Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Clinical Trial Results Synopsis

Study sponsor	Bayer Healthcare AG
Study number	14554
National clinical trial number	National Clinical Trial (NCT) number: NCT01172756
Study title:	Acute hemoDynamic effects of RIociguat (BAY 63-2521) in patients with puLmonary hypertension Associated with diasTolic heart failurE (DILATE 1): A randomized, double-blind, placebo-controlled, single-dose study in three ascending dose cohorts.
Therapeutic area	Cardiology/Coagulation
EudraCT number:	2010-018436-41
Clinical phase:	IIa
Study objectives:	Evaluation of the acute hemodynamic effects, safety, and pharmacokinetics of riociguat in patients with pulmonary hypertension (PH) associated with diastolic heart failure.
Test drug:	Riociguat / BAY 63-2521 (film-coated tablets)
Name of active ingredient:	Riociguat / BAY 63-2521
Dose:	0.5, 1.0, and 2.0 mg
Route of administration:	Oral (tablet)
Duration of treatment:	Single-dose administration
Reference drug:	Placebo (tablets)
Dose:	-
Route of administration:	Oral
Duration of treatment:	Single-dose administration

Background treatment:	Diuretics and anti-hypertensive agents.
Indication:	Pulmonary hypertension associated with diastolic heart failure
Diagnosis and main criteria for inclusion:	Pulmonary hypertension associated with diastolic heart failure, based on signs or symptoms of heart failure, left ventricular ejection fraction >50% and evidence of diastolic left ventricular dysfunction by echocardiography, and an invasively measured mean pulmonary arterial pressure ≥25 mmHg in the presence of a mean pulmonary capillary wedge pressure >15 mmHg in subjects ≥18 years of age.
Methodology:	This was a multi-center, randomized, double-blind, placebo-controlled, single-dose study in three ascending-dose cohorts. Right heart catheterization (RHC) and echocardiography (Echo)
Type of control:	Placebo
Study center(s):	5 recruiting centers: Austria (3), Czech Republic (1), Germany (1)
Study period:	**First subject, first visit:** 22 Jul 2010 **Last subject, last visit:** 15 Oct 2012
Premature study suspension /termination	After randomization of 39 of 48 planned subjects, the study was prematurely discontinued due to low enrolment.

Substantial study protocol amendments	Amendment 1 dated 17 Feb 2011 (global): - inclusion criterion #3 concerning transthoracic echocardiography was changed - inclusion criterion #5 concerning serum NT-proBNP was changed to >220 pg/mL - general exclusion criterion #2, and #4 was changed to "Participation in another clinical trial during the preceding 30 days" - cardiovascular exclusion criteria #3, #8 and #12 were changed - assessment of the exploratory biomarkers galectin-3, PIIINP, ST2, and ADMA was added Amendment 2 dated 31 Mar 2011 (global): - better specification of study procedures to permit an efficient monitoring for early signs of pulmonary edema Amendment 3 dated 29 Aug 2011 (Germany): - assessment of additional echocardiographic parameters
Number of subjects per treatment group:	**Planned**: 48 subjects, i.e. 12 per treatment group **Analyzed**: 39 subjects; placebo n=13, riociguat 0.5 mg n=8, riociguat 1.0 mg n=8, riociguat 2.0 mg n=10.

Criteria for evaluation

Efficacy:

Primary efficacy variable: peak decrease from baseline in mean pulmonary arterial pressure (PAP_{mean}).

Secondary efficacy variables: changes from baseline in

- Pulmonary capillary wedge pressure (PCWP).
- PAP_{mean}.
- Transpulmonary pressure gradient (TPG).
- Cardiac output (CO), right atrial pressure (RAP), and derived hemodynamic parameters.
- Mixed venous oxygen saturation.
- Right ventricular ejection fraction, measured by right heart catheterization (RHC) at selected sites.
- Serum N-terminal prohormone B-type natriuretic peptide (NT-proBNP), galectin-3, procollagen III N-terminal propeptide (PIIINP), ST2, and asymmetric dimethyl-arginine (ADMA) concentrations at 8 and 24 h post-dose.
- Echocardiographic parameters:
  - Left ventricular end-diastolic volume (LVEDV).
  - Left ventricular end-diastolic volume index (LVEDVI).
  - Left ventricular end-systolic volume (LVESV).
  - Left atrial (LA) area.
  - Right atrial (RA) area.
  - PAP_{syst}.
  - Tricuspid annular plane systolic excursion (TAPSE).
  - E/A ratio at rest and during Valsalva's maneuver.
  - E-wave deceleration time at rest and during Valsalva's maneuver.
  - Pericardial effusion.

Safety:	• Adverse events (AEs) of special safety interest: – Fall in invasively measured systemic systolic arterial BP <80 mmHg **or** in invasively measured systemic mean arterial BP <60 mmHg at any time during the study. – Fall in CO by ≥20% of pre-dose. – Pulmonary edema. – Syncope. • AEs and SAEs. • Concomitant medication. • General physical examination. • Vital signs (heart rate and blood pressure). • Safety laboratory investigations (hematology, general chemistry, coagulation).
Pharmacokinetics:	Based on the plasma concentration time data of the 24-h time period after the drug administration, the following pharmacokinetic (PK) parameters were calculated: PK parameters: • AUC, AUC/D, AUC_{norm}, $AUC(0\text{-}t_{last})$, C_{max}, C_{max}/D, $C_{max,norm}$, MRT, t_{max}, $t_{1/2}$ of riociguat (BAY 63-2521). • AUC, C_{max}, t_{max}, $t_{1/2}$ for metabolite M-1 (BAY 60-4552). • Other PK parameters: $AUC(t_{last}\text{-}\infty)$, points terminal for all analytes.
Statistical methods:	The primary efficacy variable was the peak decrease from baseline in mean pulmonary arterial pressure (PAP_{mean}). The primary comparison was a 2-group 2-sided t-test at the 0.05 significance level for the difference in treatment effect between 2.0 mg riociguat and placebo in the per-protocol population.
Publication(s)	None
Date created/last updated	27 Sep 2013

Study subjects

46 subjects were screened for inclusion: 42 subjects in Austria (3 centers), 3 in Germany (1 center), and 1 in the Czech Republic (1 center). 39 subjects were randomized and received 1 dose of placebo (13 subjects), 0.5 mg (8 subjects), 1.0 mg (8 subjects) or 2.0 mg riociguat (10 subjects). 2 subjects terminated the study prematurely after dosing.

All subjects were white and 39% of the subjects were men. Mean age was 71.6 years and ranged between a mean of 65.8 years (1.0 mg riociguat) and 76.2 years (placebo). The overall age range was 48 to 86 years. Mean weight was 84.7 kg and ranged between a mean of 82.5 kg (2.0 mg riociguat) and 88.0 kg (1.0 mg riociguat). The overall weight range was 49 to 115 kg. Mean height was 166 cm and ranged between a mean of 160.9 cm (0.5 mg riociguat) and 169.6 cm (1.0 mg riociguat). The overall height range was 150 to 184 cm. 36% of the subjects were current (8%) or former smokers (28%).

46% of the subjects had atrial fibrillation at baseline. At baseline, mean PAP_{mean} was 33.4±7.0 mmHg, transpulmonary pressure gradient was 13.2±4.9 mmHg, and left ventricular ejection fraction was 62±7%.

39 subjects were valid for safety and pharmacokinetic analyses and 36 subjects were valid for per-protocol analysis. 3 subjects were excluded from the per-protocol analysis set due to missing informed consent prior to the first study-related procedures (one subject in placebo group]) and missing PAP_{mean} measurements at Visit 2 (one subject in placebo and riociguat 1.0 mg group each).

Efficacy / clinical pharmacology evaluation

The objective of this double-blind, placebo-controlled study was to evaluate the acute hemodynamic effects of riociguat administered as single doses of 0.5, 1.0, and 2.0 mg in 36 subjects with PH associated with diastolic heart failure. Riociguat was administered in addition to background treatment with diuretics, anti-hypertensives, and heart-rate-control agents.

Concerning the primary endpoint of mean pulmonary artery pressure (PAP_{mean}) reduction, there was no statistically significant difference in PAP_{mean} between **riociguat 2.0 mg** and placebo (placebo -6.3 mmHg vs 2.0 mg -5.1 mmHg, $P<0.55$).

In comparison to placebo, **riociguat 2.0 mg** significantly:

- Increased stroke volume (SV) by 8.8 mL (95% CI 0.4 to 17.3; $P<0.05$).
- Increased cardiac output (CO) by 0.87 L/min (95% CI 0.33 to 1.40; $P=0.002$).
- Increased cardiac index (CI) by 0.43 L/min/m^2 (95% CI 0.18 to 9.68; $P=0.001$).
- Decreased systolic blood pressure by 12 mmHg (95% CI -22.4 to -0.9; $P=0.034$).
- Decreased diastolic blood pressure by 6 mmHg (95% CI -11.8 to -0.7; $P=0.029$).
- Decreased systemic vascular resistance (SVR) by 247 dyn*s*cm^{-5} (95% CI -490 to -4; $P=0.047$).

- Decreased systemic vascular resistance index (SVRi) by 455 dyn*s*cm^{-5}*m^2 (95% CI -905 to -4; *P*=0.048).
- Decreased right ventricular end-diastolic (RVED) area by 5.6 cm^2 (95% CI -10.9 to -0.3; *P*=0.039).

No statistically significant differences between riociguat 2.0 mg and placebo were observed with regard to other hemodynamic and echocardiographic parameters as well as NT-proBNP, galectin-3, ST2, and ADMA.

The difference in PIIINP concentrations between placebo and the riociguat 2.0 mg group was statistically significant (*P*=0.0210).

In comparison to placebo, **riociguat 1.0 mg** significantly:

- Decreased systolic blood pressure by 14 mmHg (95% CI -26.1 to -2.4; *P*=0.020).
- Decreased systemic vascular resistance (SVR) by 276 dyn*s*cm^{-5} (95% CI -545 to -8; *P*=0.044).
- Decreased systemic vascular resistance index (SVRi) by 522 dyn*s*cm^{-5}*m^2 (95% CI -1021 to -23; *P*=0.041).
- Decreased TAPSE by 2.9 mm (95% CI -5.71 to -0.12; *P*=0.042).

However, it should be considered that mean TAPSE at pre-dose was within the high normal range and the observed change may well be a chance finding, since the therapeutic goal is to increase a reduced TAPSE.

No statistically significant differences between riociguat 1.0 mg and placebo were observed with regard to other hemodynamic and echocardiographic parameters as well as NT-proBNP, galectin-3, PIIINP, ST2, and ADMA.

In the riociguat 1.0 and 2.0 mg groups, some subjects had relevant decreases in SBP by up to 50 mmHg within 3 and 4 h after single-dose administration of study drug. These findings support the uptitration approach starting with a 0.5 mg dose in the context of riociguat administration used in the phase IIb Study 14308 (LEPHT) in subjects with PH due to systolic left ventricular dysfunction.

No statistically significant differences between **riociguat 0.5 mg** and placebo were observed with regard to other hemodynamic and echocardiographic parameters as well as NT-proBNP, galectin-3, PIIINP, ST2, and ADMA.

Main efficacy parameters (right heart catheterization and echocardiography) – Means ± SD at baseline (pre-dose) and changes from baseline vs placebo – ANOVA[a] – LS-means and 95% confidence intervals – statistically significant differences in bold (per-protocol analysis set)

Parameter (unit)	Mean ± SD at baseline				Difference of LS-means (95% CI)		
	Placebo n=11	Rio--ciguat 0.5 mg n=8	Rio-ciguat 1.0 mg n=7	Rio-ciguat 2.0 mg n=10	Riociguat 0.5 mg vs placebo	Riociguat 1.0 mg vs placebo	Riociguat 2.0 mg vs placebo
PAP_{mean} (mmHg)	34.9±8.0	32.0±4.5	31.1±6.4	35.1±8.8	1.5 [-2.3; 5.3]	3.8 [-0.1; 7.8]	0.7 [-2.9; 4.3]
Cardiac index ($L/min/m^2$)	2.18± 0.82	2.67± 0.49	2.63± 0.91	2.54± 0.55	0.09 [-0.17; 0.35]	0.26 [-0.01; 0.53]	**0.43 [0.18; 0.68]**
Cardiac output (L/min)	4.21± 1.89	5.03± 0.72	5.22± 1.95	4.94± 1.49	0.21 [-0.36; 0.78]	0.52 [-0.07; 1.11]	**0.87 [0.33; 1.40]**
SBP (mmHg)	129.5± 20.2	143.3± 19.3	144.7± 22.8	141.6± 24.9	-0.7 [-12.1; 10.7]	**-14.2 [-26.1; -2.4]**	**-11.7 [-22.4; -0.9]**
DBP (mmHg)	62.3± 11.9	57.4± 9.7	61.0± 10.2	58.7± 11.2	0.0 [-5.9; 5.9]	-3.4 [-9.6; 2.8]	**-6.3 [-11.8; -0.7]**
Heart rate (BPM)	66.1± 14.1	63.4± 12.2	73.0± 28.5.	67.5± 7.6	-1.4 [-8.5; 5.8]	-2.4 [-9.9; 5.0]	2.3 [-4.4; 9.0]
Stroke volume (mL)	66.6± 34.0	81.5± 18.0	77.8± 36.7	75.1± 27.1	4.6 [-4.4; 13.6]	3.4 [-6.0; 12.8]	**8.8 [0.4; 17.3]**
SVR ($dyn*s*cm^{-5}$)	1583± 689	1246± 392	1352± 795	1294± 481	-23 [-281; 236]	**-276 [-545; -8]**	**-247 [-490; -4]**
SVRi ($dyn*s*cm^{-5}*m^2$)	2938± 1127	2356± 797	2581± 1379	2398± 633	-60 [-539; 420]	**-522 [-1021; -23]**	**-455 [-905; -4]**
PCWP (mmHg)	21.1±6.4	18.6±2.1	19.4±2.1	21.8±4.6	1.0 [-2.0; 4.0]	2.8 [-0.3; 5.9]	-0.2 [-3.0; 2.6]
Right atrial pressure (mmHg)	11.6±3.0	9.5±3.1	12.7±4.6	11.7±4.4	0.1 [-3.1; 3.4]	1.4 [-2.0; 4.8]	-0.8 [-3.9; 2.2]
PVR ($dyn*s*cm^{-5}$)	303±169	217±61	224±170	228±106	-1.0 [-67.0; 64.9]	-23.6 [-92.2; 45.1]	-16.2 [-78.2; 45.9]
RVED area (cm^2)[b]	18.6± 8.43	17.8± 5.11	25.3± 10.8	23.8± 11.5	-3.60 [-8.98; 1.78]	-4.50 [-10.9; 1.88]	**-5.59 [-10.9; -0.32]**

ANOVA=analysis of variance; BPM=beats per minute; CI=confidence interval; DBP=diastolic blood pressure; LS=least square; PAP_{mean}=mean pulmonary artery pressure; PCWP=pulmonary capillary wedge pressure; PVR=peripheral vascular resistance; RVED=right ventricular end-diastolic; SBP=systolic blood pressure; SD=standard deviation; SVR=systemic vascular resistance; SVRi=systemic vascular resistance index

Note: Results reaching statistical significance are marked in bold.

[a] ANOVA model for repeated changes from baseline with treatment and time after dose as the main effects and the treatment*time interaction

Pharmacokinetics

Plasma concentrations of riociguat in subjects with PH-LVD were in the range of riociguat plasma concentrations observed in earlier studies with riociguat in other subject populations. In line with previous studies, the inter-subject variability (geometric coefficients of variation up to 102%) of riociguat plasma concentrations was high.

Safety and tolerability
The results of this placebo-controlled study demonstrate that administration of riociguat at single doses of 0.5, 1.0, and 2.0 mg has an acceptable safety profile in subjects with subjects with PH associated with diastolic heart failure.

This conclusion is based on the following findings:

- In total, 15 subjects reported TEAEs. The **overall frequency of TEAEs** was 31% in the placebo group (4 subjects), 38% in the riociguat 0.5 mg group (3 subjects), 38% in the riociguat 1.0 mg group (3 subjects), and 50% in the riociguat 2.0 mg (5 subjects) group.
- The most frequently reported **TEAEs by MedDRA preferred terms** were "mean arterial pressure decreased" (placebo group 1 subject [8%]; riociguat 1.0 mg group 1 subject [13%]; riociguat 2.0 mg group 3 subjects [30%]) and "cardiac output decreased" (placebo group 2 subject [15%]; riociguat 2.0 mg group 1 subject [10%]). All other TEAEs were reported only in 1 subject each.
- The only reported **drug-related TEAEs by MedDRA preferred terms** were "cardiac output decreased" (placebo group 2 subjects [15%]; riociguat 2.0 mg group 1 subject [10%]) and "mean arterial pressure decreased" (riociguat 2.0 mg group 3 subjects [30%]).
- The overall frequency of **TEAEs related to procedures required by the study protocol** was 8% in the placebo group (1 subject), 25% in the riociguat 0.5 mg group (2 subjects), 13% in the riociguat 1.0 mg group (1 subject), and 10% in the riociguat 2.0 mg group (1 subject). These included 1 case each of atrial flutter, musculoskeletal pain, dyspnoea, haemothorax, pulmonary oedema, and pulmonary haemorrhage.
- **Adverse events of special interest** were reported in 23% of subjects in the placebo group (3 subjects), 13% in the riociguat 0.5 mg group (1 subject), 13% in the riociguat 1.0 mg group (1 subject), and 40% in the riociguat 2.0 mg group (4 subjects). All events occurred within 24 h after administration of study drug. Fall in invasively measured systemic systolic arterial BP <80 mmHg or in invasively measured systemic mean arterial BP <60 mmHg was reported in 5 subjects (placebo 1 subject; riociguat 1.0 mg 1 subject; riociguat 2.0 mg 3 subjects). Fall in cardiac output ≥20% of pre-dose was reported in 3 subjects (placebo 2 subjects; riociguat 2.0 mg 1 subject). Pulmonary oedema occurred in 1 subject receiving riociguat 0.5 mg on Day 1 and syncope occurred in 1 subject receiving riociguat 2.0 mg on Day 7.
- **Death** was reported in 1 subject who received riociguat 1.0 mg who died within 24 h after study drug administration. The events (haemothorax and pulmonary haemorrhage) leading to death were related the insertion of the right heart catheter (procedure required by the study protocol) and unrelated to study drug.
- The most frequently reported **serious TEAEs by MedDRA preferred terms** were "mean arterial pressure decreased" (placebo group 1 subject [8%]; riociguat 1.0 mg group 1 subject [13%]; riociguat 2.0 mg group 3 subjects [30%]) and "cardiac output decreased" (placebo group 2 subject [15%]; riociguat 2.0 mg group 1 subject [10%]). All other treatment-emergent serious AEs were reported only in 1 subject each.

- The only reported **drug-related serious TEAEs** by MedDRA preferred terms were "cardiac output decreased" (placebo group 2 subjects [15%]; riociguat 2.0 mg group 1 subject [10%]) and "mean arterial pressure decreased" (riociguat 2.0 mg group 3 subjects [30%]).
- **Laboratory investigations** showed no clinically relevant abnormalities after dosing with study medication. There was no signal for drug-induced laboratory parameter changes.
- No clinically relevant changes in **ECG**, **respiratory rate**, **supplemental oxygen use**, **arterial oxygen saturation**, and **blood gas analysis including lactate** were observed.

In contrast to previous studies performed with riociguat, the single-dose design of this study did not include a dose-titration scheme, i.e. subjects were not uptitrated by doubling of a 0.5 mg riociguat starting dose, but received single doses without titration, because titration is not an option in a single-dose study.

Although there were differences between treatment groups in frequencies of TEAEs and drug-related TEAEs irrespective of being serious or non-serious, the number of subjects is too small to draw meaningful conclusions on potential differences between the treatment groups.

Overall conclusions

- In comparison to placebo, SV increased and SBP was reduced upon single doses up to 2.0 mg riociguat in subjects with PH associated with diastolic heart failure and elevated LV filling pressures without changing PAP_{mean}, PCWP, or heart rate.
- The administration of riociguat at single doses of 0.5, 1.0, and 2.0 mg has an acceptable safety profile in subjects with subjects with PH associated with diastolic heart failure. In contrast to previous studies performed with riociguat, the design of this study did not include a dose-titration scheme, i.e. subjects were not up-titrated in steps of 0.5 mg riociguat to the next higher doses but received the administered doses without titration.
- Plasma concentrations of riociguat in subjects with PH-LVD were in the range of riociguat plasma concentrations observed in earlier studies with riociguat in other subject populations. In line with previous studies, the inter-subject variability (geometric coefficients of variation) of riociguat plasma concentrations was high.