Clinical Trial Paper

Rationale and study design of MOTION: A phase 4, prospective, single-arm, open-label study to measure outcomes in patients with pulmonary arterial hypertension not on active treatment

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ABSTRACT

In clinical trials of treatments for pulmonary arterial hypertension (PAH), objective measures, such as 6-min walk distance (6MWD) are limited in their ability to characterize the impact of PAH therapy from a patient’s perspective. Few clinical studies have evaluated the primary effects of pharmacologic treatment on patient-reported outcomes, such as symptoms, health-related quality of life (HRQoL), and productivity. MOTION (NCT02191137) is a prospective, multicenter, single-arm, open-label, phase 4 trial designed to assess whether riociguat monotherapy will improve patient-reported outcomes in patients with PAH in the United States who are not currently on treatment. Following a screening period of up to 14 days, eligible subjects will receive riociguat (0.5–2.5 mg TID) during a 10-week titration phase and a 14-week maintenance phase. The primary endpoint is change from baseline in the Living with Pulmonary Hypertension (LPH) questionnaire, a disease-specific HRQoL measure, after 24 weeks of riociguat treatment. The Short Form-12 Health Survey (SF-12) and the Work Limitations Questionnaire 8 (WLQ-8) will also be utilized to assess patient-reported outcomes. Other variables include change from baseline in World Health Organization functional class, 6MWD, and modified Borg Dyspnea Index. In addition, accelerator band activity will be validated against the 6MWD test. Safety will also be assessed. The MOTION trial will provide information on the effect of riociguat on patient-reported outcomes in PAH patients in the United States who are not currently on active treatment through the use of disease-specific and generic HRQoL measures (LPH and SF-12) and a measure of worker productivity (WLQ-8).

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1. Background and rationale

Historically, clinical trials of treatments for pulmonary arterial hypertension (PAH) have focused on improvement in exercise capacity, as measured by 6-min walking distance (6MWD), as a surrogate marker for the hemodynamic parameters known to be associated with outcomes in PAH [1,2]. However, the 6MWD is limited in its ability to characterize the impact of PAH from a patient’s perspective. The symptoms of PAH, such as dyspnea and fatigue, are distressing for patients and are related to reductions in both physical and emotional domains in health-related quality of life (HRQoL) [3,4]. Although the inclusion of patient-reported outcomes (PROs) is recommended when evaluating treatments for PAH, few clinical studies have focused on the effects of pharmacologic treatment on patient-reported symptoms and work productivity [2]. In a systematic review of 14 trials evaluating the effect of PAH treatment on PROs as secondary or exploratory endpoints, the improvements seen in HRQoL were usually smaller than the minimally important difference reported for PAH and therefore were not considered clinically relevant [5]. However, most of the trials had a duration of 12–16 weeks, and the majority used generic HRQoL questionnaires, which may explain the absence of clinically significant change [5].

Riociguat is a soluble guanylate cyclase (sGC) stimulator...
approved by the US Food and Drug Administration for the treatment of patients with PAH (World Health Organization [WHO] Group 1) to improve exercise capacity and WHO functional class (WHO FC) and delay time to clinical worsening [6]. It is also indicated for the treatment of patients with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4) after surgical treatment, or in those with inoperable CTEPH, to improve exercise capacity and WHO FC [6]. The approval of riociguat was based on the results of two phase 3 trials, PATENT-1 and CHEST-1, performed in patients with PAH and CTEPH, respectively [7,8]. In both studies, the primary endpoint was change from baseline in 6MWD; a generic QoL measure (the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D]) and a disease-specific quality-of-life measure (Living with Pulmonary Hypertension [LPH] questionnaire) were included as secondary or exploratory endpoints [7,8]. In PATENT-1, there was a statistically significant improvement in LPH (P = 0.002) and a nonsignificant improvement in Eq-5D with riociguat compared with placebo in PAH patients [8]. In CHEST-1, there was a significant improvement in Eq-5D (P < 0.001) and a nonsignificant improvement in LPH with riociguat compared with placebo in CTEPH patients [7]. Given the diverse QoL outcomes in these studies, it may be prudent to include multiple approaches to QoL measurement as generic and disease-specific measures capture different types of information.

The Measuring Outcomes in Patients With Pulmonary Arterial Hypertension not on Active Treatment (MOTION) study is designed to evaluate the effect of riociguat on PROs in PAH patients who are not currently on active treatment. The study will utilize 3 PRO measures: the LPH questionnaire, the Short Form-12 Health Survey (SF-12), and, for the employed subgroup, the Work Limitations Questionnaire 8 (WLQ-8).

In addition, the Borg Dyspnea Index will be assessed. This measure uses a 10-point subjective scoring system in which a patient rates his or her dyspnea during a particular activity. Higher scores indicate greater perceived dyspnea with the activity [9].

The study will also explore the use of a new telemetric technology (accelerator band) and evaluate if this technology correlates with improvements in 6MWD in patients with PAH. Accelerometers have previously shown correlation with 6MWD in patients with chronic heart failure [10]. As accelerometers have the potential to be used in a telemedicine setting to routinely monitor patients at home, they may provide a new modality for assessing and guiding treatment for patients with PAH [10].

2. Study design

Following a screening period of up to 14 days, eligible subjects will receive therapy with riociguat during a 10-week titration phase and a 14-week maintenance phase. All enrolled patients who receive at least 1 dose of riociguat will undergo a 30-day safety follow-up after the last dose. The primary endpoint is change from baseline in LPH after 24 weeks of treatment with riociguat. Secondary variables include change from baseline in LPH after 16 weeks; change from baseline in WLQ-8 after 16 and 24 weeks; change from baseline in SF-12 after 16 and 24 weeks; change from baseline in WHO FC after 16 and 24 weeks; change from baseline in modified Borg Dyspnea Index after 16 and 24 weeks; change from baseline in 6MWD after 16 and 24 weeks; and safety. An exploratory variable will also be assessed: accelerator band activity recorded during the 6MWD test at screening, baseline, week 16, and week 24.

The study will be carried out according to Good Clinical Practice guidelines and under the guiding principles detailed in the Declaration of Helsinki and applicable local laws and regulations. Documented approval from appropriate Institutional Review Boards/Independent Ethics Committees will be obtained for all participating centers/countries before the start of the study. The study is registered with ClinicalTrials.gov (NCT02191137) [11].

2.1. Patient selection

Principal inclusion and exclusion criteria are listed in Table 1. The inclusion and exclusion criteria are modeled after the phase 3 trials PATENT-1 and CHEST-1 and subsequent US registration of riociguat [7,8]. Most importantly, patients were required to have symptomatic PAH, including pulmonary vascular resistance (PVR) > 300 dyn·s·cm⁻², mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, and pulmonary capillary wedge pressure (PCWP) < 15 mmHg as assessed by right heart catheterization (RHC) within 6 months prior to screening. Patients with pulmonary hypertension of other WHO group types were not eligible for the study. Additional exclusionary items, such as smoking history, have been added to remain consistent with US labeling and to minimize dosing complexity.

2.2. Riociguat administration and dosage

The starting dose of riociguat is 0.5 mg TID taken orally; patients unable to tolerate this dose will be withdrawn from the study. If systolic blood pressure (SBP) is > 95 mmHg and the patient has no signs or symptoms of hypotension, the dosage will be increased by 0.5-mg increments in 2-week intervals to 1.0, 1.5, 2.0, and 2.5 mg TID (maximum total daily dose: 7.5 mg). Patients will be maintained on lower doses if higher doses are not tolerated (minimum dose: 0.5 mg TID). After the titration phase, riociguat will be continued at the optimal individual dose for the 14-week maintenance phase.

Dose reduction is possible at any point in the study due to an adverse event (AE). During the maintenance phase, the dose may be increased at the investigator’s discretion up to a maximum of 2.5 mg TID according to the schedule above. If riociguat is interrupted for ≥3 days, the patient will be re-titrated beginning with 0.5 mg TID.

2.3. Prior and concomitant therapy

Patients will be excluded if they have ongoing or prior (within 14 days of screening) active PAH treatment with prostacyclin analogs (PCAs) except for vasoreactive testing; endothelin receptor antagonists (ERAs); nonspecific phosphodiesterase (PDE) inhibitors (eg, dipyridamole or theophylline); PDE type 5 inhibitors (PDE-5i; eg, tadalafil, sildenafil, vardenafil, or avanafil); or nitrites or nitric oxide (NO) donors (eg, amyl nitrate). Concomitant therapy with PAH-specific medications, with the exception of PDE-5i and nonspecific PDE inhibitors, is permitted after riociguat titration to individual optimal dose.

2.4. Study assessments

The schedule of study visits is shown in Fig. 1. The LPH, SF-12, and WLQ-8 questionnaires will be self-administered at visits 1, 3, 8, and 10/end-of-treatment. WHO FC will be assessed at screening and visits 1, 3, 8, and 10/end-of-treatment. Modified Borg Dyspnea Scale, 6MWD, and accelerator band activity will be assessed at screening and visits 1, 3, 8, and 10/end-of-treatment. The LPH questionnaire is designed to assess HRQoL specifically in PAH patients [2]. It was adapted from the Minnesota Living with Heart Failure questionnaire (MLHF), which measures QoL in patients with left heart failure [2]. The LPH consists of 21 items scored on a 5-point Likert scale. The score for each item ranges from...
## Table 1

### Principal inclusion and exclusion criteria.

**Inclusion criteria**

- Male and female patients 18–80 years old at screening
- Women of childbearing potential must have negative screening and monthly pregnancy tests and must use reliable methods of contraception according to the REMS
- Symptomatic PAH (WHO Group 1): idiopathic; heritable; or associated with connective tissue disease, congenital heart disease (only if surgically repaired > 1 year before enrollment), anorexigen or amphetamine use, or portal hypertension with liver cirrhosis
- PVR >300 dyn·s·cm⁻⁵, PAPmean ≥25 mmHg, and PCWP <15 mmHg as assessed by RHC within 6 months before screening
- Not treated with PAH-specific pulmonary vasodilators within 14 days of screening
- 6MWD 150–450 m with relative difference ≤15% between screening and visit 1
- Written informed consent

**Exclusion criteria**

**General**

- Previous treatment with riociguat
- Currently taking nitrate and/or NO donor therapy, PDE-5i, or nonspecific PDE inhibitors
- Unable to perform a valid 6MWD test
- Pregnant and/or breast-feeding women, or women of childbearing potential not using a reliable method of contraception
- History of smoking tobacco within the last 3 months or substance abuse within 180 days before visit 1
- Anticipated life expectancy <2 years
- Participation in another clinical trial currently or within 30 days before baseline (concurrent enrollment in noninterventional registry trials is permitted)

**Pulmonary disease**

- Moderate to severe obstructive lung disease (FEV₁ <60% of normal predicted value)
- Severe restrictive lung disease (TLC <50% of normal predicted value within 12 months before enrollment)
- Severe congenital abnormalities of the lungs, thorax, or diaphragm

**Blood gas abnormalities**

- SaO₂ <92% at screening despite supplemental oxygen therapy

**Cardiovascular disease**

- SBP >160 mmHg and/or DBP >90 mmHg within 90 days before visit 1; SBP >180 mmHg and/or DBP >110 mmHg at screening or visit 1 before enrollment; SBP <95 mmHg at screening or visit 1 before enrollment
- Left heart failure, hypertrophic obstructive cardiomyopathy, or severe proven or suspected CAD
- Clinical evidence of symptomatic atherosclerotic disease
- Clinically significant congenital or acquired valvular or myocardial disease, except for tricuspid valvular insufficiency due to PH

**Other organ dysfunction**

- Clinically relevant hepatic dysfunction at screening: bilirubin >2x ULN and/or ALT or AST >3x ULN and/or signs of severe hepatic insufficiency (eg, impaired albumin synthesis with albumin <32 g/L, hepatic encephalopathy ≥ grade 1)
- Severe renal insufficiency: estimated GFR <30 mL/min at screening

**Bleeding/hemorrhage**

- Active hemoptysis or pulmonary hemorrhage, including events managed by bronchial artery embolization; history of bronchial artery embolization or massive hemoptysis (acute bleeding >240 mL in a 24-h period or recurrent bleeding >100 mL/day over a 3-day period) within 3 months before screening
- Known history of major bleeding or, in the opinion of the investigator, a high risk of bleeding

6MWD, 6 min walking distance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; DBP, diastolic blood pressure; FEV₁, forced expiratory volume in 1 s; GFR, glomerular filtration rate; NO, nitric oxide; PAH, pulmonary arterial hypertension; PAPmean, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PDE, phosphodiesterase; PDE-5i, phosphodiesterase-5 inhibitor; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; REMS, Risk Evaluation Mitigation Strategies; RHC, right-heart catheterization; SaO₂, oxygen saturation; SBP, systolic blood pressure; TLC, total lung capacity; ULN, upper limit of normal; WHO, World Health Organization.

*This is not a complete list of inclusion and exclusion criteria.*

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### Fig. 1.

**MOTION study design.**

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**Table 1**

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0 points, indicating a response of “no,” to 5 points, indicating a response of “very much.” [2] The total score, calculated by adding up the scores for the individual items, ranges from 0 to 105, with a higher score indicating worse quality of life [2]. Cognitive debriefing interviews with 38 PAH patients confirmed the LPH covered the most commonly reported PAH symptoms and impacts [2]. The LPH was subsequently validated in a population of 190 patients with PAH and demonstrated good discrimination when compared with WHO FC and 6MWD along with responsiveness to change [2].

The SF-12 and WLQ-8 will be used to assess general HRQoL and effects on work performance and productivity, respectively, and will provide complementary information to the LPH. The SF-12 contains a subset of 12 items taken from the 36-item Short-Form Health Survey (SF-36) [12]. It includes 2 items each from the physical functioning, mental health, role-emotional, and role-physical scales, and 1 item each from the bodily pain, general health, vitality, and social functioning scales [12]. The information from the SF-12 can also be used to produce physical and mental component summary measures (PCS-12 and MCS-12) [12].

The WLQ-8 is an 8-item version of 25-item WLQ, which assesses health-related limitations in functioning in 4 different dimensions of work tasks: time management, physical work activities, mental-intellectual activities, and output activities (eg, handling work-load) [13,14]. Responses are based on the prior 2-week period and are scored using 5 responses: all of the time (100%), a great deal of the time, some of the time (50%), a slight bit of the time, and none of the time (0%) [13,14]. The WLQ scale scores generate an at-work productivity loss score (“presenteeism”) [13]. This validated productivity loss score is the weighted sum of the WLQ’s four scale scores and reflects the estimated percentage difference in at-work productivity between a person (or group) completing the WLQ and an external benchmark sample of healthy workers [15].

WLQ-8 and SF-12 data will be transformed according to a process that includes computing scale scores if at least half of the items on a scale are present, transforming raw scores to a range from 0 to 100. For the WLQ-8, a higher score indicates more limitations. For the SF-12, a higher score denotes better health. The WLQ-8 productivity loss score will then be generated as well the physical component summary (PCS) and a mental component summary (MCS) score of the SF-12 (with a mean of 50 and a standard deviation of 10).

AEs will be reported at every visit and coded by the Medical Dictionary for Regulatory Activities (MedDRA). Standard laboratory blood sampling (hematology and clinical chemistry) will be performed at visits 1 and 10. Physical examination will be performed at screening and visit 10. Blood pressure will be measured at every visit except for visit 9 (a telephone call to assess AEs, concomitant medications, and a pregnancy test administered at home). Pregnancy testing will be performed starting at screening, monthly during treatment, and until 30 days after stopping riociguat.

2.5. Statistical analysis

All outcomes will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample summary statistics including mean, standard deviation, median, interquartile range, and minimum/maximum. As appropriate, 95% confidence intervals (CI) will be provided. Statistical tests will be performed with a type I two-sided significance level (alpha = 5%).

The intent-to-treat (ITT) population is synonymous with the safety analysis set and includes all patients who receive ≥1 dose of riociguat. The completers analysis set includes patients valid for ITT/safety who have an LPH score at visits 1, 3, 8, and 10. For statistical analysis with missing endpoint data, the last available observation will be carried forward. In the case of death in either the treatment period or the safety follow-up, a worst-case value will be used, for example, LPH 105, 6MWD 0 m, modified Borg dyspnea 10, and WHO FC 5 (one worse than the worst possible score if alive).

Changes from baseline in LPH to weeks 16 and 24 will be analyzed by a one-sample t-test and by summary statistics, including least-squares mean, standard error, and 95% CI. The Wilcoxon signed rank test will be applied as a sensitivity analysis, with the Shapiro-Wilk test for normality and a plot of residuals applied to investigate departures from normality. To allow for missing data following early termination or a missed assessment, a mixed models repeated measures analysis (M MMRM) will be applied to the change in LPH from baseline to weeks 4, 16, and 24 as a further sensitivity analysis. The model will include terms for random subject, fixed pooled center, baseline LPH as a covariate, and Week as a fixed categorical factor. An unstructured covariance matrix will be used; the derived last visit value will not be used in this analysis. A minimally clinically significant important difference (MCID) in the total LPH score is defined as an 11-point decrease. For physical and emotional dimensions, MCID is defined as a 4-point decrease. The percentage of subjects who achieve at least an 11-point decrease in total LPH within the 95% binomial CI will be presented.

3. Conclusions

The MOTION trial will provide information on the effect of riociguat on PROs in PAH patients in the United States who are not currently on active treatment. The primary endpoint measure, the LPH questionnaire, is a disease-specific measure designed to focus on issues most relevant to patients with PAH and, therefore, may be more sensitive to treatment changes than generic HRQoL measures. As healthcare decision makers also need to evaluate relative changes in patients’ health status across diseases and treatment interventions, a generic measure, such as SF-12, that tracks overall HRQoL is also useful. Information from WLQ-8 on the effect of PAH on worker task performance and productivity will help to address this gap in knowledge and shed light on the overall burden of disease associated with PAH.

Conflict of interest

Stephen C. Mathai, MD, MHS has served as a consultant for Actelion, Bayer HealthCare, and Gilead.

Omar Minai, MD has served as an advisor and speaker for Actelion, Bayer HealthCare, Gilead, and United Therapeutics.

Sean D. Sullivan, BScPharm, PhD has nothing to disclose.

Debra Lerner, MS, PhD has received personal fees from Bayer HealthCare and owns stock in Mylan.

Deborah Levine, MD has nothing to disclose.

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References


