Clinical trial results:
A prospective, randomized, international, multicenter, double arm, controlled, open label study of Riociguat in patients with pulmonary arterial hypertension (PAH) who are on a stable dose of phosphodiesterase 5 inhibitors (PDE 5i) with or without endothelin receptor antagonist (ERA), but not at treatment goal

Summary

EudraCT number	2016-001067-36
Trial protocol	ES PT AT CZ GB DE BE NL DK GR PL IT
Global end of trial date	02 March 2020

Results information

Result version number	v1 (current)
This version publication date	07 January 2021
First version publication date	07 January 2021

Trial information

Trial identification

Sponsor protocol code	BAY63-2521/18588

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02891850
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	16 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the proportion of subjects in each treatment arm with a satisfactory clinical response as defined by a composite primary endpoint at Week 24.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the 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	10 January 2017
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	United States: 20
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Brazil: 42
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czechia: 25
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Turkey: 8

Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Poland: 2
Worldwide total number of subjects	225
EEA total number of subjects	106

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)	173
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 21 countries between 11-JAN-2017 (first participant first visit) and 03-MAR-2020 (last participant last visit).

Pre-assignment

Screening details:

293 participants were screened in this study. Of these, 67 participants did not enter the treatment period (60 screening failures; 2 withdraw during screening; 2 withdraw following physician decision; 3 withdraw due to other reasons). 226 participants were randomized, of which 1 participant withdraw before treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Riociguat

Arm description:

Participants received BAY63-2521 tablets at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks.

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

Dosage and administration details:

0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg administered three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks, tablets administrated orally

Arm title	PDE-5i

Arm description:

Participants remained on their current pulmonary arterial hypertension (PAH) treatment on tadalafil (20 to 40 mg/day) or sildenafil (at least 60 mg/day) for 24 weeks at the discretion of the investigator.

Arm type	Active comparator
Investigational medicinal product name	Tadalafil
Investigational medicinal product code	
Other name	ADCIRCA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

20 to 40 mg/day for 24 weeks as per the investigator’s discretion, tablets administrated orally

Investigational medicinal product name	Sildenafil citrate
Investigational medicinal product code	
Other name	REVATIO
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
At least 60 mg/day for 24 weeks as per the investigator’s discretion, tablets administrated orally

Number of subjects in period 1	Riociguat	PDE-5i
Started	111	114
Completed	104	107
Not completed	7	7
Adverse event, serious fatal	-	4
Consent withdrawn by subject	2	3
Physician decision	1	-
Adverse event, non-fatal	3	-
Pregnancy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Riociguat
Reporting group description:	
Participants received BAY63-2521 tablets at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks.	
Reporting group title	PDE-5i
Reporting group description:	
Participants remained on their current pulmonary arterial hypertension (PAH) treatment on tadalafil (20 to 40 mg/day) or sildenafil (at least 60 mg/day) for 24 weeks at the discretion of the investigator.	

Reporting group values	Riociguat	PDE-5i	Total
Number of subjects	111	114	225
Age Categorical			
Units:			
Age Continuous			
Units: years			
arithmetic mean	49.4	49.2	
standard deviation	± 16.16	± 15.64	-
Gender Categorical			
Units: participants			
Female	82	95	177
Male	29	19	48
Race			
Units: Subjects			
White	86	89	175
Black or African American	4	5	9
Asian	17	19	36
American Indian or Alaska Native	1	0	1
Not Reported	3	1	4
Ethnicity			
Units: Subjects			
Hispanic or Latino	32	31	63
Not Hispanic or Latino	75	80	155
Not Reported	4	3	7

End points

End points reporting groups

Reporting group title	Riociguat

Reporting group description:

Participants received BAY63-2521 tablets at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks.

Reporting group title	PDE-5i

Reporting group description:

Participants remained on their current pulmonary arterial hypertension (PAH) treatment on tadalafil (20 to 40 mg/day) or sildenafil (at least 60 mg/day) for 24 weeks at the discretion of the investigator.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The participants who were randomized and took at least 1 medication were considered for the FAS. Participants were analyzed as randomized.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The population for safety analysis comprised all participants who received at least 1 dose of study drug. Participants in the SAF were analyzed as treated.

Primary: Number of Participants with Satisfactory Clinical Response at Week 24

End point title	Number of Participants with Satisfactory Clinical Response at Week 24

End point description:

The treatment is assessed as efficient (participants with satisfactory clinical response) in case at least 2 out of the following 3 criteria were fulfilled
• 6 Minute Walking Distance increase by ≥ 10% or ≥ 30 m from baseline to Week 24
• World Health Organization Functional Class (WHO FC) I or II at Week 24
• N-terminal pro-brain natriuretic peptide (NT-proBNP) reduction ≥ 30% from baseline to Week 24 (NT-proBNP ratio Week 24/baseline ≤ 0.7)
and
in absence of the defined criteria of clinical worsening.

End point type	Primary

End point timeframe:

At Week 24

End point values	Riociguat	PDE-5i		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111[1]	113[2]		
Units: participants				
With satisfactory clinical response	45	23		
Without satisfactory clinical response	66	90		

Notes:

[1] - Full Analysis Set (FAS) with evaluable participants

[2] - Full Analysis Set (FAS) with evaluable participants

Statistical analyses

Statistical analysis title	OR for satisfactory clinical response at Week 24
Comparison groups	PDE-5i v Riociguat
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.0007
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.526
upper limit	5.06

Notes:

[3] - Stratified by PAH category at baseline

Secondary: Change in 6 Minute Walking Distance (6MWD) with Last Observation Carried Forward from baseline to 24 weeks

End point title	Change in 6 Minute Walking Distance (6MWD) with Last Observation Carried Forward from baseline to 24 weeks

End point description:

Six-minute walk distance (6MWD) was conducted to test the physical limitations of the participant by assessing the participant's exercise capacity. The distance walked by the participant in 6 minutes was measured.

End point type	Secondary

End point timeframe:

From baseline and up to 24 weeks

End point values	Riociguat	PDE-5i		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111[4]	113[5]		
Units: meters (m)				
arithmetic mean (standard deviation)	36.448 (± 65.9748)	13.884 (± 67.1552)		

Notes:

[4] - Full Analysis Set (FAS) with evaluable participants

[5] - Full Analysis Set (FAS) with evaluable participants

Statistical analyses

Statistical analysis title	Mean difference of 6MWD at Week 24
Comparison groups	Riociguat v PDE-5i

Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.0542
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	22.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.03
upper limit	40.1

Notes:

[6] - Stratified by PAH category at baseline

Secondary: Change in N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) with Last Observation Carried Forward at Week 24

End point title	Change in N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) with Last Observation Carried Forward at Week 24

End point description:

N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in the blood are used for screening, diagnosis of acute congestive heart failure (CHF) and may be useful to establish prognosis in heart failure.

End point type	Secondary

End point timeframe:

From baseline and up to 24 weeks

End point values	Riociguat	PDE-5i		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108[7]	113[8]		
Units: picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)	-88.234 (± 533.9179)	81.414 (± 1267.6142)		

Notes:

[7] - Full Analysis Set (FAS) with evaluable participants

[8] - Full Analysis Set (FAS) with evaluable participants

Statistical analyses

Statistical analysis title	Mean difference of NT-proBNP at Week 24
Comparison groups	Riociguat v PDE-5i
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	= 0.1067
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-169.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	-426.18
upper limit	86.88

Notes:

[9] - Stratified by PAH category at baseline

Secondary: Change in World Health Organization Functional Class (WHO FC) with Last Observation Carried Forward at Week 24

End point title	Change in World Health Organization Functional Class (WHO FC) with Last Observation Carried Forward at Week 24

End point description:

The participant's functional class was determined by using the WHO classification. Possible classes range from I (patients with pulmonary hypertension (PH) but without resulting limitation of physical activity) to IV (patients with PH with inability to carry out any physical activity without symptoms).

End point type	Secondary

End point timeframe:

From baseline and up to 24 weeks

End point values	Riociguat	PDE-5i		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111[10]	113[11]		
Units: class				
arithmetic mean (standard deviation)	-0.5 (± 0.58)	-0.2 (± 0.62)		

Notes:

[10] - Full Analysis Set (FAS) with evaluable participants

[11] - Full Analysis Set (FAS) with evaluable participants

Statistical analyses

Statistical analysis title	Mean difference in WHO FC from baseline to Week 24
Comparison groups	Riociguat v PDE-5i
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	equivalence[12]
P-value	= 0.0007
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.11

Notes:

[12] - Stratified by PAH category at baseline

Secondary: Number of Participants with Adjudicated Clinical Worsening at Week 24

End point title	Number of Participants with Adjudicated Clinical Worsening at Week 24

End point description:

Clinical worsening was defined as death of any cause, hospitalization due to worsening pulmonary arterial hypertension (PAH) (adjudicated) or disease progression (adjudicated).

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	Riociguat	PDE-5i		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111[13]	113[14]		
Units: participants				
Yes	1	10		

Notes:

[13] - Full Analysis Set (FAS) with evaluable participants

[14] - Full Analysis Set (FAS) with evaluable participants

Statistical analyses

Statistical analysis title	OR for the clinical worsening at Week 24
Comparison groups	Riociguat v PDE-5i
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	= 0.0047
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.725

Notes:

[15] - Stratified by PAH category at baseline

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events were considered to be treatment emergent if they had started or worsened after the first treatment administration up to 2 days after end of treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Riociguat

Reporting group description:

Participants received riociguat/BAY63-2521 tablets at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks.

Reporting group title	PDE-5i

Reporting group description:

Participants remained on their current pulmonary arterial hypertension (PAH) treatment on tadalafil (20 to 40 mg/day) or sildenafil (at least 60 mg/day) for 24 weeks at the discretion of the investigator.

Serious adverse events	Riociguat	PDE-5i	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 111 (7.21%)	19 / 114 (16.67%)	
number of deaths (all causes)	0	4	
number of deaths resulting from adverse events	0	3	
Investigations			
Pulmonary arterial pressure increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 111 (1.80%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia supraventricular			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
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 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Drug therapy enhancement			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 111 (0.90%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
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			
Chest pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary arterial hypertension			

subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (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			
Gastroenteritis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Riociguat	PDE-5i	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 111 (69.37%)	72 / 114 (63.16%)	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Flushing			
subjects affected / exposed	1 / 111 (0.90%)	1 / 114 (0.88%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	13 / 111 (11.71%)	6 / 114 (5.26%)	
occurrences (all)	19	11	
Orthostatic hypotension			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Jugular vein distension			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences (all)	0	2	
Chest discomfort			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	5 / 111 (4.50%)	5 / 114 (4.39%)	
occurrences (all)	8	5	
Drug ineffective			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	6 / 111 (5.41%)	2 / 114 (1.75%)	
occurrences (all)	7	2	
Malaise			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	2 / 111 (1.80%)	2 / 114 (1.75%)	
occurrences (all)	2	2	
Oedema mucosal			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	3 / 111 (2.70%)	4 / 114 (3.51%)	
occurrences (all)	4	4	
Pyrexia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Hypersensitivity			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	

Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Menometrorrhagia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Adnexa uteri cyst			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 111 (0.00%)	7 / 114 (6.14%)	
occurrences (all)	0	7	
Dry throat			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	3 / 111 (2.70%)	5 / 114 (4.39%)	
occurrences (all)	4	6	
Dyspnoea exertional			
subjects affected / exposed	2 / 111 (1.80%)	0 / 114 (0.00%)	
occurrences (all)	3	0	
Epistaxis			
subjects affected / exposed	3 / 111 (2.70%)	3 / 114 (2.63%)	
occurrences (all)	3	4	
Hypoxia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Lung disorder			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Nasal congestion			

subjects affected / exposed	1 / 111 (0.90%)	1 / 114 (0.88%)	
occurrences (all)	1	1	
Nasal polyps			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Pulmonary hypertension			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	2 / 111 (1.80%)	0 / 114 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Bronchial hyperreactivity			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	3	
Depression			
subjects affected / exposed	2 / 111 (1.80%)	0 / 114 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	0 / 111 (0.00%)	3 / 114 (2.63%)	
occurrences (all)	0	3	
Sleep disorder			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Stress			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood pressure decreased			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Blood pressure systolic increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Catheterisation cardiac			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Prothrombin time prolonged			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Bone contusion			
subjects affected / exposed	1 / 111 (0.90%)	1 / 114 (0.88%)	
occurrences (all)	1	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Cardiac failure chronic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	3 / 111 (2.70%)	4 / 114 (3.51%)	
occurrences (all)	4	4	
Sinus tachycardia			

subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences (all)	0	2	
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	5 / 111 (4.50%)	2 / 114 (1.75%)	
occurrences (all)	5	2	
Headache			
subjects affected / exposed	14 / 111 (12.61%)	8 / 114 (7.02%)	
occurrences (all)	16	8	
Hypoaesthesia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 111 (0.90%)	2 / 114 (1.75%)	
occurrences (all)	1	2	
Syncope			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Anaemia megaloblastic			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Iron deficiency anaemia			
subjects affected / exposed	2 / 111 (1.80%)	0 / 114 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences (all)	0	2	
Lymphopenia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 111 (1.80%)	0 / 114 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Astigmatism			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Cataract			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Eye irritation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Glaucoma			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Retinal disorder			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Ocular discomfort			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 111 (2.70%)	0 / 114 (0.00%)	
occurrences (all)	3	0	
Abdominal distension			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	3 / 111 (2.70%)	0 / 114 (0.00%)	
occurrences (all)	3	0	
Abdominal pain lower			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	3 / 111 (2.70%)	1 / 114 (0.88%)	
occurrences (all)	3	1	
Constipation			
subjects affected / exposed	4 / 111 (3.60%)	0 / 114 (0.00%)	
occurrences (all)	5	0	
Diarrhoea			
subjects affected / exposed	6 / 111 (5.41%)	3 / 114 (2.63%)	
occurrences (all)	6	3	
Dyspepsia			
subjects affected / exposed	10 / 111 (9.01%)	0 / 114 (0.00%)	
occurrences (all)	10	0	
Flatulence			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 111 (7.21%)	1 / 114 (0.88%)	
occurrences (all)	10	1	

Gingival hypertrophy			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	5 / 111 (4.50%)	3 / 114 (2.63%)	
occurrences (all)	6	3	
Toothache			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	3 / 111 (2.70%)	0 / 114 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal hypermotility			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Reflux gastritis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 114 (0.88%)	
occurrences (all)	1	1	
Pruritus			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 111 (0.90%)	3 / 114 (2.63%)	
occurrences (all)	1	3	
Arthritis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 111 (0.90%)	6 / 114 (5.26%)	
occurrences (all)	1	6	
Muscle spasms			
subjects affected / exposed	2 / 111 (1.80%)	1 / 114 (0.88%)	
occurrences (all)	2	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 114 (0.88%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	2 / 111 (1.80%)	1 / 114 (0.88%)	
occurrences (all)	2	1	
Pain in extremity			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	2	
Pain in jaw			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Systemic lupus erythematosus			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Body tinea			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 111 (0.90%)	2 / 114 (1.75%)	
occurrences (all)	1	2	
Conjunctivitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Diverticulitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Enterobiasis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Eye infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	

Fungal infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Hepatitis E			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 111 (0.90%)	2 / 114 (1.75%)	
occurrences (all)	1	2	
Laryngitis			
subjects affected / exposed	0 / 111 (0.00%)	2 / 114 (1.75%)	
occurrences (all)	0	2	
Lower respiratory tract infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	8 / 111 (7.21%)	5 / 114 (4.39%)	
occurrences (all)	8	5	
Otitis media			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	2 / 111 (1.80%)	1 / 114 (0.88%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	0 / 111 (0.00%)	4 / 114 (3.51%)	
occurrences (all)	0	4	
Sinusitis			
subjects affected / exposed	2 / 111 (1.80%)	6 / 114 (5.26%)	
occurrences (all)	2	8	

Tonsillitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	4 / 111 (3.60%)	7 / 114 (6.14%)	
occurrences (all)	4	8	
Urinary tract infection			
subjects affected / exposed	2 / 111 (1.80%)	3 / 114 (2.63%)	
occurrences (all)	2	3	
Viral infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Febrile infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Bronchitis viral			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Mycobacterial infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Fluid retention			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Gout			

subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 111 (0.00%)	4 / 114 (3.51%)	
occurrences (all)	0	4	
Iron deficiency			
subjects affected / exposed	2 / 111 (1.80%)	4 / 114 (3.51%)	
occurrences (all)	2	4	
Decreased appetite			
subjects affected / exposed	1 / 111 (0.90%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 111 (0.00%)	1 / 114 (0.88%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2017	Amendment 4 specified following modifications: 1. Any escalation of PAH therapy including targeted PAH drug was permitted during the study at the discretion of the investigator for the individual subject (independent from and without counting as clinical worsening) in both treatment arms. 2. To reiterate that the benefit risk balance for the population in this study (i.e. PAH, Dana Point Group 1) was positive, despite the potential safety issue in Study 13605 in subjects with pulmonary hypertension associated with idiopathic interstitial pneumonia (Dana Point Group 3) which had led to its early termination. 3. To add the requirement for adequate use of effective contraceptive methods during this study. 4. To include other biomarkers (in addition to NT proBNP), at the request of the advisory committee, to further elucidate the value of selected nitric oxide pathway related biomarkers for treatment decision in this controlled study and in comparison with biomarker results from the previous, uncontrolled RESPITE study. 5. To include details for consistency with the Company Core Data Sheet (e.g. titration rules) and other studies using riociguat (e.g. extending the time for collecting AE information). 6. Subjects with "confirmed obstructive sleep apnea" (Exclusion criterion 13f) was changed to "clinically significant obstructive sleep apnea", if not effectively treated for at least 90 days; only in US/Canada.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported