



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled Phase II Study to Investigate the Efficacy and Safety of Riociguat in Patients With Diffuse Cutaneous Systemic Sclerosis (dcSSc)

Summary

EudraCT number	2014-001353-16
Trial protocol	GB DE NL BE ES CZ HU IT
Global end of trial date	28 March 2019

Results information

Result version number	v1 (current)
This version publication date	27 December 2019
First version publication date	27 December 2019

Trial information

Trial identification

Sponsor protocol code	BAY63-2521/16277
-----------------------	------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02283762
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	28 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 March 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of riociguat administered 3 times a day (TID) compared with placebo in terms of change in the mRSS from baseline to Week 52.

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	15 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Japan: 20
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	121
EEA total number of subjects	57

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)	106
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 15 January 2015 (first patient first visit) and 28 March 2019 (last patient last visit). The Main Treatment Phase has been conducted between 15 Jan 2015 (first subject first visit) and 03 Jan 2018 (last subject last visit for the main treatment phase).

Pre-assignment

Screening details:

139 patients were enrolled in 60 study centers in 15 countries worldwide. 121 patients of 139 patients were randomized and treated with at least one dose of study medication.

88 of the 121 randomized patients completed the treatment phase, of whom 87 entered the long term extension (LTE) phase.

Period 1

Period 1 title	Main treatment phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

52 weeks of double-blind treatment, consisting of:

- Dose titration period of up to 10 weeks
- Maintenance period of up to 42 weeks

Arms

Are arms mutually exclusive?	Yes
Arm title	Riociguat (Adempas, BAY63-2521)

Arm description:

Main treatment phase of 52 weeks: participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a titration period of up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received sham-titration in a dose-titration period of up to 10 weeks followed by a maintenance period.

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

Dosage and administration details:

0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg administered 3 times a day (TID); dose titration starting with 0.5 mg (up-titration every 2 weeks), orally

Arm title	Placebo
------------------	---------

Arm description:

Main treatment phase of 52 weeks: participants received matching placebo tablets to riociguat as sham-titration in a dose-titration period up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a dose-titration period of up to 10 weeks followed by a maintenance period.

Arm type	Placebo
----------	---------

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo tablets to BAY 63-2521 / Riociguat 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg administered TID; dose titration starting with 0.5 mg matching placebo tablet, orally

Number of subjects in period 1	Riociguat (Adempas, BAY63-2521)	Placebo
Started	60	61
Completed	42	46
Not completed	18	15
Consent withdrawn by subject	7	4
Physician decision	1	1
Pregnancy	-	1
Adverse event	9	9
Lack of efficacy	1	-

Period 2

Period 2 title	Long-term Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Dose titration period of up to 10 weeks (double-blind); Open-label extension period

Arms

Are arms mutually exclusive?	Yes
Arm title	Riociguat-Riociguat

Arm description:

Main treatment phase of 52 weeks: participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a titration period of up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received sham-titration in a dose-titration period of up to 10 weeks followed by a maintenance period.

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

Dosage and administration details:

0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg administered 3 times a day (TID); dose titration starting with

0.5 mg (up-titration every 2 weeks), orally

Arm title	Placebo-Riociguat
Arm description: Main treatment phase of 52 weeks: participants received matching placebo tablets to riociguat as sham-titration in a dose-titration period up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a dose-titration period of up to 10 weeks followed by a maintenance period.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo tablets to BAY 63-2521 / Riociguat 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg administered TID; dose titration starting with 0.5 mg matching placebo tablet, orally

Number of subjects in period 2^[1]	Riociguat-Riociguat	Placebo-Riociguat
Started	42	45
Completed	32	31
Not completed	10	14
Physician decision	1	2
Consent withdrawn by subject	4	3
Study terminated at site	1	-
Adverse event	2	6
Lost to follow-up	-	1
Protocol deviation	1	1
Lack of efficacy	1	1

Notes:

[1] - 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 of the 46 patients from the placebo group did not enter the LTE phase.

Baseline characteristics

Reporting groups

Reporting group title	Riociguat (Adempas, BAY63-2521)
Reporting group description:	
Main treatment phase of 52 weeks: participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a titration period of up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received sham-titration in a dose-titration period of up to 10 weeks followed by a maintenance period.	
Reporting group title	Placebo
Reporting group description:	
Main treatment phase of 52 weeks: participants received matching placebo tablets to riociguat as sham-titration in a dose-titration period up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a dose-titration period of up to 10 weeks followed by a maintenance period.	

Reporting group values	Riociguat (Adempas, BAY63-2521)	Placebo	Total
Number of subjects	60	61	121
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	51.9	49.5	
standard deviation	± 11.5	± 12.9	-
Gender Categorical Units: Subjects			
Female	47	45	92
Male	13	16	29
Race Units: Subjects			
White	43	46	89
Black	2	3	5
Asian	12	12	24
Native Hawaiian or other pacific islander	1	0	1
Not reported	2	0	2
Ethnicity Units: Subjects			
Not Hispanic or latino	59	58	117
Hispanic or Latino	1	2	3
Not reported	0	1	1
Modified Rodnan skin score (mRSS)			
The mRSS is a validated physical examination method for estimating skin thickness. It correlates with biopsy measures of collagen in the dermis and reflects prognosis and visceral involvement, especially in early disease. It is scored on 0 (normal) to 3+ (severe induration) ordinal scales over 17 body areas, with a maximum score of 51 (higher score means worse situation) and is used to categorize severity of systemic sclerosis (SSc).			
Units: score on a scale			
arithmetic mean	16.9	16.7	

standard deviation	± 3.4	± 4.1	-
Forced vital capacity (FVC) percent predicted			
Pulmonary function tests included forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO). FVC percent predicted was reported.			
Units: FVC percent predicted			
arithmetic mean	90.743	94.823	
standard deviation	± 18.523	± 17.034	-

End points

End points reporting groups

Reporting group title	Riociguat (Adempas, BAY63-2521)
-----------------------	---------------------------------

Reporting group description:

Main treatment phase of 52 weeks: participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a titration period of up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received sham-titration in a dose-titration period of up to 10 weeks followed by a maintenance period.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Main treatment phase of 52 weeks: participants received matching placebo tablets to riociguat as sham-titration in a dose-titration period up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a dose-titration period of up to 10 weeks followed by a maintenance period.

Reporting group title	Riociguat-Riociguat
-----------------------	---------------------

Reporting group description:

Main treatment phase of 52 weeks: participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a titration period of up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received sham-titration in a dose-titration period of up to 10 weeks followed by a maintenance period.

Reporting group title	Placebo-Riociguat
-----------------------	-------------------

Reporting group description:

Main treatment phase of 52 weeks: participants received matching placebo tablets to riociguat as sham-titration in a dose-titration period up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a dose-titration period of up to 10 weeks followed by a maintenance period.

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

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:

FAS was defined as all patients randomized and treated with study medication.

Subject analysis set title	Per protocol set (PPS)
----------------------------	------------------------

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

Patients were valid for the per protocol analysis set (PPS), if they met the major inclusion and exclusion criteria at randomization that may affect efficacy, were not taking excluded concomitant medications during the study that effected efficacy (not including rescue medication after Week 26), had the mRSS assessed at baseline and at least once during the main treatment phase and who were at least 80% compliant with study medication or did not have any additional major protocol deviations.

Primary: Change from baseline in modified Rodnan skin score (mRSS) to Week 52

End point title	Change from baseline in modified Rodnan skin score (mRSS) to Week 52
-----------------	--

End point description:

The mRSS is a validated physical examination method for estimating skin thickness. It correlates with biopsy measures of collagen in the dermis and reflects prognosis and visceral involvement, especially in early disease. It is scored on 0 (normal) to 3+ (severe induration) ordinal scales over 17 body areas, with a maximum score of 51 (higher score means worse situation) and is used to categorize severity of SSc. A decrease in the mean change of mRSS shows mRSS improved.

End point type	Primary
----------------	---------

End point timeframe:

Baseline to week 52

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57 ^[1]	52 ^[2]		
Units: score on a scale				
arithmetic mean (standard deviation)	-2.088 (± 5.658)	-0.769 (± 8.243)		

Notes:

[1] - FAS with evaluable data for this outcome measure.

[2] - FAS with evaluable data for this outcome measure.

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Placebo v Riociguat (Adempas, BAY63-2521)
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0815
Method	MMRM (Method 1)
Parameter estimate	Difference of LS means
Point estimate	-2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	0.3

Secondary: CRISS (American College of Rheumatology Composite Response Index for Clinical Trials) at Week 52 reported as number of participants with a CRISS probability ≥ 0.60 or < 0.60 from baseline to Week 52

End point title	CRISS (American College of Rheumatology Composite Response Index for Clinical Trials) at Week 52 reported as number of participants with a CRISS probability ≥ 0.60 or < 0.60 from baseline to Week 52
-----------------	---

End point description:

End point type	Secondary
End point timeframe:	
Week 52	

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[3]	61 ^[4]		
Units: Participants				
CRISS probability ≥ 0.60	11	11		
CRISS probability < 0.60	49	50		

Notes:

[3] - Full analysis set (FAS)

[4] - Full analysis set (FAS)

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.977
Method	Mantel-Haenszel
Parameter estimate	Percent
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.68
upper limit	14.09

Notes:

[5] - The pre-specified test was for superiority but ONLY if the primary endpoint and secondary endpoints were meeting statistical significance (hierarchical testing).

Secondary: Change from baseline in Health Assessment Questionnaire disability index (HAQ-DI) score to Week 52

End point title	Change from baseline in Health Assessment Questionnaire disability index (HAQ-DI) score to Week 52
-----------------	--

End point description:

The HAQ-DI is a composite measure from which a 'Standard Disability Index' score can be computed to assess a patient's disability level. Generally, a score of 0–1 represents mild to moderate difficulty, 1–2 moderate to severe disability and 2–3 severe to very severe disability. The HAQ-DI comprises 20 items that assess patient abilities across 8 functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Each item is rated on a 4-point scale: 0=Without ANY difficulty, 1=With SOME difficulty, 2=With MUCH difficulty, 3=UNABLE to do. The 8 scores of the 8 sections are summed and divided by 8. In the event that one section is not completed by a subject then the summed score would be divided by 7. The final overall HAQ-DI score ranges from 0 to 3 and positive change indicates worse health-related quality of life (HRQoL).

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline to week 52

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[6]	61 ^[7]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	0.888 (± 0.665)	0.693 (± 0.688)		
Change from baseline	0.054 (± 0.381)	0.127 (± 0.418)		

Notes:

[6] - Full analysis set (FAS).

Number Analyzed for Change from baseline is 56 participants.

[7] - Full analysis set (FAS).

Number Analyzed for Change from baseline is 52 participants.

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.3529
Method	MMRM (Method 1)
Parameter estimate	Difference in LS means
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.08

Notes:

[8] - The pre-specified test was for superiority but ONLY if the primary endpoint and secondary endpoints were meeting statistical significance (hierarchical testing).

Secondary: Change from baseline in patient's global assessment score to Week 52

End point title	Change from baseline in patient's global assessment score to Week 52
-----------------	--

End point description:

The patient's global assessments (a self-report) quantified the overall disease activity or severity of SSc, with scores ranging from 0 (good) to 10 (worse). Positive change in the patient's global assessments score indicates worsening.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline to week 52

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[9]	61 ^[10]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	3.933 (± 2.497)	3.770 (± 2.341)		
Change from baseline	0.689 (± 2.745)	-0.022 (± 2.226)		

Notes:

[9] - Full analysis set (FAS).

Number Analyzed for Change from baseline is 45 participants

[10] - Full analysis set (FAS).

Number Analyzed for Change from baseline is 46 participants

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.0887
Method	MMRM (Method 1)
Parameter estimate	Difference in LS means
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	1.69

Notes:

[11] - The pre-specified test was for superiority but ONLY if the primary endpoint and secondary endpoints were meeting statistical significance (hierarchical testing).

Secondary: Change from baseline in physician's global assessment score to Week 52

End point title	Change from baseline in physician's global assessment score to Week 52
End point description:	
The physician's global assessments (reported by the physician) quantified the overall disease activity or severity of SSc, with scores ranging from 0 (good) to 10 (worse). Positive change in the physician's global assessments score indicates worsening.	
End point type	Secondary
End point timeframe:	
Baseline to week 52	

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[12]	61 ^[13]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	4.333 (± 2.105)	4.016 (± 2.004)		
Change from baseline	-0.067 (± 2.157)	-0.745 (± 2.090)		

Notes:

[12] - Full analysis set (FAS).

Number Analyzed for change from baseline is 45 participants.

[13] - Full analysis set (FAS).

Number Analyzed for change from baseline is 47 participants.

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	= 0.0241
Method	MMRM (Method 1)
Parameter estimate	Difference in LS means
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	1.54

Notes:

[14] - The pre-specified test was for superiority but ONLY if the primary endpoint and secondary endpoints were meeting statistical significance (hierarchical testing).

Secondary: Change from baseline in forced vital capacity (FVC) percent predicted to Week 52

End point title	Change from baseline in forced vital capacity (FVC) percent predicted to Week 52
End point description:	
Negative change in FVC percent predicted indicates worsening.	
End point type	Secondary
End point timeframe:	
Baseline to week 52	

End point values	Riociguat (Adempas, BAY63-2521)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55 ^[15]	51 ^[16]		
Units: FVC percent predicted				
arithmetic mean (standard deviation)	-2.376 (\pm 7.515)	-2.945 (\pm 9.727)		

Notes:

[15] - FAS with evaluable data for this outcome measure.

[16] - FAS with evaluable data for this outcome measure.

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Riociguat (Adempas, BAY63-2521) v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.901
Method	MMRM (Method 1)
Parameter estimate	Difference in LS means
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	3

Notes:

[17] - The pre-specified test was for superiority but ONLY if the primary endpoint and secondary endpoints were meeting statistical significance (hierarchical testing).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first application of study drug up to 2 days after end of treatment with study drug

Adverse event reporting additional description:

All 42 patients who completed the main treatment phase from the riociguat group entered the LTE phase and continued to receive riociguat. This group is referred in the LTE phase to "riociguat-riociguat group". One of the 46 patients from the placebo group did not enter the LTE phase. This group is referred to "placebo-riociguat group".

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20.1
--------------------	------

Reporting groups

Reporting group title	Riociguat (main treatment phase)
-----------------------	----------------------------------

Reporting group description:

Main treatment phase of 52 weeks: participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a titration period of up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received sham-titration in a dose-titration period of up to 10 weeks followed by a maintenance period.

Reporting group title	Placebo (main treatment phase)
-----------------------	--------------------------------

Reporting group description:

Main treatment phase of 52 weeks: participants received matching placebo tablets to riociguat as sham-titration in a dose-titration period up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting after the completion of the Main Treatment Phase in Week 52, participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a dose-titration period of up to 10 weeks followed by a maintenance period.

Reporting group title	Riociguat-Riociguat (LTE phase)
-----------------------	---------------------------------

Reporting group description:

Main treatment phase: participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a titration period of up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting from Week 52, participants received sham-titration in a dose-titration period of up to 10 weeks followed by a maintenance period.

Reporting group title	Placebo-Riociguat (LTE phase)
-----------------------	-------------------------------

Reporting group description:

Main treatment phase: participants received matching placebo tablets to riociguat as sham-titration in a dose-titration period up to 10 weeks and a maintenance period of up to 42 weeks. Long-term extension phase: starting from Week 52, participants received increasing doses of riociguat by 0.5 mg every 2 weeks up to 2.5 mg 3 times a day (TID) in a dose-titration period of up to 10 weeks followed by a maintenance period.

Serious adverse events	Riociguat (main treatment phase)	Placebo (main treatment phase)	Riociguat-Riociguat (LTE phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 60 (15.00%)	15 / 61 (24.59%)	10 / 42 (23.81%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Acute myeloid leukaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Raynaud's phenomenon			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Prophylaxis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rhinoplasty			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal polypectomy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ultrasound kidney abnormal			

subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exposure during pregnancy			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrasystoles			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pericarditis			
subjects affected / exposed	0 / 60 (0.00%)	2 / 61 (3.28%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			

subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Scleroderma renal crisis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteolysis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal discomfort			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondropathy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic scleroderma			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	2 / 61 (3.28%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			

subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site joint infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo-Riociguat (LTE phase)		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 45 (24.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma gastric			

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Raynaud's phenomenon			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Prophylaxis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rhinoplasty			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Large intestinal polypectomy subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Ultrasound kidney abnormal			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Exposure during pregnancy			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Extrasystoles			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular failure			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Abdominal pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal pseudo-obstruction				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Scleroderma renal crisis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteolysis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pain in extremity			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scleroderma			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal osteoarthritis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chondropathy			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Systemic scleroderma			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infected skin ulcer			

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Salpingitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bursitis infective				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Medical device site joint infection			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Riociguat (main treatment phase)	Placebo (main treatment phase)	Riociguat-Riociguat (LTE phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 60 (91.67%)	49 / 61 (80.33%)	38 / 42 (90.48%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 60 (0.00%)	4 / 61 (6.56%)	0 / 42 (0.00%)
occurrences (all)	0	4	0
Hypotension			
subjects affected / exposed	7 / 60 (11.67%)	4 / 61 (6.56%)	5 / 42 (11.90%)
occurrences (all)	7	4	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 60 (5.00%)	3 / 61 (4.92%)	2 / 42 (4.76%)
occurrences (all)	6	4	2
Fatigue			

subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 7	6 / 61 (9.84%) 7	0 / 42 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 7	2 / 61 (3.28%) 2	1 / 42 (2.38%) 1
Pain subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 4	0 / 61 (0.00%) 0	1 / 42 (2.38%) 1
Pyrexia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	4 / 61 (6.56%) 4	1 / 42 (2.38%) 1
Peripheral swelling subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 6	5 / 61 (8.20%) 5	0 / 42 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	9 / 60 (15.00%) 9	5 / 61 (8.20%) 5	6 / 42 (14.29%) 6
Dyspnoea subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 9	5 / 61 (8.20%) 6	3 / 42 (7.14%) 3
Epistaxis subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 5	2 / 61 (3.28%) 2	2 / 42 (4.76%) 2
Interstitial lung disease subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4	2 / 61 (3.28%) 2	5 / 42 (11.90%) 6
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	2 / 61 (3.28%) 2	2 / 42 (4.76%) 2
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 61 (0.00%) 0	2 / 42 (4.76%) 2
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 8	3 / 61 (4.92%) 3	3 / 42 (7.14%) 3
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	13 / 60 (21.67%) 21	7 / 61 (11.48%) 7	3 / 42 (7.14%) 3
Headache subjects affected / exposed occurrences (all)	11 / 60 (18.33%) 12	12 / 61 (19.67%) 16	3 / 42 (7.14%) 4
Paraesthesia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	4 / 61 (6.56%) 5	0 / 42 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	3 / 61 (4.92%) 4	3 / 42 (7.14%) 3
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	1 / 61 (1.64%) 1	3 / 42 (7.14%) 3
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 5	1 / 61 (1.64%) 1	0 / 42 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	5 / 61 (8.20%) 5	3 / 42 (7.14%) 3
Constipation subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	4 / 61 (6.56%) 4	4 / 42 (9.52%) 5
Diarrhoea subjects affected / exposed occurrences (all)	10 / 60 (16.67%) 15	8 / 61 (13.11%) 11	5 / 42 (11.90%) 11
Dry mouth subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4	1 / 61 (1.64%) 1	1 / 42 (2.38%) 1
Dyspepsia			

subjects affected / exposed	7 / 60 (11.67%)	2 / 61 (3.28%)	1 / 42 (2.38%)
occurrences (all)	7	2	1
Dysphagia			
subjects affected / exposed	6 / 60 (10.00%)	1 / 61 (1.64%)	1 / 42 (2.38%)
occurrences (all)	7	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	15 / 60 (25.00%)	7 / 61 (11.48%)	7 / 42 (16.67%)
occurrences (all)	16	7	7
Mouth ulceration			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	3 / 42 (7.14%)
occurrences (all)	0	1	4
Nausea			
subjects affected / exposed	7 / 60 (11.67%)	6 / 61 (9.84%)	2 / 42 (4.76%)
occurrences (all)	9	6	5
Vomiting			
subjects affected / exposed	8 / 60 (13.33%)	6 / 61 (9.84%)	7 / 42 (16.67%)
occurrences (all)	14	8	11
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 60 (0.00%)	4 / 61 (6.56%)	2 / 42 (4.76%)
occurrences (all)	0	4	2
Erythema			
subjects affected / exposed	3 / 60 (5.00%)	0 / 61 (0.00%)	1 / 42 (2.38%)
occurrences (all)	4	0	1
Pruritus			
subjects affected / exposed	5 / 60 (8.33%)	5 / 61 (8.20%)	1 / 42 (2.38%)
occurrences (all)	6	9	1
Rash			
subjects affected / exposed	3 / 60 (5.00%)	2 / 61 (3.28%)	1 / 42 (2.38%)
occurrences (all)	4	2	1
Skin ulcer			
subjects affected / exposed	4 / 60 (6.67%)	7 / 61 (11.48%)	6 / 42 (14.29%)
occurrences (all)	4	9	7
Urticaria			
subjects affected / exposed	2 / 60 (3.33%)	0 / 61 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 60 (20.00%)	8 / 61 (13.11%)	4 / 42 (9.52%)
occurrences (all)	14	9	5
Back pain			
subjects affected / exposed	3 / 60 (5.00%)	4 / 61 (6.56%)	2 / 42 (4.76%)
occurrences (all)	3	4	2
Bursitis			
subjects affected / exposed	2 / 60 (3.33%)	0 / 61 (0.00%)	2 / 42 (4.76%)
occurrences (all)	2	0	3
Muscle spasms			
subjects affected / exposed	4 / 60 (6.67%)	0 / 61 (0.00%)	2 / 42 (4.76%)
occurrences (all)	6	0	3
Myalgia			
subjects affected / exposed	1 / 60 (1.67%)	3 / 61 (4.92%)	4 / 42 (9.52%)
occurrences (all)	1	3	5
Pain in extremity			
subjects affected / exposed	4 / 60 (6.67%)	2 / 61 (3.28%)	4 / 42 (9.52%)
occurrences (all)	6	2	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 60 (5.00%)	1 / 61 (1.64%)	5 / 42 (11.90%)
occurrences (all)	3	1	6
Gastroenteritis			
subjects affected / exposed	1 / 60 (1.67%)	2 / 61 (3.28%)	2 / 42 (4.76%)
occurrences (all)	1	2	2
Influenza			
subjects affected / exposed	2 / 60 (3.33%)	0 / 61 (0.00%)	3 / 42 (7.14%)
occurrences (all)	2	0	3
Nasopharyngitis			
subjects affected / exposed	5 / 60 (8.33%)	5 / 61 (8.20%)	11 / 42 (26.19%)
occurrences (all)	7	8	13
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	2 / 61 (3.28%)	3 / 42 (7.14%)
occurrences (all)	2	2	3
Upper respiratory tract infection			

subjects affected / exposed	4 / 60 (6.67%)	8 / 61 (13.11%)	7 / 42 (16.67%)
occurrences (all)	5	10	10
Urinary tract infection			
subjects affected / exposed	4 / 60 (6.67%)	2 / 61 (3.28%)	2 / 42 (4.76%)
occurrences (all)	5	2	7
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 42 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Placebo-Riociguat (LTE phase)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 45 (86.67%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	9		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

Peripheral swelling subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Interstitial lung disease subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4 3 / 45 (6.67%) 4 1 / 45 (2.22%) 1 5 / 45 (11.11%) 5		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia	6 / 45 (13.33%) 7 4 / 45 (8.89%) 4		

subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Iron deficiency anaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	23		
Dry mouth			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	8		
Mouth ulceration			

subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	7		
Vomiting			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	14		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Skin ulcer			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Urticaria			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	6		
Back pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Bursitis			

subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Influenza			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	10 / 45 (22.22%)		
occurrences (all)	10		
Pneumonia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2015	<p>Due to regulatory feedback, additional safety laboratory monitoring was included for subjects entering the study with elevated liver transaminases or bilirubin, or with an estimated glomerular filtration rate (eGFR) between 15 and 29 mL/min/1.73 m². These patients were not included in the riociguat pivotal trials in pulmonary hypertension. While there was no evidence of liver or renal toxicity with riociguat, there was an increased risk for adverse events related to the mechanism of action of the drug, such as hypotension, due to a higher plasma concentration caused by impaired riociguat metabolism/elimination by liver and kidneys.</p> <p>The list of immunosuppressant therapies requiring washout before inclusion in the study was also expanded to account for standard of care treatment among the participating countries.</p> <p>Safety laboratory tests were added at Week 26, along with other safety assessments such as ECG and lung function tests to be performed. Measurement of glutamate dehydrogenase (GLDH) was deleted from the list of standard safety parameters because the review of data from previous studies and the ongoing long-term studies did not show any clinically significant changes of this parameter in patients treated with riociguat.</p>
24 February 2016	<p>The list of secondary endpoints was changed to include a hierarchy of testing. The chosen key secondary endpoint is the (American College of Rheumatology) Composite Response Index for Clinical Trials (CRIS) and the other endpoints in the hierarchy are components of this endpoint.</p> <p>Based on feedback from the Food and Drug Administration (FDA), the protocol was adjusted to clearly differentiate between withdrawal from the study (ie, withdrawal of informed consent) or discontinuation of study treatment (with continued data collection).</p>
31 August 2016	<p>This amendment was implemented to clarify that the benefit-risk balance for the population in this study (patients with dcSSc) remains positive, despite the potential safety issue that has been reported in a study in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia (PH-IIP) leading to early termination of the concerned study. The benefit-risk assessment for patients with dcSSc was re-evaluated by the data monitoring committee (DMC) in 3 meetings and was confirmed to remain positive.</p>
02 May 2017	<p>This amendment was implemented based on the recommendation of the DMC after review of the safety analysis on 01 MAR 2017. Due to increased complaints of both palpitations and dizziness in patients with interstitial lung disease (ILD) noted by the DMC, the assessment of orthostatic changes in blood pressure and heart rate as well as the measurement of oxygen saturation (using forehead pulse oximetry) were added to the protocol assessments for all patients. As recruitment for this study was already completed, the new assessments were not implemented starting with the screening visit, but only for study visits, which was performed after implementation of this amendment.</p> <p>Additionally, an error in the description of the units provided in exclusion criterion 6 was corrected.</p>
17 April 2018	<p>This protocol amendment was prepared based on the results of the main treatment phase of the study and to better characterize the enrolled patient population. The addition of the anti-centromere was included in the autoantibody screen. A change of responsible Global Clinical Lead was made.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27746061>