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.

Websynopsis

Study sponsor:	Bayer Healthcare AG
Study number:	15096
National clinical trial number:	National Clinical Trial (NCT) number: NTC01179334
Study title:	An interaction study to evaluate changes in blood pressure following 1, 1.5, 2, and 2.5 mg riociguat tid (dose titration) compared to placebo treatment on the background of stable sildenafil pretreatment in subjects with symptomatic pulmonary arterial hypertension
Therapeutic area:	Cardiology/Coagulation
EudraCT number:	2010-018863-40
Clinical phase:	IIb
Study objectives:	Primary objective: to evaluate the effect of 1.0, 1.5, 2.0, and 2.5 mg riociguat tid (dose titration) administered simultaneously with sildenafil on blood pressure in subjects with symptomatic pulmonary arterial hypertension. Secondary objectives: to investigate the safety of the riociguat/sildenafil combination and changes in the 6-minute walking distance test, World Health Organization (WHO) functional class, N-terminal pro-brain natriuretic peptide (NT-proBNP), and variables obtained during right-heart catheterization after 12 weeks of treatment; pharmacokinetics of riociguat and sildenafil. The optimized dose, reached after individual titration (starting at 1 mg 3 times a day [tid] and, if tolerated, up-titrated after two weeks in 0.5 mg-increments to a maximum dose of 2.5 mg tid) was compared to placebo.
Test drug: **Name of active ingredient(s):**	Riociguat (Adempas, BAY 63-2521) (film-coated tablets) Riociguat / BAY 63-2521

Dose:	1.0, 1.5, 2.0, and 2.5 mg 3 times per day (tid) (up-titration every 2 weeks) In case of side effects (e.g. symptomatic hypotension), down-titration to 0.5 mg tid was allowed. Sildenafil (background treatment) Subjects continued to take daily stable sildenafil background treatment at approved dose of 20 mg tid.
Route of administration:	Oral
Duration of treatment:	12 weeks
Reference drug:	Placebo (tablets)
Dose:	Matching Placebo tid A sham titration that followed the rules of the individual dose titration scheme Sildenafil (background treatment) Subjects continued to take daily stable sildenafil background treatment at approved dose of 20 mg tid.
Route of administration:	Oral
Duration of treatment:	12 weeks
Indication:	Pulmonary arterial hypertension (PAH)
Diagnosis and main criteria for inclusion:	Symptomatic PAH (Group 1, Dana Point Updated Clinical Classification of Pulmonary Hypertension (PH); PH subtypes as specified in inclusion criteria) and baseline 6-minute walking distance (6MWD) test ≥150 m, a pulmonary vascular resistance (PVR) >300 dyn*sec*cm^{-5}, and a mean pulmonary arterial pressure >25 mmHg. Subjects on stable pre-treatment with sildenafil at a dose of 20 mg tid could be included. Unspecific treatments which could also be used for the treatment of PAH, such as oral anticoagulants, diuretics, digitalis, calcium channel blockers, or oxygen supplementation were permitted.

Methodology:	This was a double-blind, randomized, multicenter, multinational, placebo-controlled study. During the 8-week titration phase, the dose of study medication was titrated every 2 weeks based on the subject's peripheral systolic blood pressure (SBP). In accordance with a prespecified algorithm, starting from a dose of 1.0 mg tid riociguat or placebo, the dose was increased, maintained, or decreased depending on whether SBP was ≥95 mmHg, 90 – 94 mmHg, or <90 mmHg, or if signs and symptoms of hypotension were detected. The maximum permitted daily dose was 2.5 mg tid riociguat or placebo. The "optimal dose" reached at the end of the titration phase was to be maintained for a further 4 weeks in the main study phase. Dose reductions for safety reasons were allowed.
Study center(s):	11 recruiting centers in 5 countries: Czech Republic (1), Germany (6), Italy (2), Spain (1), and the United Kingdom (1)
Study period:	**First subject, first visit:** 13 Aug 2010 **Last subject, last visit:** 14 May 2013
Premature study suspension /termination	Early termination of treatment (18 Dec 2012)
Substantial study protocol amendments	Amendment 1 dated 24 Feb 2011 (global): - introduction of a maximum dose of sildenafil (80 mg tid) in Study Part 2 for safety reasons - deletion of an upper limit for the 6MWD test as an inclusion criterion - modification of inclusion criteria regarding SBP and HR. Amendment 5 dated 11 Oct 2012 (global): - Study Part 2 of the original protocol was omitted
Number of subjects per treatment group:	Planned: Riociguat group: 12 randomized Placebo group: 6 randomized

	Analyzed:	Safety	PK	PD
	Main study:			
	Riociguat group:	12	11	11
	Placebo group:	6	5	5
	LTE phase:			
	Riociguat group:	11	--	--
	Placebo group:	6	--	--

Criteria for evaluation

Efficacy:

Primary efficacy variable:

- Maximum change in supine SBP from baseline within 4 hours (h) of dosing with riociguat for the individual dose steps or placebo

Secondary efficacy variables:

- Maximum change in standing SBP from baseline within 4 h of dosing with study medication
- Maximum change in standing diastolic blood pressure (DBP) from baseline within 4 h of dosing with study medication
- Maximum change in supine DBP from baseline within 4 h of dosing with study medication.
- Maximum change in supine and standing HR from baseline within 4 h of dosing with study medication.
- Area under effect curve (AUEC) for change from baseline in standing and supine systolic and diastolic BP, and HR within 4 h of dosing with riociguat or placebo.

Safety:

Adverse events (AEs), laboratory parameters, electrocardiogram (ECG) parameters, vital signs, blood gas analysis

Other:

Exploratory efficacy parameters comprise changes from baseline after 12 weeks for 6MWD, N-terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organization (WHO) functional class, Time to clinical worsening, Borg CR 10 scale, and hemodynamic parameters.

Statistical methods:	All variables were to be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics (mean, standard deviation, minimum, median, quartiles and maximum). No formal statistical testing was planned. Countries and centers were to be combined in the analyses.
Publication(s)	None

Date created/last updated: 24 Apr 2014	**Date of Clinical Study Report:** 04 Dec 2013

This documents covers Study Part 1. Results were analyzed separately for the main phase of the trial (12 weeks of placebo-controlled treatment) and the optional long-term extension (LTE) that continued past 12 weeks of treatment. In the LTE phase, all subjects received treatment with riociguat, with results reported in total and split by treatment group in the main study.

Results Summary – Subject Disposition and Baseline

24 subjects were enrolled in 11 study centers in 5 European countries: Czech Republic (2 subjects), Germany (15), Italy (5), Spain (1), and the United Kingdom (1). 18 of the 24 subjects were randomized and received study medication: 12 subjects received riociguat at an individually titrated dose, and 6 subjects received placebo. 17 of the 18 subjects continued on to the LTE phase of the trial. At baseline, most subjects were reported having WHO functional class II (10 subjects) or III (6 subjects); class I and IV were reported for 1 subject each (both assigned to receive riociguat treatment). Baseline 6MWD tests were ≥320 m for 13 subjects and <320 m for the remaining 5 subjects. Idiopathic PAH (5/12 in the riociguat group and 4/6 in the placebo group) and connective tissue disease (5/12 in the riociguat group and 1/6 in the placebo group) were the most frequent classes of PAH in the study population.

A separate per protocol analysis set was not applicable for this study, because all subjects who completed the study per protocol were included in the pharmacodynamic (PD) analysis set. The PD analysis set used for efficacy evaluation comprised 16 subjects: 11 subjects in the riociguat group and 5 subjects in the placebo group.

All 18 subjects treated were valid for safety analysis and were similar demographically between treatment groups, with age being the only notable differentiator. All subjects were white, most subjects (12 of 18) were female, and most subjects (16 of 18) had either never smoked or were former smokers. Body mass indexes (BMIs) were similar between treatment groups, with mean values of 27-28. Age ranged from 37 to 71 years in the riociguat group, and from 49 to 74 years in the placebo group. Baseline 6MWD results were somewhat imbalanced between treatment groups: the riociguat group reported most (7 of 12) subjects with results ≥320 m, while the placebo group (n=6) reported all subjects in that category; this variable was exploratory due to the small sample size.

The mean duration of prior treatment with sildenafil was 505 (standard deviation [SD] 421) days for the riociguat group and 394 days (SD 306) for the placebo group. Prior medication frequency distributions between treatment groups were imbalanced for approximately half (11 of 19) of the subclasses occurring with a frequency of ≥20% in either treatment group. Differences were ≥20% higher in the riociguat group for bile acid preparations; corticosteroids acting locally; proton pump inhibitors; antineoplastic and immunomodulating agents; beta blocking agents, selective; bisphosphonates; benzodiazepine derivatives; other antihistamines for systemic use; and glucocorticoids.

Results Summary - Efficacy and pharmacodynamics

The primary objective of the study was to evaluate the PD of riociguat individually titrated to dose levels of 1.0, 1.5, 2.0, and 2.5 mg tid and administered simultaneously with sildenafil in subjects with PAH over a period of 12 weeks.

The PD endpoint for analysis in this study was maximum change in supine systolic blood pressure (SBP) from baseline within 4 hours of dosing with riociguat or placebo.

Most secondary endpoints were also PD in nature. The efficacy variables of the study were exploratory.

Primary PD variable

The primary PD endpoint for analysis in this study was maximum change in supine SBP from baseline within 4 hours of dosing with riociguat or placebo. The maximum change from baseline per visit was defined as the within-subject maximum decrease from baseline (or zero if baseline was lower than all subsequent supine SBP measurements in that profile) across the time points to the end of the specified period. The baseline was the last of all blood pressure (BP) readings recorded at and within 30 minutes before administration of study medication.

The overall baseline value is derived from the profile at Visit 1 taken prior to randomization to study medication, that is with background sildenafil treatment alone, when vital signs were recorded from 30 min pre-sildenafil dose up to 4 hours post-dose. Hence, the baseline values reflect the treatment effect of the background sildenafil treatment administered at Visit 1. Subsequent values reflect the treatment effect of co-administration of background sildenafil with study medication (riociguat or placebo). Outlier analyses showed in general a high variability for blood pressure in both treatment groups.

The mean maximum change in supine SBP at the overall study baseline (i.e. sildenafil treatment effect) differed between the treatment groups (-20.18 mmHg [SD 15.29] [n=11] for the riociguat group [before riociguat administration]; -7.60 mmHg [SD 3.85] for the placebo group). In the riociguat group, the baseline mean maximum change in supine SBP showed a decrease after the 1st dose in Visit 1 and maintained that decrease by the end of the treatment phase, with a mean value of -20.70 mmHg (SD 17.97) (n=10) after 12 weeks. In the placebo group, mean maximum change in supine SBP values did not show a notable change from the value at baseline until after the 3rd dose in Visit 1. Thereafter, maximum change in supine SBP decreased to a mean value of -20.20 mmHg (SD 12.91) for placebo.

Secondary PD variables

Secondary PD variables analyzed were maximum changes in standing SBP, supine and standing diastolic blood pressure (DBP), supine and standing heart rate (HR), area under effect curve (AUEC) values for each of these variables, and of supine SBP, all from baseline within 4 hours of dosing with study medication.

The overall baseline values of mean maximum change in standing SBP differed between the treatment groups (-22.73 mmHg [SD 13.90] [n=11] for the riociguat group; -9.20 mmHg [SD 3.70] [n=5] for the placebo group). In the riociguat group, mean maximum change in standing SBP increased by 7.00 mmHg (SD 17.58) by the end of the treatment phase to a mean value of -18.00 mmHg (SD 16.50) (n=10) after 12 weeks. In the placebo group, mean maximum change in standing SBP decreased by -7.60 mmHg (SD 12.70) (n=5) for the placebo group to a mean value of -16.80 mmHg (SD 10.62) (n=5), now similar to the mean value for the riociguat group.

The mean overall baseline values of AUEC of supine SBP differed between the treatment groups (43.65 mmHg*h [SD 43.45] [n=11] for the riociguat group; 7.22 mmHg*h [SD 8.79] [n=5] for the placebo group). At the end of the treatment phase, after 12 weeks, a mean AUEC of supine SBP of 46.32 mmHg*h (SD 53.57) (n=10) was observed in the riociguat

group and 42.44 mmHg*h (SD 28.19) (n=5) in the placebo group. The corresponding mean overall baseline values of AUEC of standing SBP showed similar differences (46.43 mmHg*h [SD 39.48] [n=11] for the riociguat group; 9.51 mmHg*h [SD 8.26] [n=5] for the placebo group). After 12 weeks, a mean AUEC of standing SBP of 38.96 mmHg*h (SD 47.51) (n=10) was observed in the riociguat group and 30.41 mmHg*h (SD 33.35) (n=5) in the placebo group.

The overall baseline values of mean maximum change in supine DBP at the overall study baseline differed between the treatment groups (-13.64 mmHg [SD 10.07] [n=11] for the riociguat group; -9.40 mmHg [SD 8.50] [n=5] for the placebo group). In the riociguat group, mean maximum change in supine DBP increased minimally (0.90 mmHg [SD 12.90]) at the end of the treatment phase to a mean value of -13.70 mmHg (SD 11.72) (n=10) after 12 weeks. In the placebo group, mean maximum change in supine DBP decreased more substantially by -4.40 mmHg [SD 15.76]) for the placebo group to a mean value of -13.80 mmHg (SD 12.85) (n=5), now almost the same as that of the riociguat group.

The mean overall baseline values of AUEC of supine DBP differed between the treatment groups (27.44 mmHg*h [SD 29.66] [n=11] for the riociguat group; 16.32 mmHg*h [SD 19.39] [n=5] for the placebo group). At the end of the treatment phase, a mean AUEC of supine DBP of 30.79 mmHg*h (SD 35.66) (n=10) was observed in the riociguat group and 32.92 mmHg*h (SD 35.68) (n=5) in the placebo group.

The overall baseline values of mean maximum change in standing DBP at the overall study baseline differed between the treatment groups (-14.55 mmHg [SD 8.56] [n=11] for the riociguat group; -5.80 mmHg [SD 6.38] [n=5] for the placebo group). In the riociguat group, mean maximum change in standing DBP increased minimally (1.60 mmHg [SD 8.62]) at the end of the treatment phase to a mean value of -14.40 mmHg (SD 10.59) (n=10) after 12 weeks In the placebo group, mean maximum change in standing DBP decreased more substantially by -8.40 mmHg [SD 4.93]) for the placebo group to a mean value of -14.20 mmHg (SD 10.03) (n=5), now almost the same as that of the riociguat group.

The mean overall baseline values of AUEC of standing DBP differed between the treatment groups (31.93 mmHg*h [SD 27.44] [n=11] for the riociguat group; 11.76 mmHg*h [SD 19.34] [n=5] for the placebo group). At the end of the treatment phase, a mean AUEC of standing DBP of 32.50 mmHg (SD 34.04) (n=10) was observed in the riociguat group and 24.20 mmHg*h (SD 22.54) (n=5) in the placebo group.

In supine and standing HR, a different pattern was seen, in which baseline values were similar between the treatment groups but the values diverged over time. After 12 weeks, the maximum changes in heart rate in the placebo group (9.60 beats/min [SD 5.50] supine; 10.40 beats/min [SD 6.54] standing) were notably higher than those of the riociguat group (5.90 beats/min [SD 7.14] supine; 6.50 beats/min [SD 7.17] standing). Analyses of AUEC values also confirmed these observations.

The mean overall baseline values of AUEC of supine HR differed between the treatment groups (10.77 beats/min*h [SD 16.39] [n=11] for the riociguat group; 4.50 beats/min*h [SD 5.68] (n=5) for the placebo group). At the end of the treatment phase, a mean AUEC of supine HR of 9.86 beats/min*h (SD 13.08) (n=10) was observed in the riociguat group and 18.85 beats/min*h (SD 14.86) (n=5) in the placebo group, now higher than the mean value for the riociguat group.

The mean overall baseline values of AUEC of standing HR differed slightly between the treatment groups (14.42 beats/min*h [SD 16.82] [n=11] for the riociguat group; 8.22 beats/min*h [SD 12.99] [n=5] for the placebo group). At the end of the treatment phase, a mean AUEC of standing HR of 13.18 beats/min*h (SD 15.11) (n=10)was observed in the riociguat group and 15.69 beats/min*h (SD 11.81) (n=5), now higher than but more similar to the mean value for the riociguat group.

Exploratory efficacy evaluation

Exploratory efficacy variables analyzed were changes from baseline after 12 weeks in 6MWD, N-terminal pro-brain natriuretic peptide (NT-proBNP), WHO functional class, Borg CR 10 scale (measured at the end of the 6MWD test), and RHC hemodynamics, and time to clinical worsening.

In the riociguat group, mean 6MWD increased (7.27 m [SD 48.13]) to a mean value of 366.45 m (SD 139.63) at last visit. In the placebo group, mean 6MWD values increased by a mean of 30.20 m [SD 56.22]) to a mean value of 456.40 m (SD 34.89) at last visit.

In the riociguat group, mean NT-proBNP increased (834 [SD 1858.4]) to a mean value of 1582 (SD 2154.0) at last visit. In the placebo group, mean NT-proBNP values declined by a mean of -162 (SD 259.3) to a mean value of 125 (SD 67.9) at last visit.

Most subjects in both treatment groups (9 of 11 in the riociguat group; 4 of 5 in the placebo group) experienced no change in WHO functional class from baseline at last visit. One subject in each group improved by 1 WHO functional class level, and one subject in the riociguat group improved by 2 levels.

Two subjects were reported for clinical worsening. One subject in the riociguat group was hospitalized due to pulmonary hypertension (PH) on study day 20; the event was classified as transient and clinical worsening was not confirmed; this subject died during the LTE phase (Day 225 of treatment). One subject in the placebo group experienced a decrease in 6MWD reported as due to PH on study day 85; upon further investigation the event was confirmed to be not due to PH and therefore not a protocol-defined clinical worsening event.

Mean values of change in Borg CR 10 Scale were lower for both treatment groups after 12 weeks. In the riociguat group, the mean change from baseline was -0.73 to a mean value of 3.64 (SD 2.54) at last visit. In the placebo group, the mean change from baseline was -1.50 to a mean value of 1.50 (SD 1.22) at last visit.

Differences in the mean changes of RHC hemodynamic parameters between treatment groups were most notable for RAPm (0.00 [SD 4.11] for the riociguat group; -2.00 [SD 4.18] for the placebo group), PAPsyst (-6.20 [SD 7.36] for the riociguat group; -10.20 [SD 6.06] for the placebo group), SvO_2 (0.01 [SD 10.15] for the riociguat group; 3.74 [SD 6.87] for the placebo group), and PVR (-54.57 [SD 227.49] for the riociguat group; -104.76 [SD 136.33] for the placebo group). For all of these variables, the changes were of greater magnitude in the placebo group than in the riociguat group. For CO and CI, the mean changes from baseline to 12 weeks were higher for the riociguat group (increases of 0.80 [SD 1.01] and 0.39 [SD 0.59], respectively) than for the placebo group (increases of 0.37 [SD 0.95] and 0.23 [SD 0.53], respectively).
Note: RAPm = mean right atrial pressure; PAPsyst = systolic pulmonary arterial pressure; SvO_2 = oxygen saturation; PVR = pulmonary vascular resistance; CO = cardiac output; CI = cardiac index

Results Summary - Safety

In the safety analysis set, the mean extent of exposure in the main study for the riociguat group was 460.75 mg (SD 131.09), with a range of 90.0 to 577.5 mg. Eight subjects received exposure to riociguat >500.5 mg.

A higher frequency of subjects reported treatment-emergent adverse events (TEAEs) in the riociguat group (12 of 12 subjects) than in the placebo group (4 of 6). The most frequently affected system organ classes were gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, investigations, metabolism and nutrition disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders, and vascular disorders

The most frequent preferred terms for TEAEs in the riociguat group were edema peripheral (4 of 12 subjects), hypokalemia (4 of 12), and headache (3 of 12). No preferred term affected more than 1 subject in the placebo group. In comparison to the riociguat group, hypokalemia was not reported for any subject in the placebo group, and headache was reported for only one subject (1 of 6).

The frequency of drug-related TEAEs was similar for the treatment groups (7 of 12 for the riociguat group; 3 of 6 for the placebo group). Overall, for the majority of subjects that had drug-related TEAEs, these events were assessed as either mild in severity (3 of 12 riociguat, 2 of 6 placebo) or moderate (3 of 12 riociguat, 1 of 6 placebo). One subject in the study, in the riociguat group, reported a severe drug-related TEAE. The preferred term of this event was asthenia. This term was not reported for the placebo group at any severity.

The majority of subjects in the main study had TEAEs with maximum severity assessed as either mild (riociguat 5 of 12 subjects, placebo 3 of 6) or moderate (riociguat 4 of 12, placebo 1 of 6). Only 3 subjects in the main study, all in the riociguat group, reported severe TEAEs. The preferred terms of the events were right ventricular failure, asthenia, and erysipelas. None of these terms were reported in the placebo group at any severity.

No deaths were reported during the main study. Three deaths occurred in the LTE phase for subjects taking study medication. One subject died on Day 225 relative to start of study

treatment; the last dose was 2.5 mg riociguat. The preferred term was reported as subdural hematoma and the event was assessed by the investigator as not related to study drug. A previous fall and concomitant medication Marcumar (phenprocoumon) were cited as alternative explanations. The investigator considered the events ‘fall’ and ‘cerebral hemorrhage’ as not related to riociguat. With respect to the event cerebral hemorrhage, the sponsor agrees with the investigator's judgment. However, as a causal involvement of riociguat in the fall, via a decrease in blood pressure, could not be excluded with certainty, the causal relationship was assessed as related to riociguat by the sponsor. A second subject died on Day 678 relative to start of study treatment; the last dose was 1.0 mg riociguat, taken 4 days before the subject died. The preferred term was reported as decompensation of chronic right heart failure, and the event was assessed by the investigator as not related to study drug. Underlying disease of pulmonary arterial hypertension was cited as an alternative explanation. A third subject died on Day 337 relative to start of study treatment; the last dose was 2.0 mg riociguat. The preferred term was reported as cardiac arrest, and the event was assessed by the investigator as not related to study drug. Underlying disease of pulmonary arterial hypertension was cited as an alternative explanation.

Serious TEAEs were reported for 2 subjects in the main study, both in the riociguat group (preferred terms: right ventricular failure, and erysipelas). In the LTE phase, drug-related serious TEAEs were reported for 3 subjects. The preferred terms for the events were colitis (reported for 1 subject from the riociguat group in the main study) and hypotension (reported for 2 subjects, 1 from each treatment group in the main study).

TEAEs leading to discontinuation were reported for 1 subject in the main study, in the riociguat group (preferred term: vision blurred). In the LTE phase, 6 subjects discontinued study medication due to an adverse event (AE). The preferred terms for the events were abdominal pain upper (in a subject from the placebo group of the main study), vomiting (in a subject from the placebo group of the main study), and hypotension (reported for 4 subjects).

Syncope was not reported for any subject in the main study.

Suspected hypotension was reported as a TEAE for 2 subjects in the main study, both in the riociguat group. One subject reported 2 sequential events classified as hypotension under the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 preferred terms of low blood pressure (system organ class: vascular disorders) and intermittent low systolic blood pressure (system organ class: investigations). Both events were assessed by the investigator as related to study drug but non-serious. The event of low blood pressure was considered of moderate intensity and the outcome was reported as recovered/resolved, dose not changed. The event of intermittent low systolic blood pressure was considered of mild intensity and the outcome was not recovered / not resolved, dose not changed. The other subject reported an event of systolic hypotension (system organ class: vascular disorders), assessed by the investigator as related to study drug but non-serious. The event was considered of moderate intensity and the outcome was reported as recovered/resolved, dose reduced.

In the LTE phase, 8 subjects reported TEAEs of special interest. The preferred terms (according to MedDRA version 16.0) for the events were loss of consciousness (1 subject),

syncope (1 subject), and hypotension (reported for 7 subjects, 5 from the riociguat group and 2 from the placebo group in the main study). All events of hypotension except one were assessed as related to study drug, including 2 events classified as severe.

Shifts in laboratory safety parameters varied between the treatment groups but no meaningful conclusions could be drawn due to the low number of subjects.

No clinically relevant differences were found for baseline values or changes from baseline for laboratory safety parameters, and the findings were in line with those reported in other Phase III studies with riociguat.

Changes over the course of the study were similar for SBP, DBP, and mean systemic arterial blood pressure (MAP). Heart rates showed some variability in change over time. For standing HR, baseline values differed between the groups (mean value 79.17 beats/min for the riociguat group and 65.67 beats/min for the placebo group). Changes over the course of the study varied between groups. In the riociguat group, standing HR decreased by a mean change from baseline of -1.92 beats/min, to a mean value at last visit of 77.25 beats/min. In the placebo group, standing HR increased by a mean change from baseline of 7.50 beats/min, to a mean value at last visit of 73.17 beats/min. ECG evaluations showed no clinically relevant findings or trends.

Outlier analyses showed in general a higher variability in blood pressure readings for the riociguat group compared to the placebo group.

Weight and blood gas analysis showed comparability over time between treatment groups. Data were not sufficient to evaluate changes in lung function over time.

Other evaluations

Pharmacokinetic analysis confirmed that the plasma concentration of riociguat has a high variability.

Overall conclusions

Administration of riociguat in an individually titrated regimen in combination with stable sildenafil background treatment for the 12-week main study did not change supine SBP to a clinically relevant degree. No over-additive effects were observed.

During the double-blind phase, in the subject population with a background treatment of stable dosing with sildenafil, riociguat appeared generally safe. However, during the long-term extension phase, a high rate of discontinuations was observed (3 deaths and 6 discontinuations due to AEs) over 17 subjects during an average treatment period of approximately 10 months. The limited information on efficacy from the small sample, both during the double-blind main phase and the open-label long-term extension, did not indicate a signal of efficacy and clinical benefit. Therefore, the overall benefit-risk balance for the combination is not positive and combined use should be avoided in clinical use. This

conclusion is in line with the earlier decision not to initiate the investigation of higher doses of background sildenafil treatment (study Part 2).

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Adempas
Brand/Trade Name(s) ex-US	
Generic Name	Riociguat
Main Product Company Code	BAY63-2521
Other Company Code(s)	
Chemical Description	IUPAC Name: Methyl N-[4,6-Diamino-2-[1-[(2-fluorophenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl]-N-methyl-carbaminate
Other Product Aliases	

Date of last Update/Change: 04 Nov 2013