 May 2020

Results information

Result version number	v1 (current)
This version publication date	21 May 2021
First version publication date	21 May 2021

Trial information

Trial identification

Sponsor protocol code	PEA Bridging Study

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03273257
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	International CTEPH Association (ICA)
Sponsor organisation address	c/o artax Fide Consult AG, Gartenstrasse 95, Basel, Switzerland,
Public contact	Gérald Simonneau, International CTEPH Association (ICA), info@cteph-association.org
Scientific contact	David Jenkins, International CTEPH Association (ICA), 041 413797970, info@cteph-association.org

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	20 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2020
Global end of trial reached?	Yes
Global end of trial date	05 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy of riociguat on preoperative PVR in patients with operable CTEPH.

Protection of trial subjects:

Patients were treated at expert centres with many years of experience in the management of CTEPH, and all patients were to receive the recommended gold standard treatment for operable CTEPH, i.e. PEA surgery. As per the protocol, surgery was to be performed by the principal surgeon of the site. Moreover, an unblinded, independent data safety monitoring board periodically reviewed safety data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	France: 1
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	6
From 65 to 84 years	8

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients were recruited at 3 expert centres for CTEPH in France, Germany and the UK between August 2018 and May 2020.

Pre-assignment

Screening details:

Patients could undergo a screening period of up to 90 days prior to the baseline visit in order to assess eligibility of patients and to allow for the washout of prohibited medications. A total of 17 patients were screened; of those, 14 were enrolled into the study.

Period 1

Period 1 title	Randomisation (no drug treatment yet)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm

Arm description:

Patients were randomised to receive riociguat for 90 days prior to surgery

Arm type	Active comparator
Investigational medicinal product name	Riociguat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Riociguat will be initiated at 1 mg tid. The dosage will be increased by 0.5 mg at 2 week intervals based on tolerability as assessed by systolic blood pressure up to a maximum dose of 2.5 mg tid.

Downtitration to 0.5 mg tid is foreseen for patients with low optimal tolerability.

Arm title	Placebo

Arm description:

Patients were randomised to receive placebo for 90 days prior to surgery

Arm type	Placebo
Investigational medicinal product name	Matching placebo to riociguat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was given tid, mimicking the dosing scheme for riociguat

Number of subjects in period 1	Treatment arm	Placebo
Started	7	7
Completed	7	7

Period 2	
Period 2 title	Treatment period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm

Arm description:

Patients received riociguat for 90 days prior to surgery.

Arm type	Active comparator
Investigational medicinal product name	Riociguat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Riociguat will be initiated at 1 mg tid. The dosage will be increased by 0.5 mg at 2 week intervals based on tolerability as assessed by systolic blood pressure up to a maximum dose of 2.5 mg tid.

Downtitration to 0.5 mg tid is foreseen for patients with low optimal tolerability.

Arm title	Placebo

Arm description:

Patients received placebo for 90 days prior to surgery.

Arm type	Placebo
Investigational medicinal product name	Matching placebo to riociguat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was given tid, mimicking the dosing scheme for riociguat

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: One patient died after randomisation, but before starting study treatment. As per the SAP, baseline characteristics are reported for the ITT population, which is defined as patients having received at least one dose of IMP. Therefore, the patient who died before starting treatment was not included in the analysis of baseline characteristics, and a new period had to be defined to account for this.

Number of subjects in period 2[2][3]	Treatment arm	Placebo
Started	7	6
Completed	6	5
Not completed	1	1
Inability to schedule PEA according to protocol	1	1

Notes:

[2] - 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: One patient died after randomisation, but before starting study treatment. As per the SAP, baseline characteristics are reported for the ITT population, which is defined as patients having received at least one dose of IMP. Therefore, the patient who died before starting treatment was not included in the analysis of baseline characteristics; however, he is considered to have enrolled in the trial.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One patient in the placebo arm died after randomisation, but before starting study treatment.

Period 3

Period 3 title	PEA (no more drug treatment)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm

Arm description:

Patients had received riociguat for 90 days prior to surgery and underwent PEA surgery during this period

Arm type	Active comparator
Investigational medicinal product name	Riociguat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Riociguat will be initiated at 1 mg tid. The dosage will be increased by 0.5 mg at 2 week intervals based

Dosage and administration details:

Placebo was given tid, mimicking the dosing scheme for riociguat

Number of subjects in period 3	Treatment arm	Placebo
Started	6	5
Completed	6	5

Period 4

Period 4 title	Post-surgery observation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm

Arm description:

Patients had received riociguat for 90 days prior to surgery and had undergone PEA surgery

Arm type	Active comparator
Investigational medicinal product name	Riociguat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Riociguat will be initiated at 1 mg tid. The dosage will be increased by 0.5 mg at 2 week intervals based on tolerability as assessed by systolic blood pressure up to a maximum dose of 2.5 mg tid.

Downtitration to 0.5 mg tid is foreseen for patients with low optimal tolerability.

Arm title	Placebo

Arm description:

Patients had received placebo for 90 days prior to surgery and had undergone PEA surgery

Arm type	Placebo

Investigational medicinal product name	Matching placebo to riociguat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was given tid, mimicking the dosing scheme for riociguat

Number of subjects in period 4	Treatment arm	Placebo
Started	6	5
Completed	3	3
Not completed	3	2
Study terminated	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment arm
Reporting group description: Patients received riociguat for 90 days prior to surgery.	
Reporting group title	Placebo
Reporting group description: Patients received placebo for 90 days prior to surgery.	

Reporting group values	Treatment arm	Placebo	Total
Number of subjects	7	6	13
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	66	67	
full range (min-max)	48 to 75	52 to 74	-
Gender categorical Units: Subjects			
Female	4	1	5
Male	3	5	8
Race Units: Subjects			
White	6	6	12
Black African	1	0	1
Received beta blockers between enrolment and PEA Units: Subjects			
Yes	3	0	3
No	4	6	10
Received vitamin K antagonists between enrolment and PEA Units: Subjects			
Yes	1	2	3
No	6	4	10
Received new/direct oral anticoagulants between enrolment and PEA Units: Subjects			

Yes	6	4	10
No	1	2	3

Body mass index Units: kg/m^2			
arithmetic mean	31.2	25.4	
standard deviation	± 3.9	± 1.7	-
PVR at diagnosis Units: dyn*sec/cm^5			
arithmetic mean	944.0	1007.5	
standard deviation	± 92.7	± 368.2	-
mPAP at diagnosis Units: mmHg			
arithmetic mean	50.3	53.2	
standard deviation	± 8.4	± 4.8	-

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description: Patients were randomised to receive riociguat for 90 days prior to surgery	
Reporting group title	Placebo
Reporting group description: Patients were randomised to receive placebo for 90 days prior to surgery	
Reporting group title	Treatment arm
Reporting group description: Patients received riociguat for 90 days prior to surgery.	
Reporting group title	Placebo
Reporting group description: Patients received placebo for 90 days prior to surgery.	
Reporting group title	Treatment arm
Reporting group description: Patients had received riociguat for 90 days prior to surgery and underwent PEA surgery during this period	
Reporting group title	Placebo
Reporting group description: Patients had received placebo for 90 days prior to surgery and underwent PEA surgery during this period	
Reporting group title	Treatment arm
Reporting group description: Patients had received riociguat for 90 days prior to surgery and had undergone PEA surgery	
Reporting group title	Placebo
Reporting group description: Patients had received placebo for 90 days prior to surgery and had undergone PEA surgery	

Primary: Change in PVR from baseline to immediately before PEA

End point title	Change in PVR from baseline to immediately before PEA
End point description:	
End point type	Primary
End point timeframe: 90 days	

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[1]	5[2]		
Units: percent change from baseline				
arithmetic mean (standard deviation)	-28.4 (± 16.2)	-6.9 (± 27.9)		

Notes:

[1] - One subject was discontinued during the treatment phase

[2] - One subject was discontinued during the treatment phase

Statistical analyses

Statistical analysis title	Statistical analysis of primary endpoint
Comparison groups	Treatment arm v Placebo
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139
Method	2-sample Wilcoxon rank sum test

Secondary: Change in PVR from baseline to 6 months post-PEA

End point title	Change in PVR from baseline to 6 months post-PEA

End point description:

End point type	Secondary

End point timeframe:
270 days

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[3]	3[4]		
Units: percent change from baseline				
arithmetic mean (standard deviation)	-68.1 (± 9.8)	-83.0 (± 2.2)		

Notes:
[3] - One subject was discontinued during the treatment phase and 3 during post-surgery follow-up
[4] - One subject was discontinued during the treatment phase and 2 during post-surgery follow-up

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause death, PH-related hospitalisation, need for PAH-targeted therapy or WHO functional class unchanged or worse between randomisation and 6 months post-PEA (composite endpoint)

End point title	All-cause death, PH-related hospitalisation, need for PAH-targeted therapy or WHO functional class unchanged or worse between randomisation and 6 months post-PEA (composite endpoint)

End point description:

End point type	Secondary

End point timeframe:
270 days

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Number of patients				
Experienced endpoint event	6	5		
Did not experience endpoint event	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative circulatory arrest time

End point title	Intraoperative circulatory arrest time

End point description:

End point type	Secondary

End point timeframe:
intraoperative

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: minutes				
arithmetic mean (standard deviation)	32 (± 9)	40 (± 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative surgery-related complications

End point title	Intraoperative surgery-related complications

End point description:

The occurence of any of the following complications will be assessed:
- Bleeding and/or blood loss >1 L in 12 hours
- Airway bleed with need for extracorporeal membrane oxygenation
- Any use of extracorporeal membrane oxygenation for respiratory or haemodynamic support, specified as venovenous or veno-arterial
- Prolonged ventilation >96 hours
- Need for tracheostomy

- Need for drainage of pericardial effusion
- Neurological complications, ie, stroke, cerebral, subdural bleeding
- Reintubation or noninvasive ventilation for reperfusion response
- Haemoptysis requiring any intervention
- Renal failure requiring dialysis
- Wound infections
- Pneumonia
- Prolonged need for inotropic support (≥ 5 days)

End point type	Secondary

End point timeframe:
intraoperative

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Number of patients				
Experienced endpoint event	0	0		
Did not experience endpoint event	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical evaluation of specimen: ease of dissection plane

End point title	Surgical evaluation of specimen: ease of dissection plane

End point description:

End point type	Secondary

End point timeframe:
intraoperative

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Number of patients				
Easier than normal	1	1		
Normal	3	4		
More difficult than normal	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical evaluation of specimen: completeness of disease clearance

End point title	Surgical evaluation of specimen: completeness of disease clearance

End point description:

End point type	Secondary

End point timeframe:
intraoperative

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Number of patients				
Better than expected	0	0		
As expected	6	5		
Worse than expected	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical evaluation of specimen: appearance of clot

End point title	Surgical evaluation of specimen: appearance of clot

End point description:

End point type	Secondary

End point timeframe:
intraoperative

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Number of patients				
More solid than usual	0	0		
Normal	4	5		
More friable than usual	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical evaluation of specimen: appearance of vessel wall

End point title	Surgical evaluation of specimen: appearance of vessel wall

End point description:

End point type	Secondary

End point timeframe:
intraoperative

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Number of patients				
More solid than usual	0	0		
Normal	4	5		
More friable than ususal	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause death

End point title	All-cause death

End point description:

End point type	Secondary

End point timeframe:
270 days

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: Number of patients				
Died	0	0		
Did not die	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Withdrawal during randomised treatment phase

End point title	Withdrawal during randomised treatment phase

End point description:

Only withdrawals after randomisation but before PEA are included

End point type	Secondary

End point timeframe:

90 days

End point values	Treatment arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Number of patients				
Withdrew	1	1		
Did not withdraw	6	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From informed consent until study completion (270-360 days) or early termination	
Adverse event reporting additional description:	
Events reported are treatment-emergent adverse events, i.e. any event not present before exposure to study drug or any event already present that worsened in either intensity or frequency after exposure to study drug, in patients who actually received any study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Treatment arm
Reporting group description:	
Patients received riociguat for 90 days prior to surgery, then underwent PEA surgery and were subsequently followed up for 6 months	
Reporting group title	Placebo
Reporting group description:	
Patients received placebo for 90 days prior to surgery, then underwent PEA surgery and were subsequently followed up for 6 months	

Serious adverse events	Treatment arm	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension	Additional description: Worsening symptoms of CTEPH, including increased NT-proBNP, peripheral oedema and breathlessness		
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Mediastinitis			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment arm	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	5 / 6 (83.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Surgical and medical procedures			
Drug therapy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	
occurrences (all)	2	4	
Feeling cold			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

Oedema peripheral			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

Rhinorrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Anxiety disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Delirium			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Inflammatory marker increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Procedural haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vaccination complication			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Bradycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Tachyarrhythmia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	3 / 7 (42.86%)	2 / 6 (33.33%)	
occurrences (all)	4	2	
Lethargy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Memory impairment			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	1	4	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	4 / 7 (57.14%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Eructation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Flatulence			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Toothache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Chest wall haematoma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	0 / 7 (0.00%)	3 / 6 (50.00%)	
occurrences (all)	0	4	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pain in extremity			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Post procedural infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dyslipidaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Hypomagnesaemia			

subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	0 / 6 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated after enrolling only 14 out of 88 planned patients due to slow recruitment and further limitations imposed by the COVID-19 pandemic. No firm conclusions can be drawn based on the study data due to the limited sample size.

Notes: