Clinical trial results:
An open-label phase IIIb study of riociguat in patients with in-operable CTEPH, or recurrent or persisting pulmonary hypertension (PH) after surgical treatment who are not satisfactorily treated and cannot participate in any other CTEPH trial

Summary

EudraCT number	2012-002104-40
Trial protocol	SE DE PT ES BE CZ DK NL IT AT GB
Global end of trial date	01 December 2015

Results information

Result version number	v1 (current)
This version publication date	16 December 2016
First version publication date	16 December 2016

Trial information

Trial identification

Sponsor protocol code	BAY63-2521/16097

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01784562
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	01 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to assess safety and tolerability as well as clinical effects of riociguat treatment, and to provide access to riociguat for subjects with in-operable chronic thromboembolic pulmonary hypertension (CTEPH), or recurrent or persisting pulmonary hypertension (PH) after surgical treatment that were not satisfactorily treated and could not participate in any other CTEPH trial.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 March 2013
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	Netherlands: 19
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Turkey: 20

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Mexico: 7
Worldwide total number of subjects	300
EEA total number of subjects	227

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)	130
From 65 to 84 years	170
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 71 study centers in 19 countries, between 07 March 2013 (first subject first visit) and 01 December 2015 (last subject last visit).

Pre-assignment

Screening details:

Overall 315 subjects were screened, of them 15 were screen failures and 300 subjects were assigned to the treatment.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Riociguat up to 2.5 mg tid

Arm description:

Subjects received riociguat film-coated tablets with starting dose of 1 milligram (mg) three times daily (tid). An individual riociguat dose was titrated every 2 weeks based on blood pressure titration rules and subject's well-being. Dose modifications were done in 0.5 mg riociguat steps and the maximum dose was 2.5 mg tid.

Arm type	Experimental
Investigational medicinal product name	Riociguat
Investigational medicinal product code	BAY63-2521
Other name	Adempas
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received riociguat film-coated tablets with starting dose of 1 mg tid. An individual riociguat dose was titrated every 2 weeks based on blood pressure titration rules and subject's well-being. Dose modifications were done in 0.5 mg riociguat steps and the maximum dose was 2.5 mg tid.

Number of subjects in period 1	Riociguat up to 2.5 mg tid
Started	300
Completed	258
Not completed	42
Physician decision	5
Screening failure	1
Consent withdrawn by subject	7
Protocol violation	4
Death	5
Adverse event	15
Lost to follow-up	3

Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Riociguat up to 2.5 mg tid
Reporting group description:	
Subjects received riociguat film-coated tablets with starting dose of 1 milligram (mg) three times daily (tid). An individual riociguat dose was titrated every 2 weeks based on blood pressure titration rules and subject's well-being. Dose modifications were done in 0.5 mg riociguat steps and the maximum dose was 2.5 mg tid.	

Reporting group values	Riociguat up to 2.5 mg tid	Total	
Number of subjects	300	300	
Age categorical			
Units: Subjects			
Adults (18-64 years)	130	130	
From 65-84 years	170	170	
Age continuous			
Units: years			
arithmetic mean	63.9		
standard deviation	± 12.5	-	
Gender categorical			
Units: Subjects			
Female	185	185	
Male	115	115	
WHO Functional Class (FC)			
The WHO functional assessment of pulmonary arterial hypertension (PAH) ranged from functional class I (subjects with pulmonary hypertension [PH] but without resulting limitation of physical activity); class II (subjects with PH resulting in slight limitation of physical activity); class III (subjects with PH resulting in marked limitation of physical activity) to class IV (subjects with PH with inability to carry out any physical activity without symptoms). Changes to a lower WHO functional class resemble improvement; changes to a higher functional class resemble deterioration of PAH.			
Units: Subjects			
Class I	5	5	
Class II	112	112	
Class III	175	175	
Class IV	8	8	
6-Minute Walking Distance (6MWD) Test			
6MWD test (optional) was used to measure the subjects functional exercise capacity. 213 subjects performed the 6MWD test at baseline.			
Units: meter			
arithmetic mean	373.63		
standard deviation	± 117.02	-	

End points

End points reporting groups

Reporting group title	Riociguat up to 2.5 mg tid

Reporting group description:

Subjects received riociguat film-coated tablets with starting dose of 1 milligram (mg) three times daily (tid). An individual riociguat dose was titrated every 2 weeks based on blood pressure titration rules and subject's well-being. Dose modifications were done in 0.5 mg riociguat steps and the maximum dose was 2.5 mg tid.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS (N=300) included all subjects who have been included in the study, were assigned to study treatment, and have received and taken at least 1 study drug administration.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; and another medically important serious event as judged by the investigator. Adverse events were considered to be treatment emergent if they had started or worsened after first administration of study medication up to 2 calendar days after end of treatment with study medication.

End point type	Primary

End point timeframe:

Treatment-emergent AEs were collected from start of study treatment up to 2 days after the last drug intake

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Riociguat up to 2.5 mg tid			
Subject group type	Reporting group			
Number of subjects analysed	300[2]			
Units: Subjects				
TEAE	273			
TESAE	89			

Notes:

[2] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in the 6-Minute Walking Distance (6MWD) Test at Specified Timepoint

End point title	Change From Baseline in the 6-Minute Walking Distance (6MWD) Test at Specified Timepoint

End point description:

6MWD test were used to measure the subjects functional exercise capacity. The standardized walking course was 30 meters in length. This test was an optional assessment for ethical reasons, to open the early access of riociguat for subjects for as many subjects as possible, including subjects unable to walk and thus, unable to perform the walking test. Due to the optional nature data were not available for all the subjects and resulted in a large number of missing data. In the below table, "n" signifies the number of subjects who were evaluable for the specified category, respectively.

End point type	Other pre-specified

End point timeframe:

Week 12 and Termination visit (after end of treatment which ranged from 2 days to 864 days)

End point values	Riociguat up to 2.5 mg tid			
Subject group type	Reporting group			
Number of subjects analysed	300[3]			
Units: meter				
arithmetic mean (standard deviation)				
Week 12 (n=130) Termination Visit (n=105)	32.96 (± 42.33) 36.95 (± 52.89)			

Notes:

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline In World Health Organization (WHO) Functional Class at Specified Timepoint

End point title	Change From Baseline In World Health Organization (WHO) Functional Class at Specified Timepoint

End point description:

The WHO functional assessment of PAH ranged from functional class I (subjects with PH but without resulting limitation of physical activity); class II (subjects with PH resulting in slight limitation of physical activity); class III (subjects with PH resulting in marked limitation of physical activity) to class IV (subjects with PH with inability to carry out any physical activity without symptoms. These subjects manifest signs of right-heart failure). Changes to a lower WHO functional class resemble improvement; changes to a higher functional class resemble deterioration of PAH. In the below table, "n" signifies the number of subjects who were evaluable for the specified category, respectively.

End point type	Other pre-specified

End point timeframe:

Week 12 and Termination visit (after end of treatment which ranged from 2 days to 864 days)

End point values	Riociguat up to 2.5 mg tid			
Subject group type	Reporting group			
Number of subjects analysed	300[4]			
Units: percentage of subjects				
number (not applicable)				
Week 12; -2 (n= 264)	0			
Week 12; -1 (n= 264)	22			
Week 12; 0 (n= 264)	73.1			
Week 12; 1 (n= 264)	4.9			
Week 12; 2 (n= 264)	0			
Termination Visit; -2 (n= 284)	1.1			
Termination Visit; -1 (n= 284)	23.9			
Termination Visit; 0 (n= 284)	67.3			
Termination Visit; 1 (n= 284)	7			
Termination Visit; 2 (n= 284)	0.4			

Notes:

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs were collected from start of study treatment up to 2 days after the last drug intake

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Riociguat up to 2.5 mg tid

Reporting group description:

Subjects received riociguat film-coated tablets with starting dose of 1 mg tid. An individual riociguat dose was titrated every 2 weeks based on blood pressure titration rules and subject's well-being. Dose modifications were done in 0.5 mg riociguat steps and the maximum dose was 2.5 mg tid.

Serious adverse events	Riociguat up to 2.5 mg tid		
Total subjects affected by serious adverse events			
subjects affected / exposed	89 / 300 (29.67%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine cancer			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon neoplasm			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleomorphic malignant fibrous histiocytoma			

subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Colon cancer			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemodynamic instability			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	4 / 300 (1.33%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Aortic stenosis			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Pulmonary artery therapeutic procedure			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	3 / 300 (1.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hernia			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	4 / 300 (1.33%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Chronic respiratory failure				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 300 (1.67%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	3 / 300 (1.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Lung disorder				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				

subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
International normalised ratio increased			
subjects affected / exposed	3 / 300 (1.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Head injury			

subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Femur fracture				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	5 / 300 (1.67%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	3 / 300 (1.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Atrial tachycardia				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Cardiac failure acute				

subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	8 / 300 (2.67%)			
occurrences causally related to treatment / all	1 / 9			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cor pulmonale				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Intracardiac thrombus				

subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wolff-Parkinson-White syndrome				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular extrasystoles				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac flutter				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleuropericarditis				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				

subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	17 / 300 (5.67%)			
occurrences causally related to treatment / all	7 / 26			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	5 / 300 (1.67%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Iron deficiency anaemia				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain upper				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	2 / 300 (0.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				

subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal stenosis			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loose tooth			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Joint swelling				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteitis				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal wall abscess				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	4 / 300 (1.33%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	7 / 300 (2.33%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Implant site infection				
subjects affected / exposed	1 / 300 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atypical mycobacterial pneumonia			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected bite			
subjects affected / exposed	1 / 300 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	2 / 300 (0.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Riociguat up to 2.5 mg tid		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	234 / 300 (78.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	26 / 300 (8.67%)		
occurrences (all)	29		
Cardiac disorders			
Palpitations			
subjects affected / exposed	20 / 300 (6.67%)		
occurrences (all)	29		
Nervous system disorders			
Headache			
subjects affected / exposed	54 / 300 (18.00%)		
occurrences (all)	78		
Dizziness			

subjects affected / exposed	54 / 300 (18.00%)		
occurrences (all)	67		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	23 / 300 (7.67%)		
occurrences (all)	26		
Oedema peripheral			
subjects affected / exposed	53 / 300 (17.67%)		
occurrences (all)	59		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	18 / 300 (6.00%)		
occurrences (all)	22		
Dyspepsia			
subjects affected / exposed	60 / 300 (20.00%)		
occurrences (all)	73		
Gastrooesophageal reflux disease			
subjects affected / exposed	31 / 300 (10.33%)		
occurrences (all)	34		
Nausea			
subjects affected / exposed	43 / 300 (14.33%)		
occurrences (all)	50		
Vomiting			
subjects affected / exposed	34 / 300 (11.33%)		
occurrences (all)	44		
Diarrhoea			
subjects affected / exposed	45 / 300 (15.00%)		
occurrences (all)	53		
Constipation			
subjects affected / exposed	31 / 300 (10.33%)		
occurrences (all)	36		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	38 / 300 (12.67%)		
occurrences (all)	44		
Dyspnoea			

subjects affected / exposed	27 / 300 (9.00%)		
occurrences (all)	28		
Epistaxis			
subjects affected / exposed	22 / 300 (7.33%)		
occurrences (all)	29		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	20 / 300 (6.67%)		
occurrences (all)	20		
Muscle spasms			
subjects affected / exposed	17 / 300 (5.67%)		
occurrences (all)	19		
Infections and infestations			
Bronchitis			
subjects affected / exposed	17 / 300 (5.67%)		
occurrences (all)	20		
Nasopharyngitis			
subjects affected / exposed	31 / 300 (10.33%)		
occurrences (all)	39		
Urinary tract infection			
subjects affected / exposed	16 / 300 (5.33%)		
occurrences (all)	18		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	16 / 300 (5.33%)		
occurrences (all)	17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2013	Amendment included following changes: 1. The duration of treatment with riociguat during the study was limited to 18 months, starting when the first subject entered the study in the UK. 2. Timing of the diagnosis of CTEPH and the right heart catheter test prior to the study. 3. Option for urine pregnancy test (instead of serological test). 4. Timing of assessments relevant for titration (systolic blood pressure in relation to study medication intake). 5. Assessment criteria for subject operability.

Notes:

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.

Clinical effects (6MWD, WHO FC) were recorded as primary endpoint; but planned and analysed as exploratory in accordance with protocol. Both reported as other pre-specified endpoint. Decimal places automatically truncated if last digit=0.

Notes: