Clinical trial results:
Evaluation of the pharmacodynamic effects of riociguat in subjects with pulmonary hypertension and heart failure with preserved ejection fraction in a randomized, double blind, placebo controlled, parallel group, multicenter study

Summary

EudraCT number	2014-003055-60
Trial protocol	AT DE
Global end of trial date	30 September 2020

Results information

Result version number	v1 (current)
This version publication date	26 August 2022
First version publication date	26 August 2022

Trial information

Trial identification

Sponsor protocol code	RIO-40400

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02744339
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Study Team Prof. Bonderman and Prof. Kastner, Medical University of Vienna, 0043 140400 48560, theresa-marie.dachs@meduniwien.ac.at
Scientific contact	Study Team Prof. Bonderman and Prof. Kastner, Medical University of Vienna, 0043 140400 48560, theresa-marie.dachs@meduniwien.ac.at

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	11 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2020
Global end of trial reached?	Yes
Global end of trial date	30 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The presence of pulmonary hypertension (PH) severely aggravates the clinical course of heart failure with preserved ejection fraction (HFpEF). To date, neither established heart failure therapies nor pulmonary vasodilators proved beneficial. The primary objective of this study was to evaluate the efficacy of continuous treatment with the oral soluble guanylate cyclase stimulator riociguat in subjects with symptomatic PH -HFpEF (LVEF ≥50%).

Protection of trial subjects:

The present clinical trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Eligible subjects had to meet all inclusion criteria and none of the exclusion criteria. All subjects signed the informed consent form prior to enrolement and were informed, that withdrawal from the study was possible at any time for any reason. Subjects were closely monitored throughout the study treatment period and an independent data monitoring committee regularly reviewed safety data.

Background therapy:

The dose regimen of the background treatment had to be stable for >30 days before randomization. Diuretic therapy had to be stable for ≥1 week. Patients in need of intravenous (i.v.) diuretics, inotropes or i.v. vasodilators ≤30 days before randomization were excluded.
The intake of 1) Phosphodiesterase type 5 inhibitors, 2) Nitric oxide donors, e.g. nitrates, 3) Phosphodiesterase inhibitors, e.g. dipyridamole or theophylline, 4) Inotropes or i.v. vasodilators and 5) Prostacyclin analogs or endothelin receptor antagonists was not allowed during the pre-treatment and the treatment phases of this study. Patients who medically required such drugs were not included in this study. Patients who newly required such drugs during the study had to be withdrawn.

Evidence for comparator:

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Actual start date of recruitment	03 November 2014
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	Austria: 107
Country: Number of subjects enrolled	Germany: 7
Worldwide total number of subjects	114
EEA total number of subjects	114

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)	19
From 65 to 84 years	95
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This randomized, double-blind, placebo-controlled, parallel-group, multicenter trial evaluated the effect of riociguat in subjects with symptomatic pulmonary hypertension and heart failure with preserved ejection fraction. The study was conducted at 5 study centers across Germany and Austria between 17-Mar-2016 and 30-Sep-2020.

Pre-assignment

Screening details:

Only subjects who met all study inclusion and none of the exclusion criteria were eligible to enroll in this study. Withdrawal from the clinical trial was possible at any time for any reason. Of 118 subjects screened, 114 were considered eligible to enrole in the study and start study drug treatment. 88 patients completed the study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Subjects, investigators, and anyone involved in trial conduct or analysis remained blinded with regard to the randomised treatment assignment up to database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Riociguat

Arm description:

Film-coated tablets of riociguat in doses of 0.5 mg, 1 mg, or 1.5 mg were administered orally three times daily (TID) for 26 weeks in subjects with pulmonary hypertension and heart failure with preserved ejection fraction.
The study phase consisted of an eight-week (up-)titration phase followed by 18 weeks of fixed-dose treatment. Patients started with a dose of 0.5 mg riociguat TID and were (up-)titrated to doses of 1.0 and 1.5 mg TID.

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

Dosage and administration details:

Doses of 0.5, 1.0, or 1.5 mg (as per individual dose titration) three times daily, oral route of administration

Arm title	Placebo

Arm description:

Film-coated tablets of placebo matching riociguat (identical and therefore indistinguishable) were administered orally three times daily for 26 weeks in subjects with pulmonary hypertension and heart failure with preserved ejection fraction.

Arm type	Placebo

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

Dosage and administration details:

Film-coated tablets of placebo matching riociguat were administered orally three times daily for 26 weeks.

Number of subjects in period 1	Riociguat	Placebo
Started	58	56
Completed	40	48
Not completed	18	8
Consent withdrawn by subject	7	2
Diagnosis of AL-Amyloidosis	1	-
Non-tolerable adverse event	4	-
Serious adverse event (including death)	4	3
Lowest dose not tolerated	2	-
Adverse event of special interest	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Riociguat
Reporting group description:	
Film-coated tablets of riociguat in doses of 0.5 mg, 1 mg, or 1.5 mg were administered orally three times daily (TID) for 26 weeks in subjects with pulmonary hypertension and heart failure with preserved ejection fraction. The study phase consisted of an eight-week (up-)titration phase followed by 18 weeks of fixed-dose treatment. Patients started with a dose of 0.5 mg riociguat TID and were (up-)titrated to doses of 1.0 and 1.5 mg TID.	
Reporting group title	Placebo
Reporting group description:	
Film-coated tablets of placebo matching riociguat (identical and therefore indistinguishable) were administered orally three times daily for 26 weeks in subjects with pulmonary hypertension and heart failure with preserved ejection fraction.	

Reporting group values	Riociguat	Placebo	Total
Number of subjects	58	56	114
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	8	19
From 65-84 years	47	48	95
85 years and over	0	0	0
Gender categorical			
Differentiation between male and female gender.			
Units: Subjects			
Female	46	37	83
Male	12	19	31
RACE Units: Subjects			
White	57	56	113
Other	1	0	1
Left ventricular ejection fraction			
Mean ± SD Left ventricular ejection fraction of patients included in the full analysis set (FAS). The FAS included all randomised patients who satisfied the major study entry criteria, had a valid measurement of the primary endpoint at baseline and had at least one valid post-baseline measure of efficacy at week eight or 26.			
Units: Percent			
arithmetic mean	61.0	60.1	
standard deviation	± 6.7	± 6.0	-
Mean pulmonary artery pressure			
Mean ± SD pulmonary artery pressure of patients included in the full analysis set (FAS). The FAS included all randomised patients who satisfied the major study entry criteria, had a valid measurement of the primary endpoint at baseline and had at least one valid post-baseline measure of			

efficacy at week eight or 26.			
Units: mmHg			
arithmetic mean	36.3	35.9	
standard deviation	± 10.23	± 9.60	-
Mean pulmonary artery wedge pressure			
Mean ± SD pulmonary artery wedge pressure of patients included in the full analysis set (FAS). The FAS included all randomised patients who satisfied the major study entry criteria, had a valid measurement of the primary endpoint at baseline and had at least one valid post-baseline measure of efficacy at week eight or 26.			
Units: mmHg			
arithmetic mean	20.3	21.2	
standard deviation	± 4.59	± 5.11	-
Estimated glomerular filtration rate			
Calculated by the Modification of Diet in Renal Disease formula.			
Units: ml/min/1.73m^2			
arithmetic mean	63.4	61.7	
standard deviation	± 21.9	± 20.1	-
Cardiac output			
Mean ± SD cardiac output of patients included in the full analysis set (FAS). The FAS included all randomised patients who satisfied the major study entry criteria, had a valid measurement of the primary endpoint at baseline and had at least one valid post-baseline measure of efficacy at week eight or 26)			
Units: L/min			
arithmetic mean	5.16	5.05	
standard deviation	± 1.131	± 1.494	-

End points

End points reporting groups

Reporting group title	Riociguat

Reporting group description:

Film-coated tablets of riociguat in doses of 0.5 mg, 1 mg, or 1.5 mg were administered orally three times daily (TID) for 26 weeks in subjects with pulmonary hypertension and heart failure with preserved ejection fraction.
The study phase consisted of an eight-week (up-)titration phase followed by 18 weeks of fixed-dose treatment. Patients started with a dose of 0.5 mg riociguat TID and were (up-)titrated to doses of 1.0 and 1.5 mg TID.

Reporting group title	Placebo

Reporting group description:

Film-coated tablets of placebo matching riociguat (identical and therefore indistinguishable) were administered orally three times daily for 26 weeks in subjects with pulmonary hypertension and heart failure with preserved ejection fraction.

Primary: Cardiac output

End point title	Cardiac output

End point description:

The primary efficacy variable was the change in cardiac output (CO) at rest from baseline to week 26 of treatment, measured by right heart catheterization. CO average using thermodilution principles was calculated from three different measurements. In case of atrial fibrillation (AF), five measurements were performed and averaged.

End point type	Primary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	48		
Units: L/min				
arithmetic mean (standard deviation)	0.365 (± 1.263)	-0.105 (± 0.921)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo

Statistical analysis description:

H0: $\beta 1 \leq \beta 2$ where $\beta 1$ refers to the effect of riociguat and $\beta 2$ to the effect of placebo.

Comparison groups	Riociguat v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0142
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	0.541
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.112
upper limit	0.971

Secondary: Pulmonary artery wedge pressure

End point title	Pulmonary artery wedge pressure

End point description:

The change in pulmonary artery wedge pressure (PAWP) from baseline to week 26 of treatment, measured by right heart catheterization, was assessed as a secondary efficacy variable.

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	48		
Units: mmHg				
arithmetic mean (standard deviation)	-0.2 (± 6.74)	-0.4 (± 8.33)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus Placebo

Statistical analysis description:

Analogous to the primary efficacy variable, all secondary variables were compared between treatment regimens using an analysis of covariance (ANCOVA) model with baseline value as covariate, centre, treatment regimen, and the interaction term of centre and treatment regimen as fixed effects (without adjustment for multiplicity). The primary comparison was a one-sided test at the 2·5% significance level for the difference in treatment effects between riociguat and placebo.

Comparison groups	Riociguat v Placebo

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9601
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.239
upper limit	3.406

Secondary: Transpulmonary pressure gradient

End point title	Transpulmonary pressure gradient

End point description:

The change in transpulmonary pressure gradient (TPG) from baseline to week 26 of treatment, measured by right heart catheterization, was assessed as a secondary efficacy variable. TPG was calculated as the difference between mean pulmonary artery pressure and pulmonary artery wedge pressure.

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	47		
Units: mmHg				
arithmetic mean (standard deviation)	-2.5 (± 5.89)	0.0 (± 7.10)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo

Statistical analysis description:

Analogous to the primary efficacy variable, all secondary variables were compared between treatment regimens using an analysis of covariance (ANCOVA) model with baseline value as covariate, centre, treatment regimen, and the interaction term of centre and treatment regimen as fixed effects (without adjustment for multiplicity). The primary comparison was a one-sided test at the 2·5% significance level for the difference in treatment effects between riociguat and placebo.

Comparison groups	Riociguat v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-5.669
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.251
upper limit	-2.086

Secondary: Pulmonary vascular resistance

End point title	Pulmonary vascular resistance

End point description:

The change in pulmonary vascular resistance (PVR) from baseline to week 26 of treatment was calculated as the difference between mean pulmonary artery pressure and pulmonary artery wedge pressure by, times 80 and devided by cardiac output (all parameters derived from right heart catheterization).

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	47		
Units: dyn.s.cm^-5				
arithmetic mean (standard deviation)	-38.1 (± 126.8)	6.6 (± 137.7)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo

Statistical analysis description:

Analogous to the primary efficacy variable, all secondary variables were compared between treatment regimens using an analysis of covariance (ANCOVA) model with baseline value as covariate, centre, treatment regimen, and the interaction term of centre and treatment regimen as fixed effects (without adjustment for multiplicity). The primary comparison was a one-sided test at the 2·5% significance level for the difference in treatment effects between riociguat and placebo.

Comparison groups	Riociguat v Placebo

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-108.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-186.89
upper limit	-30.86

Secondary: Systemic vascular resistance

End point title	Systemic vascular resistance

End point description:

The change in systemic vascular resistance (SVR) from baseline to week 26 of treatment was assessed as a secondary efficacy variable. SVR was calculated as the difference between mean systemic arterial pressure and mean right atrial pressure, times 80 and devided by cardiac output (all parameters derived from right heart catheterization).

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	41		
Units: dyn.s.cm^-5				
arithmetic mean (standard deviation)	-91.1 (± 500.0)	-54.9 (± 392.1)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo

Statistical analysis description:

Analogous to the primary efficacy variable, all secondary variables were compared between treatment regimens using an analysis of covariance (ANCOVA) model with baseline value as covariate, centre, treatment regimen, and the interaction term of centre and treatment regimen as fixed effects (without adjustment for multiplicity). The primary comparison was a one-sided test at the 2·5% significance level for the difference in treatment effects between riociguat and placebo.

Comparison groups	Riociguat v Placebo

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5555
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-54.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-236.99
upper limit	128.44

Secondary: Left atrial area

End point title	Left atrial area

End point description:

The change in left atrial area (LAA) from baseline to week 26 of treatment, measured by cardiac magnetic resonance imaging, was assessed as a secondary efficacy variable.

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	22		
Units: mm^2				
arithmetic mean (standard deviation)	-86.4 (± 452.55)	-32.9 (± 712.00)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo[1]

Statistical analysis description:

Analogous to the primary efficacy variable, all continuous secondary variables were compared between treatment regimens using an analysis of covariance (ANCOVA) model with baseline value as covariate, centre, treatment regimen, and the interaction term of centre and treatment regimen as fixed effects (without adjustment for multiplicity). The primary comparison was a one-sided test at the 2·5% significance level for the difference in treatment effects between riociguat and placebo.

Comparison groups	Riociguat v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5068
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	166.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0

Notes:

[1] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.
Justification: n.a.

Secondary: Right ventricular stroke volume

End point title	Right ventricular stroke volume

End point description:

The change in right ventricular stroke volume (RVSV) from baseline to week 26 of treatment, measured by cardiac magnetic resonance imaging, was assessed as a secondary efficacy variable.

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	24		
Units: mL				
arithmetic mean (standard deviation)	-0.7 (± 18.45)	-6.3 (± 25.22)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo[2]

Statistical analysis description:

Analogous to the primary efficacy variable, all continuous secondary variables were compared between treatment regimens using an analysis of covariance (ANCOVA) model with baseline value as covariate, centre, treatment regimen, and the interaction term of centre and treatment regimen as fixed effects (without adjustment for multiplicity). The primary comparison was a one-sided test at the 2·5% significance level for the difference in treatment effects between riociguat and placebo.

Comparison groups	Riociguat v Placebo

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8449
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	1.1035
Confidence interval	
level	95 %
sides	2-sided
lower limit	0

Notes:

[2] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.
Justification: n.a.

Secondary: Right ventricular ejection fraction

End point title	Right ventricular ejection fraction

End point description:

The change in right ventricular ejection fraction (RVEF) from baseline to week 26 of treatment, measured by cardiac magnetic resonance imaging, was assessed as a secondary efficacy variable.

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	24		
Units: percent				
arithmetic mean (standard deviation)	-3.16 (± 9.01)	-1.98 (± 8.42)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo[3]

Statistical analysis description:

Analogous to the primary efficacy variable, all continuous secondary variables were compared between treatment regimens using an analysis of covariance (ANCOVA) model with baseline value as covariate, centre, treatment regimen, and the interaction term of centre and treatment regimen as fixed effects (without adjustment for multiplicity). The primary comparison was a one-sided test at the 2·5% significance level for the difference in treatment effects between riociguat and placebo.

Comparison groups	Riociguat v Placebo

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7272
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-0.8824
Confidence interval	
level	95 %
sides	2-sided
upper limit	0

Notes:

[3] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.
Justification: n.a.

Secondary: N-terminal prohormone B-type natriuretic peptide

End point title	N-terminal prohormone B-type natriuretic peptide

End point description:

The change in serum levels of median N-terminal prohormone B-type natriuretic peptide (NT-proBNP) from baseline to week 26 of treatment was assessed as a secondary efficacy variable.

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	43		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	60.35 (-184.20 to 238.00)	76.00 (-169.50 to 533.00)		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo

Statistical analysis description:

For the continuous, non-normally distributed secondary endpoint NT-proBNP, differences were assessed using the two-sample Wilcoxon rank-sum test at a two-sided 5% significance level.

Comparison groups	Riociguat v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5647
Method	Wilcoxon (Mann-Whitney)

Secondary: World Health Organization functional class improvement

End point title	World Health Organization functional class improvement

End point description:

Changes concerning the World Health Organization (WHO) functional class improvement were analysed by dichotomising into the outcomes "improvement by at least one class" and "no improvement or worsening".

End point type	Secondary

End point timeframe:

Change from baseline to week 26.

End point values	Riociguat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: Subjects	11	10		

Statistical analyses

Statistical analysis title	Superiority of riociguat versus placebo

Statistical analysis description:

Changes concerning the WHO functional class were analysed by dichotomising into two outcomes "improvement by at least one class" and "no improvement or worsening". Differences between treatment groups were assessed by Fisher´s exact test.

Comparison groups	Riociguat v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.1567
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5507
upper limit	2.4294

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the course of the clinical study (i.e. from signing the informed consent form to the observational phase) were collected, documented, and reported to the sponsor by the investigator.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Riociguat

Reporting group description:

Film-coated tablets of riociguat in doses of 0.5 mg, 1 mg, or 1.5 mg were administered orally three times daily (TID) for 26 weeks in subjects with pulmonary hypertension and heart failure with preserved ejection fraction. The study phase consisted of an eight-week (up-)titration phase followed by 18 weeks of fixed-dose treatment. Patients started with a dose of 0.5 mg riociguat TID and were (up-)titrated to doses of 1.0 and 1.5 mg TID.

Reporting group title	Placebo

Reporting group description:

Film-coated tablets of placebo matching riociguat (identical and therefore indistinguishable) were administered orally three times daily for 26 weeks in subjects with pulmonary hypertension and heart failure with preserved ejection fraction.

Serious adverse events	Riociguat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 58 (34.48%)	19 / 56 (33.93%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arthrodesis			

subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral revascularisation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery angioplasty			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral prostatectomy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stent insertion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoid operation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			

subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
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	2 / 58 (3.45%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 58 (5.17%)	6 / 56 (10.71%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 58 (1.72%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 58 (3.45%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed connective tissue disease			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (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			
Endocarditis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	3 / 56 (5.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 58 (3.45%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 58 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	1 / 58 (1.72%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Riociguat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 58 (93.10%)	55 / 56 (98.21%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 58 (3.45%)	4 / 56 (7.14%)	
occurrences (all)	2	4	
Vascular disorders			
Hypotension			
subjects affected / exposed	13 / 58 (22.41%)	7 / 56 (12.50%)	
occurrences (all)	13	7	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 58 (5.17%)	4 / 56 (7.14%)	
occurrences (all)	3	4	
Atrial fibrillation			
subjects affected / exposed	4 / 58 (6.90%)	2 / 56 (3.57%)	
occurrences (all)	4	2	
Cardiac failure			
subjects affected / exposed	3 / 58 (5.17%)	8 / 56 (14.29%)	
occurrences (all)	3	8	
Palpitations			
subjects affected / exposed	2 / 58 (3.45%)	3 / 56 (5.36%)	
occurrences (all)	2	3	
Tachycardia			

subjects affected / exposed	5 / 58 (8.62%)	1 / 56 (1.79%)	
occurrences (all)	5	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 58 (8.62%)	10 / 56 (17.86%)	
occurrences (all)	5	10	
Headache			
subjects affected / exposed	6 / 58 (10.34%)	6 / 56 (10.71%)	
occurrences (all)	6	6	
Syncope			
subjects affected / exposed	4 / 58 (6.90%)	2 / 56 (3.57%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 58 (3.45%)	7 / 56 (12.50%)	
occurrences (all)	2	7	
Fatigue			
subjects affected / exposed	7 / 58 (12.07%)	7 / 56 (12.50%)	
occurrences (all)	7	7	
Oedema peripheral			
subjects affected / exposed	17 / 58 (29.31%)	17 / 56 (30.36%)	
occurrences (all)	17	17	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 58 (6.90%)	6 / 56 (10.71%)	
occurrences (all)	4	6	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 58 (8.62%)	3 / 56 (5.36%)	
occurrences (all)	5	3	
Diarrhoea			
subjects affected / exposed	5 / 58 (8.62%)	6 / 56 (10.71%)	
occurrences (all)	5	6	
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 58 (12.07%)	3 / 56 (5.36%)	
occurrences (all)	7	3	

Nausea			
subjects affected / exposed	5 / 58 (8.62%)	4 / 56 (7.14%)	
occurrences (all)	5	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 58 (18.97%)	7 / 56 (12.50%)	
occurrences (all)	11	7	
Dyspnoea			
subjects affected / exposed	15 / 58 (25.86%)	12 / 56 (21.43%)	
occurrences (all)	15	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 58 (5.17%)	3 / 56 (5.36%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 58 (10.34%)	2 / 56 (3.57%)	
occurrences (all)	6	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 58 (3.45%)	3 / 56 (5.36%)	
occurrences (all)	2	3	
Nasopharyngitis			
subjects affected / exposed	4 / 58 (6.90%)	6 / 56 (10.71%)	
occurrences (all)	4	6	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	5 / 58 (8.62%)	5 / 56 (8.93%)	
occurrences (all)	5	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2019	Opening of a new study site in Graz/Austria.
07 May 2020	The sponsor’s medical expert for the present study was changed from Assoc. Prof. Priv.-Doz. Dr. Diana Bonderman to Ass.-Prof. Dr. Johannes Kastner.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None.

Notes: