



Clinical trial results:

A multicenter, non-randomized, non-blinded, non-controlled study to investigate the impact of multiple doses of BAY 63-2521 on safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with pulmonary hypertension in a 12 week 3 times a day individual dose titration scheme

Summary

EudraCT number	2006-003520-10
Trial protocol	DE
Global end of trial date	12 September 2014

Results information

Result version number	v2 (current)
This version publication date	02 September 2016
First version publication date	23 June 2016
Version creation reason	<ul style="list-style-type: none">• New data added to full data set• Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY63-2521/12166
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00454558
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, D-51368 Leverkusen, Germany,
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	12 September 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety, tolerability, and feasibility of individual titration of riociguat according to peripheral systolic blood pressure. In addition, long-term safety and tolerability of riociguat were investigated during the optional open-label extension period.

Protection of trial subjects:

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

Background therapy:

Basic pulmonary hypertension medications such as diuretics, oral anticoagulants, digitalis, calcium channel blockers given up to the approved dose in arterial hypertension, and oxygen supplementation, as well as an extended basic therapy with oral bosentan were allowed.

Evidence for comparator: -

Actual start date of recruitment	12 February 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	42
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 16 centres in Germany between 12 February 2007 (first subject first visit) and 29 July 2014 (last subject last visit).

Pre-assignment

Screening details:

Of the 78 subjects enrolled in the main study, 3 were screening failures. A total of 75 subjects received study drug and valid for the safety analysis in the main study, 3 prematurely discontinued study drug treatment due to adverse events. Only 68 subjects participated in the optional open-label extension period after Day 84 of the main study.

Period 1

Period 1 title	Main Study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Riociguat (Adempas, BAY63-2521) Main Study
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Arm description:

Subjects received Riociguat (Adempas, BAY63-2521) immediate release (IR) tablets with biweekly titrations of doses starting from 1.0 milligram (mg) thrice in a day (TID) up to 2.5 mg TID in steps of plus (+) 0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks.

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

Dosage and administration details:

Subjects received Riociguat (Adempas, BAY63-2521) IR tablets with biweekly titrations of doses starting from 1.0 mg TID up to 2.5 mg TID in steps of +0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks.

Number of subjects in period 1	Riociguat (Adempas, BAY63-2521) Main Study
Started	75
Completed	72
Not completed	3
Adverse event	3

Period 2

Period 2 title	Long-term Extension (LTE) Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Riociguat (Adempas, BAY63-2521) LTE Phase
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Arm description:

Subjects who were willing to continue, entered the optional 84-month LTE phase until the premature termination of product development or until official approval and commercial availability of BAY63-2521 at a minimum dose of 0.5 mg TID and maximum dose of 2.5 mg TID.

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

Dosage and administration details:

Subjects who were willing to continue, entered the optional 84month LTE phase until the premature termination of product development or until official approval and commercial availability of BAY63-2521 at a minimum dose of 0.5 mg TID and maximum dose of 2.5 mg TID.

Number of subjects in period 2	Riociguat (Adempas, BAY63-2521) LTE Phase
Started	68
Completed	36
Not completed	32
Consent withdrawn by subject	4
Insufficient therapeutic effect	1
Non-compliant with study drug	1
Death	11
Adverse event	6
Lost to follow-up	1
Investigator decision, not protocol driven	8

Baseline characteristics

Reporting groups

Reporting group title	Riociguat (Adempas, BAY63-2521) Main Study
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Reporting group description:

Subjects received Riociguat (Adempas, BAY63-2521) immediate release (IR) tablets with biweekly titrations of doses starting from 1.0 milligram (mg) thrice in a day (TID) up to 2.5 mg TID in steps of plus (+) 0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks.

Reporting group values	Riociguat (Adempas, BAY63-2521) Main Study	Total	
Number of subjects	75	75	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	60.3 ± 11.8	-	
Gender Categorical Units: Subjects			
Female	41	41	
Male	34	34	

End points

End points reporting groups

Reporting group title	Riociguat (Adempas, BAY63-2521) Main Study
Reporting group description: Subjects received Riociguat (Adempas, BAY63-2521) immediate release (IR) tablets with biweekly titrations of doses starting from 1.0 milligram (mg) thrice in a day (TID) up to 2.5 mg TID in steps of plus (+) 0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks.	
Reporting group title	Riociguat (Adempas, BAY63-2521) LTE Phase
Reporting group description: Subjects who were willing to continue, entered the optional 84-month LTE phase until the premature termination of product development or until official approval and commercial availability of BAY63-2521 at a minimum dose of 0.5 mg TID and maximum dose of 2.5 mg TID.	
Subject analysis set title	Safety set (Main Study)
Subject analysis set type	Safety analysis
Subject analysis set description: Safety set (N=75) included all subjects who received 1 dose of the study drug in the main study.	
Subject analysis set title	Pharmacokinetic (PK)/Pharmacodynamic (PD) set (Main Study)
Subject analysis set type	Per protocol
Subject analysis set description: PK/PD set (N=72) included all subjects who completed the 12-week treatment without major changes versus protocol in the main study.	

Primary: Number of Subjects With Systolic Blood Pressure Less Than 90 Millimeter of Mercury in the Long-term Extension Phase

End point title	Number of Subjects With Systolic Blood Pressure Less Than 90 Millimeter of Mercury in the Long-term Extension Phase ^[1]
End point description:	
End point type	Primary
End point timeframe: From Day 84 (end of main study) until up to 7.25 years (87 months) of the 84-month LTE	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Descriptive statistics were done and inferential statistics were not planned as this is an open, single-group study.	

End point values	Riociguat (Adempas, BAY63-2521) LTE Phase			
Subject group type	Reporting group			
Number of subjects analysed	68 ^[2]			
Units: Subjects	16			

Notes:

[2] - All subjects who entered the LTE phase.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Adverse Events Related to

Heart Rate and Blood Pressure in the Main Study

End point title	Number of Subjects With Treatment-emergent Adverse Events Related to Heart Rate and Blood Pressure in the Main Study ^[3]
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End point description:

An adverse event (AE) is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Treatment-emergent AEs (TEAE) were AEs that began while the subject was taking study treatment or up to 2 days after the end of study treatment. TEAEs with regard to heart rate and blood pressure included tachycardia/sinus tachycardia, hypotension, and syncope.

End point type	Primary
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End point timeframe:

From initiation of study treatment until 12 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done and inferential statistics were not planned as this is an open, single-group study.

End point values	Riociguat (Adepas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	75 ^[4]			
Units: Subjects				
Tachycardia/sinus tachycardia	11			
Hypotension	11			
Syncope	4			

Notes:

[4] - Safety set (main study).

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Categorized According to Their Absolute QTc Values (Bazett and Fridericia) at Specified Time Points in the Main Study

End point title	Number of Subjects Categorized According to Their Absolute QTc Values (Bazett and Fridericia) at Specified Time Points in the Main Study ^[5]
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End point description:

Subjects were categorized (less than or equal to [\leq] 450, greater than [$>$] 450 to 500 and >500 milliseconds [msec]) and distributed according to their absolute QTc values, calculated by Bazett and Fridericia formulae.

End point type	Primary
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End point timeframe:

Pre-study and Days 0, 1, 14, 28, 42, 56, 70, 84, and 85

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done and inferential statistics were not planned as this is an open, single-group study.

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	40 ^[6]			
Units: Subjects				
Bazett: <=450 msec at pre-study	36			
Bazett: >450-500 msec at pre-study	1			
Bazett: >500 msec at pre-study	0			
Bazett: <=450 msec on Day 0	36			
Bazett: >450-500 msec on Day 0	3			
Bazett: >500 msec on Day 0	0			
Bazett: <=450 msec on Day 1	29			
Bazett: >450-500 msec on Day 1	6			
Bazett: >500 msec on Day 1	0			
Bazett: <=450 msec on Day 14	34			
Bazett: >450-500 msec on Day 14	5			
Bazett: >500 msec on Day 14	0			
Bazett: <=450 msec on Day 28	35			
Bazett: >450-500 msec on Day 28	4			
Bazett: >500 msec on Day 28	0			
Bazett: <=450 msec on Day 42	31			
Bazett: >450-500 msec on Day 42	6			
Bazett: >500 msec on Day 42	0			
Bazett: <=450 msec on Day 56	34			
Bazett: >450-500 msec on Day 56	3			
Bazett: >500 msec on Day 56	0			
Bazett: <=450 msec on Day 70	34			
Bazett: >450-500 msec on Day 70	4			
Bazett: >500 msec on Day 70	0			
Bazett: <=450 msec on Day 84	31			
Bazett: >450-500 msec on Day 84	5			
Bazett: >500 msec on Day 84	0			
Bazett: <=450 msec on Day 85	13			
Bazett: >450-500 msec on Day 85	0			
Bazett: >500 msec on Day 85	0			
Fridericia: <=450 msec at pre-study	37			
Fridericia: >450-500 msec at pre-study	0			
Fridericia: >500 msec at pre-study	0			
Fridericia: <=450 msec on Day 0	39			
Fridericia: >450-500 msec on Day 0	0			
Fridericia: >500 msec on Day 0	0			
Fridericia: <=450 msec on Day 1	35			
Fridericia: >450-500 msec on Day 1	0			
Fridericia: >500 msec on Day 1	0			
Fridericia: <=450 msec on Day 14	38			
Fridericia: >450-500 msec on Day 14	1			
Fridericia: >500 msec on Day 14	0			
Fridericia: <=450 msec on Day 28	37			
Fridericia: >450-500 msec on Day 28	2			
Fridericia: >500 msec on Day 28	0			
Fridericia: <=450 msec on Day 42	37			

Fridericia: >450-500 msec on Day 42	0			
Fridericia: >500 msec on Day 42	0			
Fridericia: <=450 msec on Day 56	37			
Fridericia: >450-500 msec on Day 56	0			
Fridericia: >500 msec on Day 56	0			
Fridericia: <=450 msec on Day 70	37			
Fridericia: >450-500 msec on Day 70	1			
Fridericia: >500 msec on Day 70	0			
Fridericia: <=450 msec on Day 84	34			
Fridericia: >450-500 msec on Day 84	2			
Fridericia: >500 msec on Day 84	0			
Fridericia: <=450 msec on Day 85	13			
Fridericia: >450-500 msec on Day 85	0			
Fridericia: >500 msec on Day 85	0			

Notes:

[6] - Safety set (main study) with electrocardiogram valid for QT/QTc evaluation at all time points.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug in the Main Study and the Long-term Extension Phase

End point title	Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug in the Main Study and the Long-term Extension Phase ^[7]
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End point description:

An AE is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. TEAEs were AEs that began while the subject was taking study treatment or up to 2 days after the end of study treatment. Here n = number of subjects evaluable at the specific period.

End point type	Primary
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End point timeframe:

From the start of main study (12 weeks) until the end of LTE phase (84 months)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done and inferential statistics were not planned as this is an open, single-group study.

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Subjects				
Main Study (n = 75)	0			
LTE Phase (n = 68)	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 6-minute Walk Time Distance (6MWD) at Specified Time Points

End point title	Change From Baseline in 6-minute Walk Time Distance (6MWD) at Specified Time Points
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End point description:

6MWD is a measure for the objective evaluation of a subject's functional exercise capacity. In the below table, 'n' signifies the number of subjects evaluable for the corresponding time points. '99999' in the table below indicates that value could not be estimated since there was only 1 subject evaluable at LTE Month 84.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as ≤ 1 week prior to start of main study), Day 84 (end of main study), LTE Months 12, 24, 36, 48, 60, 72, and 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	68 ^[8]			
Units: Meters				
arithmetic mean (standard deviation)				
Baseline (n=68)	364.9 (\pm 103.3)			
Change at Day 84 (n=66)	66.3 (\pm 71)			
Change at LTE Month 12 (n=52)	58.3 (\pm 78.8)			
Change at LTE Month 24 (n=48)	72.7 (\pm 94.4)			
Change at LTE Month 36 (n=49)	64.2 (\pm 93.3)			
Change at LTE Month 48 (n=42)	69.1 (\pm 104.5)			
Change at LTE Month 60 (n=40)	55.1 (\pm 102.2)			
Change at LTE Month 72 (n=36)	57.8 (\pm 103.6)			
Change at LTE Month 84 (n=1)	297 (\pm 99999)			

Notes:

[8] - All subjects who entered the LTE phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With World Health Organization (WHO) Functional Class Assessment at Specified Time Points

End point title	Number of Subjects With World Health Organization (WHO) Functional Class Assessment at Specified Time Points
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End point description:

The WHO functional assessment of pulmonary arterial hypertension ranged from functional class I (subjects with pulmonary hypertension but without resulting limitation of physical activity) to class IV (subjects with pulmonary hypertension with inability to carry out any physical activity without symptoms. These subjects manifest signs of right-heart failure). In the below table, 'n' signifies the number of subjects evaluable for the corresponding time points.

End point type	Secondary
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End point timeframe:

Pre-study (<=1 week prior to start of study), Day 84 (end of main study), LTE Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, and 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	68 ^[9]			
Units: Subjects				
Pre-study: WHO Functional Class I (n=68)	0			
Pre-study: WHO Functional Class II (n=68)	14			
Pre-study: WHO Functional Class III (n=68)	53			
Pre-study: WHO Functional Class IV (n=68)	1			
Day 84: WHO Functional Class I (n=68)	2			
Day 84: WHO Functional Class II (n=68)	30			
Day 84: WHO Functional Class III (n=68)	36			
Day 84: WHO Functional Class IV (n=68)	0			
LTE Month 3: WHO Functional Class I (n=62)	2			
LTE Month 3: WHO Functional Class II (n=62)	31			
LTE Month 3: WHO Functional Class III (n=62)	28			
LTE Month 3: WHO Functional Class IV (n=62)	1			
LTE Month 6: WHO Functional Class I (n=56)	2			
LTE Month 6: WHO Functional Class II (n=56)	29			
LTE Month 6: WHO Functional Class III (n=56)	25			
LTE Month 6: WHO Functional Class IV (n=56)	0			
LTE Month 9: WHO Functional Class I (n=52)	4			
LTE Month 9: WHO Functional Class II (n=52)	27			
LTE Month 9: WHO Functional Class III (n=52)	21			
LTE Month 9: WHO Functional Class IV (n=52)	0			
LTE Month 12: WHO Functional Class I (n=53)	3			
LTE Month 12: WHO Functional Class II (n=53)	27			
LTE Month 12: WHO Functional Class III (n=53)	23			
LTE Month 12: WHO Functional Class IV (n=53)	0			

LTE Month 15: WHO Functional Class I (n=53)	3			
LTE Month 15: WHO Functional Class II (n=53)	26			
LTE Month 15: WHO Functional Class III (n=53)	24			
LTE Month 15: WHO Functional Class IV (n=53)	0			
LTE Month 18: WHO Functional Class I (n=52)	3			
LTE Month 18: WHO Functional Class II (n=52)	25			
LTE Month 18: WHO Functional Class III (n=52)	24			
LTE Month 18: WHO Functional Class IV (n=52)	0			
LTE Month 21: WHO Functional Class I (n=51)	3			
LTE Month 21: WHO Functional Class II (n=51)	28			
LTE Month 21: WHO Functional Class III (n=51)	18			
LTE Month 21: WHO Functional Class IV (n=51)	2			
LTE Month 24: WHO Functional Class I (n=49)	3			
LTE Month 24: WHO Functional Class II (n=49)	29			
LTE Month 24: WHO Functional Class III (n=49)	17			
LTE Month 24: WHO Functional Class IV (n=49)	0			
LTE Month 27: WHO Functional Class I (n=51)	3			
LTE Month 27: WHO Functional Class II (n=51)	29			
LTE Month 27: WHO Functional Class III (n=51)	19			
LTE Month 27: WHO Functional Class IV (n=51)	0			
LTE Month 30: WHO Functional Class I (n=51)	2			
LTE Month 30: WHO Functional Class II (n=51)	29			
LTE Month 30: WHO Functional Class III (n=51)	20			
LTE Month 30: WHO Functional Class IV (n=51)	0			
LTE Month 33: WHO Functional Class I (n=50)	2			
LTE Month 33: WHO Functional Class II (n=50)	31			
LTE Month 33: WHO Functional Class III (n=50)	17			
LTE Month 33: WHO Functional Class IV (n=50)	0			
LTE Month 36: WHO Functional Class I (n=50)	3			
LTE Month 36: WHO Functional Class II (n=50)	30			
LTE Month 36: WHO Functional Class III (n=50)	17			

LTE Month 36: WHO Functional Class IV (n=50)	0			
LTE Month 39: WHO Functional Class I (n=50)	3			
LTE Month 39: WHO Functional Class II (n=50)	25			
LTE Month 39: WHO Functional Class III (n=50)	22			
LTE Month 39: WHO Functional Class IV (n=50)	0			
LTE Month 42: WHO Functional Class I (n=48)	3			
LTE Month 42: WHO Functional Class II (n=48)	23			
LTE Month 42: WHO Functional Class III (n=48)	22			
LTE Month 42: WHO Functional Class IV (n=48)	0			
LTE Month 45: WHO Functional Class I (n=47)	3			
LTE Month 45: WHO Functional Class II (n=47)	25			
LTE Month 45: WHO Functional Class III (n=47)	18			
LTE Month 45: WHO Functional Class IV (n=47)	1			
LTE Month 48: WHO Functional Class I (n=44)	3			
LTE Month 48: WHO Functional Class II (n=44)	25			
LTE Month 48: WHO Functional Class III (n=44)	16			
LTE Month 48: WHO Functional Class IV (n=44)	0			
LTE Month 51: WHO Functional Class I (n=44)	3			
LTE Month 51: WHO Functional Class II (n=44)	27			
LTE Month 51: WHO Functional Class III (n=44)	14			
LTE Month 51: WHO Functional Class IV (n=44)	0			
LTE Month 54: WHO Functional Class I (n=42)	4			
LTE Month 54: WHO Functional Class II (n=42)	25			
LTE Month 54: WHO Functional Class III (n=42)	13			
LTE Month 54: WHO Functional Class IV (n=42)	0			
LTE Month 57: WHO Functional Class I (n=42)	4			
LTE Month 57: WHO Functional Class II (n=42)	23			
LTE Month 57: WHO Functional Class III (n=42)	14			
LTE Month 57: WHO Functional Class IV (n=42)	1			
LTE Month 60: WHO Functional Class I (n=41)	3			
LTE Month 60: WHO Functional Class II (n=41)	23			

LTE Month 60: WHO Functional Class III (n=41)	15			
LTE Month 60: WHO Functional Class IV (n=41)	0			
LTE Month 63: WHO Functional Class I (n=41)	3			
LTE Month 63: WHO Functional Class II (n=41)	22			
LTE Month 63: WHO Functional Class III (n=41)	15			
LTE Month 63: WHO Functional Class IV (n=41)	1			
LTE Month 66: WHO Functional Class I (n=39)	4			
LTE Month 66: WHO Functional Class II (n=39)	21			
LTE Month 66: WHO Functional Class III (n=39)	14			
LTE Month 66: WHO Functional Class IV (n=39)	0			
LTE Month 69: WHO Functional Class I (n=38)	3			
LTE Month 69: WHO Functional Class II (n=38)	23			
LTE Month 69: WHO Functional Class III (n=38)	12			
LTE Month 69: WHO Functional Class IV (n=38)	0			
LTE Month 72: WHO Functional Class I (n=37)	3			
LTE Month 72: WHO Functional Class II (n=37)	21			
LTE Month 72: WHO Functional Class III (n=37)	13			
LTE Month 72: WHO Functional Class IV (n=37)	0			
LTE Month 75: WHO Functional Class I (n=33)	4			
LTE Month 75: WHO Functional Class II (n=33)	18			
LTE Month 75: WHO Functional Class III (n=33)	11			
LTE Month 75: WHO Functional Class IV (n=33)	0			
LTE Month 78: WHO Functional Class I (n=19)	1			
LTE Month 78: WHO Functional Class II (n=19)	7			
LTE Month 78: WHO Functional Class III (n=19)	11			
LTE Month 78: WHO Functional Class IV (n=19)	0			
LTE Month 81: WHO Functional Class I (n=10)	1			
LTE Month 81: WHO Functional Class II (n=10)	4			
LTE Month 81: WHO Functional Class III (n=10)	5			
LTE Month 81: WHO Functional Class IV (n=10)	0			
LTE Month 84: WHO Functional Class I (n=2)	1			

LTE Month 84: WHO Functional Class II (n=2)	0			
LTE Month 84: WHO Functional Class III (n=2)	1			
LTE Month 84: WHO Functional Class IV (n=2)	0			

Notes:

[9] - All subjects who entered the LTE phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Echocardiographic Results - Tei Index at Day 84 in the Main Study

End point title	Change From Baseline in Echocardiographic Results - Tei Index at Day 84 in the Main Study
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End point description:

Tei index = myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by right ventricular ejection time). In the below table, 'n' signifies the number of subjects evaluable for the corresponding time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as ≤ 1 week prior to start of study) and Day 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	72 ^[10]			
Units: Ratio				
arithmetic mean (standard deviation)				
Baseline (n=46)	0.708 (\pm 0.341)			
Change at Day 84 (n=35)	-0.176 (\pm 0.28)			

Notes:

[10] - PK/PD set (main study).

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Echocardiographic Results - Pulmonary Arterial Systolic Pressure (PASP) at Day 84 in the Main Study

End point title	Change From Baseline in Echocardiographic Results - Pulmonary Arterial Systolic Pressure (PASP) at Day 84 in the Main Study
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End point description:

PASP is composed of the right ventricular systolic pressure as measured over the tricuspid regurgitation jet (4xtricuspid regurgitation jet peak velocity) plus the systolic venous pressure according to width of the vena cava inferior measured in M-mode. In the below table, 'n' signifies the number of subjects

evaluable for the corresponding time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
End point timeframe:	
Baseline (pre-study defined as <=1 week prior to start of study) and Day 84	

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	72 ^[11]			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n=65)	73.6 (± 20.6)			
Change at Day 84 (n=58)	-6.9 (± 16.7)			

Notes:

[11] - PK/PD set (main study).

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Echocardiographic Results - Tricuspid Annular Plane Systolic Excursion (TAPSE) at Day 84 in the Main Study

End point title	Change From Baseline in Echocardiographic Results - Tricuspid Annular Plane Systolic Excursion (TAPSE) at Day 84 in the Main Study
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End point description:

In a modified apical 4-chamber view, the excursions of the tricuspid annular plane were measured by positioning the M-mode cursor on the lateral portion of the tricuspid annulus; this movement reflected the base to apex shortening of the right ventricle in systole; movement >2 centimeters (cm) indicates good contraction, 12 cm indicate poor contraction, and less than (<) 1 cm indicates heart failure. In the below table, 'n' signifies the number of subjects evaluable for the corresponding time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
End point timeframe:	
Baseline (pre-study defined as <=1 week prior to start of study) and Day 84	

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	72 ^[12]			
Units: centimeters				
arithmetic mean (standard deviation)				
Baseline (n=64)	1.741 (± 0.586)			
Change at Day 84 (n=59)	0.276 (± 0.491)			

Notes:

[12] - PK/PD set (main study).

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Blood/Artery/Atrial/Capillary Pressure at Day 84 in the Main Study

End point title	Change From Baseline in Swan-Ganz Hemodynamic Parameters - Blood/Artery/Atrial/Capillary Pressure at Day 84 in the Main Study
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End point description:

The following Swan-Ganz hemodynamic parameters related to blood/artery/atrial/capillary pressure during right heart catheterization were measured: mean right atrial pressure (RAPmean), systolic pulmonary artery pressure (PAPsyst), diastolic pulmonary artery pressure (PAPdiast), mean pulmonary artery pressure (PAPmean), pulmonary capillary wedge pressure (PCWP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). In the below table, 'n' signifies the number of subjects evaluable for the respective outcomes at that time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as ≤ 1 week prior to start of study) and Day 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[13]			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline: RAPmean (n=50)	6.6 (± 4.3)			
Change at Day 84: RAPmean (n=50)	0.3 (± 5.2)			
Baseline: PAPsyst (n=50)	77.5 (± 15.1)			
Change at Day 84: PAPsyst (n=48)	-7.3 (± 14.1)			
Baseline: PAPdiast (n=50)	27.5 (± 10.9)			
Change at Day 84: PAPdiast (n=48)	-4.8 (± 9.2)			
Baseline: PAPmean (n=50)	45.3 (± 10.8)			
Change at Day 84: PAPmean (n=50)	-5.3 (± 8.6)			
Baseline: PCWP (n=50)	8 (± 4.2)			
Change at Day 84: PCWP (n=50)	1.2 (± 4.4)			
Baseline: SBP (n=47)	129.3 (± 19.3)			
Change at Day 84: SBP (n=47)	-7.5 (± 18.2)			
Baseline: DBP (n=47)	78.4 (± 12.8)			
Change at Day 84: DBP (n=47)	-7.2 (± 14.2)			
Baseline: MAP (n=45)	95.5 (± 16.6)			
Change at Day 84: MAP (n=45)	-5.3 (± 17.7)			

Notes:

[13] - PK/PD population (main study) with available measurements for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Heart Rate at Day 84 in the Main Study

End point title	Change From Baseline in Swan-Ganz Hemodynamic Parameters - Heart Rate at Day 84 in the Main Study
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End point description:

Heart rate was measured during right heart catheterization. In the below table, 'n' signifies the number of subjects evaluable at the corresponding time points.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as ≤ 1 week prior to start of study) and Day 84

End point values	Riociguat (Adepas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[14]			
Units: beats per minute				
arithmetic mean (standard deviation)				
Baseline (n=49)	77 (± 12.1)			
Change at Day 84 (n=50)	0.9 (± 11.8)			

Notes:

[14] - PK/PD population (main study) with available measurements for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Vascular Resistance at Day 84 in the Main Study

End point title	Change From Baseline in Swan-Ganz Hemodynamic Parameters - Vascular Resistance at Day 84 in the Main Study
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End point description:

Systemic and pulmonary vascular resistance parameters were calculated as follows: Systemic vascular resistance (SVR) = $80 \times (\text{MAP} - \text{RAP}_{\text{mean}}) / \text{cardiac output}$, and pulmonary vascular resistance (PVR) = $80 \times (\text{PAP}_{\text{mean}} - \text{PCWP}) / \text{cardiac output}$. SVR and PVR were expressed in $\text{dyne} \times \text{second} \times \text{centimeter}^{-5}$. 1 dyne = 1 gram \times centimeter \times second⁻² = 10^{-5} Newton. In the below table, 'n' signifies the number of subjects evaluable for the respective outcomes at that time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as ≤ 1 week prior to start of study) and Day 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[15]			
Units: dyne*second*centimeter ⁵				
arithmetic mean (standard deviation)				
Baseline: SVR (n=45)	1815 (\pm 638)			
Change at Day 84: SVR (n=44)	-399 (\pm 589)			
Baseline: PVR (n=50)	778 (\pm 351)			
Change at Day 84: PVR (n=48)	-253 (\pm 209)			

Notes:

[15] - PK/PD population (main study) with available measurements for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Percentage Vascular Resistance Ratio at Day 84 in the Main Study

End point title	Change From Baseline in Swan-Ganz Hemodynamic Parameters - Percentage Vascular Resistance Ratio at Day 84 in the Main Study
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End point description:

Ratio of PVR/SVR was reported in terms of percentage. $SVR=80*(MAP-RAP_{mean})/cardiac\ output$, and $PVR=80*(PAP_{mean}-PCWP)/cardiac\ output$. In the below table, 'n' signifies the number of subjects evaluable at the corresponding time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as ≤ 1 week prior to start of study) and Day 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[16]			
Units: Percentage of Ratio				
arithmetic mean (standard deviation)				
Baseline (n=45)	45.2 (\pm 15.8)			
Change at Day 84 (n=44)	-6.2 (\pm 14.5)			

Notes:

[16] - PK/PD population (main study) with available measurements for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Vascular Resistance Index at Day 84 in the Main Study

End point title	Change From Baseline in Swan-Ganz Hemodynamic Parameters - Vascular Resistance Index at Day 84 in the Main Study
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End point description:

Systemic and pulmonary vascular resistance indices were calculated as follows: SVR index (SVRI)=80*(MAP-RAPmean)/cardiac output*body surface area, and PVR index (PVRI)=80*(PAPmean PCWP)/cardiac output*body surface area. SVRI and PVRI were expressed in dyne*second*centimeter⁵*square meter. 1 dyne=1 gram*centimeter*second²= 10⁵ Newton. In the below table, 'n' signifies the number of subjects evaluable for the respective outcomes at that time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as <=1 week prior to start of study) and Day 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[17]			
Units: dyne*second*centimeter ⁵ *square meter				
arithmetic mean (standard deviation)				
Baseline: SVRI (n=45)	3380 (± 1081)			
Change at Day 84: SVRI (n=44)	-736 (± 1125)			
Baseline: PVRI (n=50)	1436 (± 615)			
Change at Day 84: PVRI (n=48)	-466 (± 385)			

Notes:

[17] - PK/PD population (main study) with available measurements for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Cardiac Output at Day 84 in the Main Study

End point title	Change From Baseline in Swan-Ganz Hemodynamic Parameters - Cardiac Output at Day 84 in the Main Study
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End point description:

Cardiac output was measured in triplicate, performed and calculated by cardiac output device. In the below table, 'n' signifies the number of subjects evaluable at the corresponding time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as <=1 week prior to start of study) and Day 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[18]			
Units: liter per minute				
arithmetic mean (standard deviation)				
Baseline (n=50)	4.2 (± 1.2)			
Change at Day 84 (n=48)	0.88 (± 0.98)			

Notes:

[18] - PK/PD population (main study) with available measurements for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Cardiac Index at Day 84 in the Main Study

End point title	Change From Baseline in Swan-Ganz Hemodynamic Parameters - Cardiac Index at Day 84 in the Main Study
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End point description:

Cardiac index = cardiac output / body surface area. In the below table, 'n' signifies the number of subjects evaluable at the corresponding time points. Please find the statistical analyses in the attachment below.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as ≤1 week prior to start of study) and Day 84

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[19]			
Units: liter per minute per square meter				
arithmetic mean (standard deviation)				
Baseline (n=50)	2.24 (± 0.59)			
Change at Day 84 (n=48)	0.48 (± 0.51)			

Notes:

[19] - PK/PD population (main study) with available measurements for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in N-terminal Pro-hormone B-type Natriuretic

Peptide (NT-proBNP) Levels at Specified Time Points

End point title	Change From Baseline in N-terminal Pro-hormone B-type Natriuretic Peptide (NT-proBNP) Levels at Specified Time Points
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End point description:

In the below table, 'n' signifies the number of subjects evaluable for the respective outcomes at that time points.

End point type	Secondary
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End point timeframe:

Baseline (pre-study defined as ≤ 1 week prior to start of main study), Day 84 (end of main study), LTE Months 12, 24, 36, 48, 60, and 69

End point values	Riociguat (Adempas, BAY63-2521) Main Study			
Subject group type	Reporting group			
Number of subjects analysed	72 ^[20]			
Units: picogram per milliliter				
arithmetic mean (standard deviation)				
Baseline (n=53)	9081 (\pm 5204)			
Change at Day 84 (n=51)	-1736 (\pm 2952)			
Change at LTE Month 12 (n=36)	-1334 (\pm 4138)			
Change at LTE Month 24 (n=37)	-214 (\pm 3342)			
Change at LTE Month 36 (n=37)	305 (\pm 5305)			
Change at LTE Month 48 (n=34)	2169 (\pm 8072)			
Change at LTE Month 60 (n=24)	2636 (\pm 7277)			
Change at LTE Month 69 (n=0)	99999 (\pm 99999)			

Notes:

[20] - PK/PD set (main study).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of an AE that began while the subject was taking study treatment or up to 2 days after the end of study treatment

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

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

Subjects received Riociguat (Adempas, BAY63-2521) immediate release (IR) tablets with biweekly titrations of doses starting from 1.0 milligram (mg) thrice in a day (TID) up to 2.5 mg TID in steps of plus (+) 0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks. Subjects who were willing to continue, entered the long-term extension (LTE) phase until the premature termination of product development or until official approval and commercial availability of BAY63-2521 at a minimum dose of 0.5 mg TID and maximum dose of 2.5 mg TID.

