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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study sponsor	Bayer Healthcare Pharmaceuticals Inc.
Study number	12934
National clinical trial number	National Clinical Trial (NCT) number: NTC00810693
Study title:	Randomized, double-blind, placebo-controlled, multi-centre, multi-national study to evaluate the efficacy and safety of oral BAY 63-2521 (1 mg, 1.5 mg, 2 mg, or 2.5 mg tid) in patients with symptomatic pulmonary arterial hypertension (PAH). **PATENT-1 study.**
Therapeutic area	Cardiology/Coagulation
EudraCT number:	2008-003482-68
Clinical phase:	III
Study objectives:	To assess the efficacy and safety of oral riociguat in treatment-naïve subjects and subjects pre-treated with an endothelin receptor antagonist or a prostacyclin analogue with symptomatic PAH. 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 (main comparison) and a riociguat group (with capped dose titration from 1.0 mg to 1.5 mg tid).
Test drug: **Name of active ingredient(s):** **Dose:**	Riociguat / BAY 63-2521 (film-coated tablets) Riociguat / BAY 63-2521 Riociguat 1.0-2.5 mg group: 1.0–2.5 mg tid (individual dose titration) Riociguat 1.0-1.5 mg group: 1.0–1.5 mg tid (capped dose titration) In case of side effects (e.g. symptomatic hypotension), down-titration to 0.5 mg tid was allowed.

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
Route of administration:	Oral
Duration of treatment:	12 weeks
Indication:	Pulmonary arterial hypertension (PAH)
Diagnosis and main criteria for inclusion:	Symptomatic PAH (Group 1, Venice Clinical Classification of Pulmonary Hypertension (PH); PH subtypes as specified in inclusion criteria) with an eligibility and baseline 6-minute walking distance (6MWD) test between 150 m and 450 m, a pulmonary vascular resistance (PVR) >300 dyn*sec*cm^{-5}, and a mean pulmonary arterial pressure >25 mmHg. Both treatment-naïve subjects and subjects pre-treated with an endothelin receptor antagonist or a prostacyclin analogue (inhaled or subcutaneous; *oral administration permitted in Japan, as per amendment 7*) could be included. Unspecific treatments for the treatment of PH 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 depended on the treatment to which the subject was assigned. 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.
Type of control:	Placebo
Study center(s):	124 recruiting centers in 30 countries: Argentina (1), Australia (6), Austria (3), Belgium (2), Brazil (4), Canada (3), China (5), Czech Republic (1), Denmark (1), France (9), Germany (9), Greece (1), Israel (2), Italy (5), Japan (15), Mexico (6), New Zealand (1), Poland (1), Portugal (4), Russia (2), Singapore (2), South Korea (4), Spain (3), Sweden (3), Switzerland (1), Taiwan (3), Thailand (2), Turkey (3), United Kingdom (4), USA (18)
Study period:	**First subject, first visit:** 17 Dec 2008 **Last subject, last visit:** 14 May 2012
Premature study suspension /termination	N/A

Substantial study protocol amendments	Amendment 3 dated 20 Mar 2009 (Spain): - inclusion of treatment-naïve subjects in the study was prohibited Amendment 4 dated 10 Jun 2009 (global): - pre-treatment phase extended to "up to 2 weeks" - change from Modified Borg Dyspnoea Scale to Borg CR 10 Scale - addition of dizziness and syncope as undesirable effects - addition of collection of healthcare resource information Amendment 5 dated 25 Jan 2010 (Argentina): - inclusion of treatment-naïve subjects in the study was prohibited Amendment 6 dated 22 Mar 2010 (global): - adjustment of upper age limit from 75 to 80 years with stricter PCWP criteria - deletion of two exclusion criteria (one related to allergies, the other related to evidence of pulmo-veno-occlusive disease or pulmonary capillary hemangiomatosis) - collection of smoking status information, smoking added as interaction - addition of vomiting and gastritis as undesirable effects - visit window for safety follow-up visit extended from 30 (+2) days to 30 (+5) days Amendment 7 dated 23 Mar 2010 (Japan): - simultaneous treatment with oral beraprost 180 µg per day and an endothelin receptor antagonist allowed Amendment 8 dated 15 Feb 2011 (global): - measurements of calcium and phosphate and calcitriol were added - duration AEs were to be considered treatment-emergent was changed from up to 7 days to up to 2 days after the end of treatment with study medication
Number of subjects per treatment group:	Planned: Riociguat 1.0-2.5 mg group: 250 valid for ITT Placebo group: 125 valid for ITT Riociguat 1.0-1.5 mg group: 63 valid for ITT (ITT = intent to treat)

	Analyzed:	ITT/Safety	Per protocol
	Riociguat 1.0-2.5 mg group:	254	218
	Placebo group:	126	106
	Riociguat 1.0-1.5 mg group:	63	55

Criteria for evaluation

Efficacy:

Primary efficacy variable:

- Change from baseline in 6MWD after 12 weeks

Secondary efficacy variables:

- Change from baseline in PVR after 12 weeks
- Change from baseline in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) after 12 weeks
- Change from baseline in World Health Organization (WHO) functional class after 12 weeks
- Time to clinical worsening
- Change from baseline in Borg CR 10 Scale or Modified Borg Dyspnoea Scale (measured at the end of the 6MWD test) after 12 weeks
- Change from baseline in EQ-5D questionnaire after 12 weeks
- Change from baseline in Living with Pulmonary Hypertension (LPH) questionnaire after 12 weeks

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

Other: Hemodynamic parameters: Mean pulmonary arterial pressure, cardiac index

Statistical methods: The primary efficacy analysis was the analysis of the change in 6MWD from baseline to week 12 (last observation until week 12) in subjects valid for ITT, with imputation of missing values for subjects who withdrew or died before 12 weeks. The riociguat 1.0-2.5 mg and placebo groups were compared using analysis of covariance (ANCOVA), with baseline 6MWD as a covariate and treatment group, stratification group (therapy-naïve / add-on), and region as main effects. The primary statistical method would be the stratified Wilcoxon test if the Shapiro-Wilk test for normality of residuals was statistically significant. Least squares (LS) mean and 95% confidence intervals (CIs) of the treatment difference were calculated based on the ANCOVA. Superiority of the riociguat 1.0-2.5 mg group over the placebo group was to be declared if the two-sided significance level was less than or equal to 0.05.

Publication(s)	Archer SL. Riociguat for pulmonary hypertension--a glass half full. N Engl J Med. 2013 Jul 25;369(4):386-8. Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, Keogh AM, Langleben D, Kilama MO, Fritsch A, Neuser D, Rubin LJ; PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013 Jul 25;369(4):330-40.
Date created/last updated	25 Sep 2013

Study subjects

586 subjects were enrolled in 124 study centers in 30 countries worldwide. 141 of the 586 enrolled subjects were not randomized. 445 of the 586 subjects were randomized. 443 of the 445 randomized subjects received study medication (254 in the riociguat 1.0-2.5 mg group, 126 in the placebo group, 63 in the riociguat 1.0-1.5 mg group).

405 (91.0%) of the 445 randomized subjects completed the treatment phase. The remaining 40 randomized subjects prematurely discontinued study medication (38 subjects) or did not receive the study medication (2 subjects).

All 443 randomized, treated subjects were included in the ITT and safety analysis sets. 379 subjects were considered valid for per protocol analyses.

In the ITT analysis set (primary analysis set), the treatment groups were comparable with respect to demographic characteristics. Almost 80% of subjects were female. The majority of subjects in each treatment group were white (52-63%). A third of subjects in each group were classified as Asian (30-35%). Very few subjects were classified as black (<2%). Mean age was similar in all three treatment groups (riociguat 1.0-2.5 mg: 51.1 years, placebo: 50.7 years, riociguat 1.0-1.5 mg 48.8 years). Between 22% and 26% of subjects in each treatment group were aged ≥65 years; the oldest subject was 80 years of age. Body weight and body mass index at baseline were comparable in all three treatment groups, with a mean body mass index of 26-27 kg/m^2 in each treatment group. The majority of subjects in each treatment group had never smoked (62% to 67%); 6% to 8% of subjects in each treatment group were current smokers. Alcohol use was similar in all three treatment groups, with the majority of subjects reporting no alcohol consumption (58% to 67%) and about one third of subjects reporting light consumption (32% to 39%).

Most subjects in the ITT analysis set had a primary diagnosis of idiopathic PAH (riociguat 1.0-2.5 mg: 58.7% of subjects; placebo: 66.7%; riociguat 1.0-1.5 mg: 61.9%) or PAH due to connective tissue disease (28.0%; 19.8%; 23.8%). More than 90% of subjects in each treatment group had a WHO functional class of II or III. About half of the subjects in each treatment group were treatment-naïve and half were pre-treated for PAH. Most of the pre-treated subjects were receiving an endothelin receptor antagonist. The frequency of subjects

pre-treated with a prostacyclin analogue (inhaled, subcutaneous or oral) was less than 10% in all treatment groups.

Efficacy evaluation

The study achieved its objective of demonstrating superiority of riociguat over placebo for the primary efficacy variable 6MWD. As shown by the primary efficacy analysis, treatment with riociguat 1.0-2.5 mg tid resulted in a statistically significant and clinically relevant improvement in 6MWD from baseline to week 12 (last observation until week 12) as compared to placebo in the ITT analysis set. The estimated overall treatment effect from the ANCOVA was 35.78 m (95% CI: 20.06 m to 51.51 m; p<0.0001, stratified Wilcoxon test).

Primary analysis: Change in 6MWD (meter) from baseline to last visit - ITT analysis set

Statistic	**Riociguat 1.0–2.5 mg N=254**	**Placebo N=126**	**Riociguat 1.0–1.5 mg N=63**
Baseline, mean (SD)	361.4 (67.7)	367.8 (74.6)	363.2 (66.6)
Change from baseline to last visit, mean (SD)	29.6 (65.8)	–5.6 (85.5)	31.1 (79.3)
Treatment comparison	**Riociguat 1.0-2.5 mg – placebo**		
LS mean difference	35.78		
95% CI	20.06 to 51.51		
p-value (ANCOVA)	<0.0001		
p-value (stratified Wilcoxon test)	<0.0001		

ANCOVA model with baseline value, treatment group, region, and stratification group as fixed effects, stratified Wilcoxon test by region and stratification group; SD = Standard deviation

Last visit = Last observed value (not including follow-up) for subjects who completed the study or withdrew, except imputed worst value in case of death or clinical worsening without a termination visit or a measurement at that termination visit

The treatment effect was consistent for the ITT and per protocol analysis sets. Sensitivity analyses indicated that there was clear evidence of a treatment effect regardless of the imputation method used to take account for missing data.

The change in 6MWD from baseline to week 12 (last observation until week 12) was increased to a similar degree both in therapy-naïve subjects and in pre-treated subjects in the riociguat 1.0-2.5 mg group as compared to placebo (treatment effect estimates of 38.36 m [95% CI: 14.46 m to 62.26 m] for therapy-naïve subjects and 35.65 m [95% CI: 15.04 m to 56.26 m] for pre-treated subjects). A positive treatment effect was observed in almost all other prespecified subgroups.

Treatment with riociguat also resulted in a consistent improvement across the secondary efficacy variables PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg CR 10 Scale, EQ-5D questionnaire, and LPH questionnaire. The only secondary endpoint without a nominally significant improvement for the riociguat 1.0-2.5 mg group compared to placebo was the EQ-5D questionnaire utility score (p=0.0663). In the predefined order for the hierarchical testing, LPH was below EQ-5D. Thus, in addition to 6MWD, statistical significance was formally achieved for PVR, NT-proBNP, WHO functional class, time to

clinical worsening, and Borg Scale. The results for secondary efficacy variables in the per protocol population were consistent with those for the ITT population.

Secondary efficacy variables: Summary of hierarchical testing - ITT analysis set

Variable	Stratified Wilcoxon test p-value*	Statistically significant	Statistically significant in hierarchical testing
6MWD (primary)	**<0.0001**	Yes	Yes
PVR	**<0.0001**	Yes	Yes
NT-proBNP	**<0.0001**	Yes	Yes
WHO functional class	**0.0033**	Yes	Yes
Clinical worsening	**0.0046** [a]	Yes	Yes
Borg CR 10 scale [b]	**0.0022**	Yes	Yes
EQ-5D questionnaire	**0.0663**	No	No
LPH questionnaire	**0.0019**	Yes	No

* The normality of ANCOVA residuals has been rejected for all secondary efficacy variables where ANCOVA was applied (PVR, NT-proBNP, EQ5D and LPH), so that the stratified Wilcoxon test was used as primary analysis.

[a] Stratified log-rank test p-value for time to clinical worsening.

[b] Subjects enrolled before amendment 3 used the Modified Borg Dyspnoea Scale.

Prespecified exploratory analyses of additional hemodynamic parameters (e.g. cardiac index, pulmonary artery pressure) were consistent with the favorable findings for the secondary efficacy variable PVR. The proportion of subjects with a cardiac index of at least 2.5 L/min/m2 increased in the riociguat 1.0-2.5 mg group from 45.1% at baseline to 76.4% at week 12 (last observation until week 12), while a slight decrease from 48.1% to 44.4% was observed in the placebo group over the same time period. In the riociguat 1.0-2.5 mg group,reductions were observed in pulmonary artery pressures (PAPmean); changes in the placebo group were less pronounced than in the riociguat1.0-2.5 mg group.

Efficacy findings for the riociguat 1.0-1.5 mg group, which was analyzed only descriptively, were consistent with those for the riociguat 1.0-2.5 mg group.

Safety evaluation

The results of the safety analyses of this placebo-controlled study indicate that riociguat has an acceptable safety profile when given as an individual dose titration regimen (riociguat 1.0-2.5 mg group) or as a capped dose titration regimen (riociguat 1.0-1.5 mg group) for a duration of 12 weeks in subjects with symptomatic PAH.

The overall frequency of treatment-emergent AEs (TEAEs) was similar in all three treatment groups (89.4% of subjects in the riociguat 1.0-2.5 mg group, 85.7% in the placebo group, and 92.1% in the riociguat 1.0-1.5 mg group).

The most frequent TEAEs (≥10% of subjects in any treatment group) were headache (riociguat 1.0-2.5 mg 27.2%, placebo 19.8%, riociguat 1.0-1.5 mg 31.7%), dyspepsia (18.9%,

7.9%, 12.7%), peripheral edema (17.3%, 11.1%, 22.2%), dizziness (15.7%, 11.9%, 23.8%), nausea (15.7%, 12.7%, 15.9%), diarrhea (13.8%, 10.3%, 9.5%), vomiting (10.2%, 8.7%, 11.1%), nasopharyngitis (10.2%, 11.1%, 9.5%), dyspnea (6.3%, 11.1%, 6.3%), and cough (4.7%, 10.3%, 4.8%). TEAEs reported at least 5% more frequently in the riociguat 1.0-2.5 mg group than in the placebo group were headache (27.2% vs. 19.8%), dyspepsia (18.9% vs. 7.9%), peripheral edema (17.3% vs. 11.1%), anemia (8.3% vs. 2.4%), and hypotension (9.8% vs. 2.4%). The majority of TEAE frequencies in the riociguat 1.0-1.5 mg group were similar to those in the riociguat 1.0-2.5 mg group.

Overall, the majority of TEAEs were assessed as either mild or moderate in severity. Severe TEAEs were reported for 11.0% of subjects in the riociguat 1.0-2.5 mg group, 15.1% of subjects in the placebo group, and 9.5% of subjects in the riociguat 1.0-1.5 mg group.

Death occurred less frequently in subjects treated with riociguat than in those who received placebo (riociguat 1.0-2.5 mg 2 subjects, 0.8%; placebo 3 subjects, 2.4%; riociguat 1.0-1.5 mg 1 subject, 1.6%). Serious TEAEs were reported less frequently in the riociguat 1.0-2.5 mg group (29 subjects, 11.4%) than in the placebo group (23 subjects, 18.3%), while in the riociguat 1.0-1.5 mg group serious TEAEs occurred at a frequency similar to that in the placebo group (11 subjects, 17.5%). TEAEs leading to discontinuation occurred less frequently in both riociguat groups than in the placebo group (riociguat 1.0-2.5 mg 8 subjects, 3.1%; placebo 9 subjects, 7.1%; riociguat 1.0-1.5 mg 1 subject, 1.6%).

Suspected TEAEs of syncope (preferred terms of “loss of consciousness”, “presyncope”, or “syncope”) were reported less frequently in the riociguat 1.0-2.5 mg group (8 subjects, 3.1%) than in the placebo group (7 subjects, 5.6%). No difference was observed between the two riociguat groups with respect to such events (8 subjects [3.1%] vs. 2 subjects [3.2%]). The preferred term “syncope” was reported for 3 (1.2%) subjects in the riociguat 1.0-2.5 mg group, 5 (4.0%) subjects in the placebo group, and 0 subjects in the riociguat 1.0-1.5 mg group. Hypotension was reported as a TEAE more frequently in the riociguat 1.0-2.5 mg group (25 subjects, 9.8%) than in the placebo group (3 subjects, 2.4%) or in the riociguat 1.0-1.5 mg group (2 subjects, 3.2%). Blood pressure decreased was reported as a TEAE in 1 subject in each treatment group. With one exception, all cases of hypotension or blood pressure decreased were rated by the investigator as of mild or moderate intensity. The frequency of discontinuation of study medication due to syncope or hypotension in the riociguat groups was low and comparable to that in the placebo group.

In analyses of laboratory safety parameters, trends to lower mean values for hemoglobin, hematocrit, potassium and urate were observed in the riociguat groups as compared to the placebo group. For all other laboratory safety parameters, mean and median changes between baseline and subsequent study visits were small and comparable between the treatment groups.

Treatment-emergent values below the lower limit of normal for erythrocytes, hematocrit, hemoglobin, leukocytes, lymphocytes, and neutrophils were observed more frequently in the riociguat 1.0-2.5 mg group than in the placebo group. Similar findings for erythrocytes, hemoglobin, and hematocrit were observed in the riociguat 1.0-1.5 mg group. Anemia was reported as a TEAE more frequently on riociguat 1.0-2.5 mg (8.3%) than on placebo (2.4%)

or on riociguat 1.0-1.5 mg (1.6%), but the treatment groups did not differ with regard to use of new concomitant antianemia medication (6.7% vs. 4.0% vs. 6.3% of subjects) or blood substitutes and perfusion solutions (20.5% vs. 24.6% vs. 17.5%) or with regard to the frequency of treatment-emergent bleeding events (11.0% vs. 9.5% vs. 11.1%). There were no differences between the treatment groups with regard to aPTT or INR.

Increases in clinical chemistry parameters (in particular liver function parameters, creatine kinase, creatinine, urate) were less frequent in the riociguat 1.0-2.5 mg group than in the placebo group. Treatment-emergent values below the lower limit of normal for calcium were reported only in the riociguat 1.0-2.5 mg group (20.5% of subjects). However, this finding should be treated with caution because the parameter was measured in relatively few subjects in each group.

As expected with the known pharmacological mechanism of action of riociguat, mean SBP decreased to a greater extent in both active treatment groups than in the placebo group. SBP values lower than 95 mmHg were measured more frequently in the riociguat groups than in the placebo group, in particular in the riociguat 1.0-2.5 mg group, suggesting a stronger overall effect of this dosing regimen on SBP. Riociguat also decreased diastolic blood pressure, but the effect was less pronounced than for SBP. No change in heart rate was observed after 12 weeks of treatment with riociguat.

No clinically relevant changes in body weight, ECG parameters, or blood gas analysis parameters were identified.

Overall conclusions

Administration of riociguat in a dosage of 1.0-2.5 mg as an individual dose titration regimen results in a statistically significant and clinically meaningful improvement in 6MWD as compared to placebo in subjects with symptomatic PAH after 12 weeks.

In addition, consistent with the effects observed for the 6MWD, riociguat has superior effects over placebo on the predefined secondary efficacy variables PVR, NT-proBNP, WHO functional class, time to clinical worsening, and Borg Scale that are statistically significant and clinically relevant.

In the subject population under investigation, riociguat is safe and well tolerated as an individual dose titration regimen.

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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	

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