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	11348
National clinical trial number	National Clinical Trial (NCT) number: NCT00855465
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 chronic thromboembolic pulmonary hypertension (CTEPH). **CHEST-1 study**
Therapeutic area	Cardiology/Coagulation
EudraCT number:	2007-000072-16
Clinical phase:	III
Study objectives:	To assess the efficacy and safety of oral riociguat in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or recurrent or persisting pulmonary hypertension (PH) after surgical treatment. 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:	Riociguat / BAY 63-2521 (film-coated tablets)
Name of active ingredient(s):	Riociguat / BAY 63-2521
Dose:	1.0–2.5 mg tid (individual 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:	16 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:	16 weeks
Indication:	Chronic thromboembolic pulmonary hypertension (CTEPH)
Diagnosis and main criteria for inclusion:	CTEPH and an eligibility and baseline 6-minute walking distance (6MWD) test between 150 m and 450 m. CTEPH was defined either as inoperable (adjudicated by an experienced surgeon or a central adjudication committee), with a pulmonary vascular resistance (PVR) >300 dyn*sec*cm^{-5} measured at least 90 days after start of full anticoagulation and a mean pulmonary artery pressure >25 mmHg, or as persisting or recurrent PH after pulmonary endarterectomy (subjects had to have a PVR >300 dyn*sec*cm^{-5} measured at least 180 days after surgery). (*PVR inclusion criterion changed from 480 to 300 dyn*sec*cm^{-5} by amendment 5*)
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 pre-specified 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 "optimal dose" reached at the end of the titration phase was to be maintained for a further 8 weeks in the main study phase. Dose reductions for safety reasons were allowed.
Type of control:	Placebo

Study center(s):	89 recruiting centers in 26 countries: Argentina (1), Australia (1), Austria (2), Belgium (2), Brazil (3), Canada (5), China (5), Czech Republic (1), Denmark (1), France (8), Germany (12), Italy (1), Japan (15), Mexico (4), Netherlands (1), Poland (2), Portugal (1), Russia (2), Slovakia (1), South Korea (2), Spain (2), Switzerland (1), Taiwan (1), Turkey (3), United Kingdom (3), USA (9)
Study period:	**First subject, first visit:** 23 Feb 2009 **Last subject, last visit:** 27 Jun 2012
Premature study suspension /termination	N/A
Substantial study protocol amendments	Amendment 3 dated 16 Jun 2009 (global): - Clarifications regarding some inclusion/ exclusion criteria - Specification of 6MWD test - Change of the Borg Dyspnoea Score - Collection of health care resource information - Definition of physical training program - Timelines for study medication dosing specified - Methodology for blood pressure measurement added - Undesirable effects dizziness and syncope added - Description of the central operability assessment process added Amendment 4 dated 24 Mar 2010 (global): - Adjustment of upper age limit from 75 to 80 years with stricter PCWP criteria to rule out significant left heart disease - Clarifications of contraception methods in exclusion criteria - Clarifications on pregnancy testing - Clarification on 6MWD test for inclusion and other exclusion criteria - Deletion of one exclusion criterion related to allergies - Changes in assessment periods - Use of the Modified Borg Dyspnoea Scale - Collection of smoking status - Smoking added as interaction - Undesirable effects vomiting and gastritis added

	- Visit window for follow-up extended to 30 +5 days Amendment 5 dated 11 Oct 2010 (global): - Subject's baseline PVR, required for study inclusion, was reduced from >480 to >300 dyn*sec*cm^{-5} - The inoperability assessment process was further specified and harmonized with the information provided in study-specific manuals. Amendment 6 (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: 174 valid for ITT Placebo group: 87 valid for ITT (ITT = intent to treat) Analyzed: ITT/Safety / Per protocol Riociguat 1.0-2.5 mg group: 173 / 143 Placebo group: 88 / 75
Criteria for evaluation	
Efficacy:	<u>Primary efficacy variable:</u> • Change from baseline in 6MWD after 16 weeks <u>Secondary efficacy variables:</u> • Change from baseline in PVR after 16 weeks • Change from baseline in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) after 16 weeks • Change from baseline in World Health Organization (WHO) functional class after 16 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 16 weeks • Change from baseline in EQ-5D questionnaire after 16 weeks • Change from baseline in Living with Pulmonary Hypertension (LPH) questionnaire after 16 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 16 (last observation until week 16) in subjects valid for ITT, with imputation of missing values for subjects who withdrew or died before 16 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 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)	Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C; CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013 Jul 25;369(4):319-29. Archer SL. Riociguat for pulmonary hypertension--a glass half full. N Engl J Med. 2013 Jul 25;369(4):386-8.
Date created/last updated	25 Sep 2013

Study subjects

446 subjects were enrolled in 89 study centers in 26 countries worldwide. 184 of the 446 enrolled subjects were not randomized. 262 of the 446 subjects were randomized. 261 of the 262 randomized subjects received study medication (173 in the riociguat 1.0-2.5 mg group, 88 in the placebo group).

243 (92.7%) of the 262 randomized subjects completed the treatment phase. The remaining 19 randomized subjects prematurely discontinued study medication (18 subjects) or did not receive the study medication (1 subject).

All 261 randomized, treated subjects were included in the ITT and safety analysis sets. 218 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. More than 60% of subjects were female (68% in the

riociguat 1.0-2.5 mg group vs. 61% in the placebo group). The majority of subjects in each treatment group were white (69% vs. 74%), and about 20% of subjects in each group were classified as Asian (21% vs. 23%). Few subjects were classified as black (<5%). Mean age was very similar in both treatment groups (59.3 years vs. 59.2 years). Just over 40% of subjects in each treatment group were aged ≥65 years (43% vs. 41%); the oldest subject was 80 years of age. Body weight and body mass index at baseline were comparable in both treatment groups, with a mean body mass index of 27.1 kg/m^2 in the riociguat 1.0-2.5 mg group and 27.7 kg/m^2 in the placebo group. The majority of subjects in each treatment group had never smoked (65% vs. 53%). Alcohol use was similar in both treatment groups, with the majority of subjects reporting no alcohol consumption (52% vs. 51%) and most other subjects reporting light consumption (45% vs. 44%).

In both treatment groups, the majority of the subjects had a diagnosis of inoperable CTEPH (69.9% of subjects in the riociguat 1.0-2.5 mg group, 77.3% of subjects in the placebo group). More than 60% of subjects in each treatment group were in WHO functional class III at baseline (riociguat 1.0-2.5 mg 61.8%, placebo 68.2%). Most other subjects in each group were in functional class II (riociguat 1.0-2.5 mg 31.8%, placebo 28.4%).

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 16 (last observation until week 16) as compared to placebo in the ITT analysis set. The estimated overall treatment effect from the ANCOVA was 45.69 m (95% CI: 24.74 m to 66.63 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=173**	**Placebo N=88**
Baseline		
Mean (SD)	342.3 (81.9)	356.0 (74.7)
Median (Min-Max)	360.0 (150-557)	372.0 (152-474)
Change from baseline to last visit		
Mean (SD)	38.9 (79.3)	–5.5 (84.3)
Median (Min-Max)	42.0 (–376-335)	5.0 (–389-226)
Treatment comparison	**Riociguat 1.0-2.5 mg – placebo**	
LS mean difference	45.69	
95% CI	24.74 to 66.63	
p-value (ANCOVA)	<0.0001	
p-value (stratified Wilcoxon test)	<0.0001	

ANCOVA model with baseline value, treatment group, and region as fixed effects, stratified Wilcoxon test by region; 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.

In subjects with inoperable CTEPH, the treatment effect for change in 6MWD from baseline to week 16 (last observation until week 16) was 53.92 m (95% CI: 28.53 m to 79.31 m); in subjects with postoperative CTEPH, the treatment effect was 26.72 m (95% CI: –9.68 m to 63.13 m). In subjects with a WHO functional class of III/IV at baseline, the treatment effect for change in 6MWD from baseline to week 16 (last observation until week 16) was 52.97 m (95% CI: 26.50 m to 79.43 m); in subjects with a WHO functional class of I/II at baseline, the treatment effect was 25.45 m (95% CI: –8.85 m to 59.75 m).

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. Secondary endpoints without a statistically significant improvement for the riociguat 1.0-2.5 mg group compared to placebo were time to clinical worsening (p=0.1724) and the LPH questionnaire total score (p=0.1220). In the predefined order for the hierarchical testing, the Borg CR 10 Scale and the EQ-5D questionnaire utility score were below time to clinical worsening. Thus, in addition to 6MWD, statistical significance was formally achieved for PVR, NT-proBNP, and WHO functional class. The results for secondary efficacy variables in the per protocol population were consistent with those for the ITT population. The only difference was for the LPH total score, where there was a nominally significant improvement in the per protocol population (p=0.0353).

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	**0.0026**	Yes	Yes
Clinical worsening	**0.1724** [a]	No	No
Borg CR 10 scale [b]	**0.0035**	Yes	No
EQ-5D questionnaire	**<0.0001**	Yes	No
LPH questionnaire	**0.1220**	No	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.

Pre-specified 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/m^2 increased in the riociguat 1.0-2.5 mg group from 32.3% at baseline to 58.1% at week 16 (last observation until week 16), while a slight decrease from 28.9% to 27.7% 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 generally small and in the opposite direction to those in the active treatment 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) for a duration of 16 weeks in subjects with inoperable or postoperative CTEPH.

The overall frequency of treatment-emergent AEs (TEAEs) was similar in both treatment groups (91.9% of subjects in the riociguat 1.0-2.5 mg group and 86.4% subjects in the placebo group).

The most frequent TEAEs (≥10% of subjects in either treatment group) were headache (riociguat 1.0-2.5 mg 24.3%, placebo 13.6%), dizziness (22.5%, 12.5%), dyspepsia (17.9%, 8.0%), peripheral edema (15.6%, 20.5%), nasopharyngitis (15.0%, 9.1%), nausea (11.0%, 8.0%), cough (5.2%, 18.2%), and dyspnea (4.6%, 13.6%). TEAEs reported at least 5% more frequently in the riociguat 1.0-2.5 mg group than in the placebo group were headache (24.9% vs. 13.6%), dizziness (22.5% vs. 12.5%), dyspepsia (17.9% vs. 8.0%), nasopharyngitis (15.0% vs. 9.1%), diarrhea (9.8% vs. 4.5%), vomiting (9.8% vs. 3.4%), and hypotension (9.2% vs. 3.4%).

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 and 11.4% of subjects in the placebo group.

Death occurred less frequently in subjects treated with riociguat 1.0-2.5 mg (2 subjects, 1.2%) than in those who received placebo (3 subjects, 3.4%). Serious TEAEs were reported more frequently in the riociguat 1.0-2.5 mg group (34 subjects, 19.7%) than in the placebo group (14 subjects, 15.9%). TEAEs leading to discontinuation occurred at a similar frequency in both treatment groups (riociguat 1.0-2.5 mg 5 subjects, 2.9%; placebo 2 subjects, 2.3%).

Suspected TEAEs of syncope (preferred terms of “presyncope” or “syncope”) were reported at low and comparable frequencies in both treatment groups (riociguat 1.0-2.5 mg 6 subjects, 3.5%; placebo 3 subjects, 3.4%); the preferred term “syncope” was reported for 4 (2.3%) subjects in the riociguat 1.0-2.5 mg group and 3 (3.4%) subjects in the placebo group. Hypotension or orthostatic hypotension was reported as a TEAE more frequently in the riociguat 1.0-2.5 mg group (17 subjects, 9.8%) than in the placebo group (3 subjects, 3.4%). Blood pressure decreased was reported as a TEAE in a comparable frequency of subjects in

each treatment group (3 subjects [1.7%] vs. 1 subject [1.1%]). With one exception, all cases of hypotension, orthostatic hypotension, and blood pressure decreased were rated by the investigator as of mild or moderate intensity. No subjects were withdrawn from study medication due to syncope or hypotension.

In analyses of laboratory safety parameters, trends to lower mean values for hemoglobin, hematocrit, and urate were observed in the riociguat 1.0-2.5 mg group 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. Anemia was reported as a TEAE more frequently on riociguat 1.0-2.5 mg (6 subjects, 3.5%) than on placebo (1 subject, 1.1%), but the treatment groups did not differ with regard to use of new concomitant antianemia medication (4.6% vs. 2.3% of subjects) or blood substitutes and perfusion solutions (15.0% vs. 17.0%) or with regard to the frequency of treatment-emergent bleeding events (13.3% vs. 11.4%). There were no differences between the treatment groups with regard to activated partial thromboplastin time (aPTT) or international normalized ratio (INR).

Increases in clinical chemistry parameters (in particular liver function parameters, cystatin C, lipase, urate, and urea) 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 (4 subjects, 11.1%). Treatment-emergent phosphate values below the lower limit of normal were more frequent in the riociguat 1.0-2.5 mg group (5 subjects, 12.8%) than in the placebo group (1 subject, 4.2%). However, these findings for calcium and phosphate should be treated with caution because the parameters were 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 the riociguat 1.0-2.5 mg group than in the placebo group. SBP values lower than 95 mmHg were measured more frequently in the riociguat 1.0-2.5 mg group than in the placebo group at all visits during the 16-week treatment phase, but no trend to a higher frequency of such values was observed over time in the riociguat 1.0-2.5 mg group. Riociguat also decreased diastolic blood pressure, but the effect was less pronounced than for SBP. No change in heart rate was observed after 16 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 inoperable or postoperative CTEPH after 16 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, and WHO functional class 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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87	Dr. K Kerr	Univ. of California San Diego - La Jolla	Pulmonary & Critical Care Division 9444 Medical Center Drive	92093	La Jolla	United States
88	Dr. H W Farber	Boston Medical Center	Pulmonary / Allergy / Asthma Doctors Office Building 720 Harrison Avenue 4th Floor	02118	Boston	United States
89	Dr. S Hansdottir	University of Iowa Hospitals & Clinics	T411 GH 200 Hawkins Drive	52242	Iowa City	United States

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