Serious adverse events	Riociguat (Adempas, BAY63-2521)		
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 68 (79.41%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatocellular carcinoma			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Uterine leiomyoma			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Haematoma			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vasculitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angioplasty			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lung transplant			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bilevel positive airway pressure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Large intestinal polypectomy			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mechanical ventilation			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary endarterectomy			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hernia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Impaired healing			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary arterial hypertension			

subjects affected / exposed	9 / 68 (13.24%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	13 / 68 (19.12%)		
occurrences causally related to treatment / all	2 / 14		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheterisation cardiac			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular resistance pulmonary increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorder postoperative			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incisional hernia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal column injury			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous haematoma			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular pseudoaneurysm			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic right ventricular failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences causally related to treatment / all	2 / 14		
deaths causally related to treatment / all	0 / 1		

Right ventricular failure			
subjects affected / exposed	13 / 68 (19.12%)		
occurrences causally related to treatment / all	0 / 20		
deaths causally related to treatment / all	0 / 5		
Cor pulmonale			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery disease			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sick sinus syndrome			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	14 / 68 (20.59%)		
occurrences causally related to treatment / all	6 / 36		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gingival bleeding			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Intestinal haemorrhage			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cardiac cirrhosis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prerenal failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma infection			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphangitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Septic shock			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tooth infection			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Riociguat (Adempas, BAY63-2521)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 68 (94.12%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	24 / 68 (35.29%)		
occurrences (all)	32		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	6		
Fatigue			

subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 11		
Oedema subjects affected / exposed occurrences (all)	19 / 68 (27.94%) 29		
Oedema peripheral subjects affected / exposed occurrences (all)	30 / 68 (44.12%) 59		
Peripheral swelling subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4		
Reproductive system and breast disorders Gynaecomastia subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	19 / 68 (27.94%) 22		
Dysphonia subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 5		
Dyspnoea subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 11		
Epistaxis subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 12		
Pleural effusion subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4		
Pulmonary arterial hypertension subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4		
Nasal congestion			

<p>subjects affected / exposed occurrences (all)</p> <p>Pulmonary hypertension subjects affected / exposed occurrences (all)</p> <p>Respiratory failure subjects affected / exposed occurrences (all)</p>	<p>4 / 68 (5.88%) 4</p> <p>13 / 68 (19.12%) 16</p> <p>6 / 68 (8.82%) 7</p>		
<p>Psychiatric disorders</p> <p>Insomnia subjects affected / exposed occurrences (all)</p> <p>Depression subjects affected / exposed occurrences (all)</p>	<p>5 / 68 (7.35%) 9</p> <p>5 / 68 (7.35%) 5</p>		
<p>Investigations</p> <p>International normalised ratio increased subjects affected / exposed occurrences (all)</p>	<p>5 / 68 (7.35%) 5</p>		
<p>Injury, poisoning and procedural complications</p> <p>Contusion subjects affected / exposed occurrences (all)</p> <p>Muscle strain subjects affected / exposed occurrences (all)</p> <p>Fall subjects affected / exposed occurrences (all)</p>	<p>4 / 68 (5.88%) 4</p> <p>4 / 68 (5.88%) 4</p> <p>4 / 68 (5.88%) 4</p>		
<p>Cardiac disorders</p> <p>Palpitations subjects affected / exposed occurrences (all)</p> <p>Atrial fibrillation subjects affected / exposed occurrences (all)</p>	<p>6 / 68 (8.82%) 9</p> <p>6 / 68 (8.82%) 8</p>		

Right ventricular failure subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		
Tachycardia subjects affected / exposed occurrences (all)	12 / 68 (17.65%) 16		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	26 / 68 (38.24%) 38		
Head discomfort subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4		
Sciatica subjects affected / exposed occurrences (all)	7 / 68 (10.29%) 7		
Headache subjects affected / exposed occurrences (all)	15 / 68 (22.06%) 23		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	12 / 68 (17.65%) 18		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	7 / 68 (10.29%) 7		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 6		
Constipation subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 12		
Abdominal distension subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		

Abdominal pain subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 5		
Abdominal pain upper subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 11		
Gastritis subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 5		
Dyspepsia subjects affected / exposed occurrences (all)	23 / 68 (33.82%) 33		
Diarrhoea subjects affected / exposed occurrences (all)	16 / 68 (23.53%) 22		
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 14		
Vomiting subjects affected / exposed occurrences (all)	14 / 68 (20.59%) 18		
Nausea subjects affected / exposed occurrences (all)	12 / 68 (17.65%) 16		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 6		
Rash subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 5		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 6		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	7 / 68 (10.29%)		
occurrences (all)	9		
Back pain			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	11		
Myalgia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Osteoarthritis			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	5		
Musculoskeletal pain			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	9 / 68 (13.24%)		
occurrences (all)	10		
Pain in extremity			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	5		
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	10		
Gastroenteritis			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	12		
Bronchitis			
subjects affected / exposed	13 / 68 (19.12%)		
occurrences (all)	20		
Nasopharyngitis			
subjects affected / exposed	41 / 68 (60.29%)		
occurrences (all)	111		
Pneumonia			

subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4		
Influenza subjects affected / exposed occurrences (all)	9 / 68 (13.24%) 20		
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 16		
Sinusitis subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 9		
Respiratory tract infection subjects affected / exposed occurrences (all)	15 / 68 (22.06%) 35		
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	11 / 68 (16.18%) 13		
Iron deficiency subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2007	After 2 subjects were enrolled, protocol was corrected for consistent requirements for biomarker samples.
28 March 2007	1. Further allowed concomitant medications added (and corresponding exclusion criterion deleted): calcium channel blockers given up to the dose approved for arterial hypertension, such as nifedipine up to 120 milligram per day (mg/day), diltiazem up to 360 mg/day, amlodipine up to 10 mg/day. 2. Additional laboratories for safety laboratory added due to new study centers. 3. PAPmean reduced from 30 to 25 millimeter of mercury as inclusion criterion. 4. Change in exclusion criteria: resting heart rate less than 55 beats per minute or more than 105 beats per minute. 5. Number of valid subjects to be treated increased to 25. 6. Optional openlabel extension phase introduced for subjects willing to stay on riociguat following the initial 12week treatment phase. 7. Cancellation of fasting period on Day 0. 8. Addition of troponin I as additional cardiac marker.
08 May 2007	1. Change of clinical phase to "clinical pharmacology study phase I/II". 2. Inclusion criteria: change of upper age limit from 65 to 75 years of age. 3. Inclusion criteria: change of upper limit of body mass index from 30 to 35 kilogram per square meter. 4. Exclusion criteria: increase of PCWP limit to >15 millimeter of mercury. 5. Correction of the Borg modified dyspnea score rating scale. 6. Shortening of final study visit procedures in subjects participating in the extension phase.
16 October 2007	1. Number of subjects to be treated increased to 60. 2. Interim analysis after 25 subjects completed the 12-week treatment phase. 3. Further allowed concomitant medications added (and corresponding exclusion criterion deleted): Bosentan. 4. After the availability of all data an unplanned analysis was performed including all subjects of the 12-week dose titration period to supply the most important information as soon as possible. 5. Box-Whisker-Plots are displayed instead of profile curves for PK concentrations.
29 May 2008	1. Supply of new riociguat tablets at doses of 1.0, 1.5, and 2.0 mg. 2. Introduction of the optional openlabel extension period to assess the longterm safety and tolerability of riociguat in subjects having completed the main study as study objective. 3. Introduction of end of optional open label extension period visit and 6-monthly follow-up. 4. Introduction of events of special interests (death, heart/lung transplantation, arterial septostomy, pulmonary endarterectomy, start of new pulmonary hypertensionspecific treatment. 5. Subjects were to be withdrawn from the study in case of use of the following medications : - Unspecific phosphodiesterase (PDE) inhibitors, such as dipyridamole, theophylline, pentoxifylline, enoximone, milrinone, or pimobendan. - Specific PDE inhibitors such as sildenafil, vardenafil, or tadalafil. - No donors, such as nitrates. 6. Introduction of additional warnings based on the results of clinical pharmacological studies: - Due to possible PK interactions between riociguat and strong cytochrome P450 3A4 inhibitors, such as ketoconazole, concomitant treatment was to be applied with caution, such as additional blood pressure monitoring. - Antacids like aluminum hydroxide/magnesium hydroxide, such as maaloxan, were not to be taken simultaneously with riociguat because a negative impact on the bioavailability of the study drug had been observed. To avoid such interaction, antacids were to be taken not before 1 hour after intake of riociguat.

25 March 2010	1. Smoking status questioning added to the protocol as riociguat clearance is increased in smokers compared to nonsmokers. 2. "Syncope" was defined as a safetyrelevant event of special interest and thus was to be reported as a serious adverse event. 3. Subject participation in another clinical trial was added as criterion for removal. 4. In the extension part of the study, the dose titration scheme was identical to that of the main study; however, in case that the 1 mg TID dose was not tolerated, the riociguat dose could be reduced to a minimum dose of 0.5 mg TID.
13 December 2012	1. Optional Open Label Extension Period (OOLEP) procedures were changed to facilitate studyrelated activities as follows: A separate subject information and informed consent form was added and was signed by all subjects participating in this period. Deviation of +/-14 days from the scheduled every 3 months visit added as permissible. Every 3 months visits no longer required smoking status, but a physical exam was performed and status of concomitant medication was determined 1 hour before study treatment. Laboratory sampling and electrocardiogram (ECG) were only to be performed locally at the investigator's discretion. Vital signs, modified Borg dyspnea score, PK sampling, and AE questioning were reduced. Return of all unused medication by the subject and dispensing of a 3-month supply of study medication was performed. The End of OOLEP Visit was 30 (+5) days after the last dose. WHO functional class, 6MWT, ECG, safety laboratory, troponin I, prohormone, modified Borg dyspnea score, and smoking status were no longer required at this visit; physical exam results, heart rate and blood pressure, and pregnancy test data if applicable were captured, and AEs and events of special interest were documented. Subjects who permanently stopped riociguat in the OOLEP due to reasons other than consent withdrawal were no longer required to be followed up; subjects were to return to the hospital for the End of OOLEP Visit. 2. ECG and laboratory test abnormalities as well as change in modified Borg dyspnea score was not to be analyzed due to data for these procedures in this trial period no longer being captured. 3. Premature termination of study or closure of center criterion added: "If subjects can be transferred to another trial or therapy program with riociguat which ensures that subjects benefit can be treated until the drug receives official approval and will be commercially available." 4. A routine right heart catheterization was considered.
03 April 2013	After all subjects had already been enrolled, the following changes were made which concerned the Optional Extension Period and End of Open Label Extension Period Visit: 1. Recording of events of special interest (death, heart/lung transplantation, atrial septostomy, pulmonary endarterectomy, start of new PH specific treatment [endothelin antagonists, prostacyclin analogues, PDE type 5-inhibitors]) in this period was clarified as "With the exception of death (to be recorded on the end of study page), the first occurrence of each of the events of special interest was to be captured at each visit of the optional open label extension period and end of open label extension period visit (safety visit)". 2. For the estimation of the combined endpoint "time to clinical worsening" in this period, the following clarifications were added: the first occurrence of events of special interest was to be considered and incidence tables of the overall rate were to be presented, together with the Kaplan-Meier survival curve. 3. Safety analyses in this period were clarified as "change-from-baseline analyses".

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.

Decimal places were automatically truncated if last decimal equals zero.

Notes: