Bayer HealthCare
Bayer Schering Pharma

Riociguat Clinical Trial Program

Riociguat (BAY 63-2521) is an oral agent being investigated as a new approach to treat chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH), two life-threatening types of pulmonary hypertension (PH). Riociguat is the first member of a novel class of therapeutics called soluble guanylate cyclase (sGC) stimulators.[1]

Riociguat showed promising results in phase II trials conducted in patients with CTEPH and PAH by significantly improving exercise capacity and hemodynamic parameters such as pulmonary vascular resistance, cardiac output and pulmonary arterial pressure compared to baseline values. The phase II data also indicated riociguat has a favorable safety profile.[2] Based on the positive phase II findings, Bayer Schering Pharma initiated two phase III trials investigating the efficacy, safety and duration of effect of riociguat for the treatment of inoperable CTEPH and PAH.

RIOCIGUAT PHASE III TRIAL PROGRAM

The phase III program consists of four trials, two per indication (one pivotal trial and one extension trial, respectively):

- **Ch**ronic Thrombo**e**mbolic Pulmonary Hypertension sGC-**S**timulator **T**rial (CHEST)
  The randomized, placebo-controlled pivotal trial CHEST-1 will investigate the efficacy and safety of riociguat in patients with inoperable CTEPH. The primary outcome measure after 16 weeks of treatment will be patient's exercise capacity, measured by the change from baseline in the six-minute walk test (6-MWT). All patients having completed CHEST-1 will be offered the option to enter the open label extension trial, CHEST-2, after the initial treatment duration of 16 weeks.

- **P**ulmonary **A**rterial Hyper**ten**sion sGC-Stimulator **T**rial (PATENT)
  The randomized, placebo-controlled pivotal trial PATENT-1 will investigate the efficacy and safety of riociguat in patients with PAH. The primary outcome measure after 12 weeks of treatment will be patient's exercise capacity, measured by the change from baseline in the 6-MWT. All patients having completed PATENT-1 will be offered the option to enter the open label extension trial, PATENT-2, after initial treatment duration of 12 weeks.

Objectives

The CHEST-1 trial assesses the efficacy and safety of oral riociguat in patients with inoperable CTEPH or recurrent or persisting PH after surgical treatment. The CHEST-2 trial investigates the sustainability of the efficacy results as well as longer-term safety aspects of riociguat for CTEPH patients.

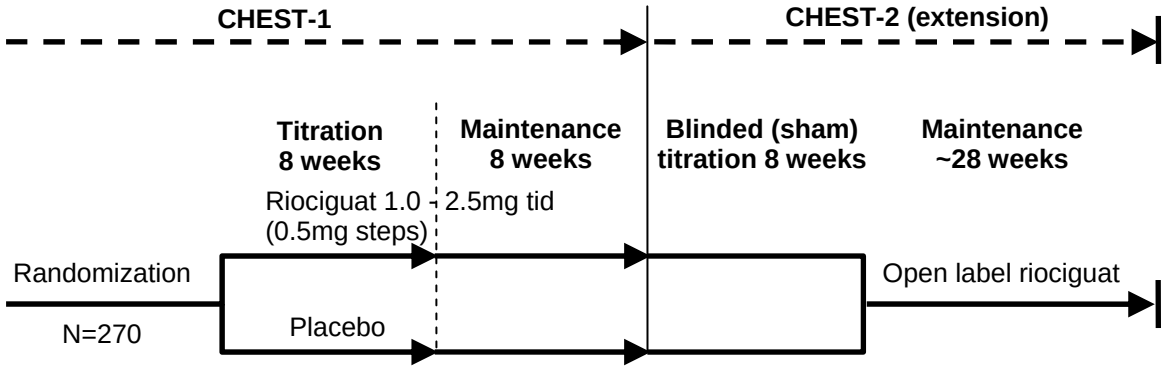
The PATENT-1 trial assesses the efficacy and safety of oral riociguat in patients with symptomatic PAH, either treatment naïve or pre-treated with an endothelin receptor antagonist or a prostacycline analogue. The PATENT-2 trial investigates the sustainability of the efficacy results as well as longer-term safety aspects of riociguat for PAH patients.

Designs

The phase III trials are multi-center studies. The study program includes a randomized, double-blind, placebo-controlled pivotal trial phase (CHEST-1 and PATENT-1), and an open-label extension trial phase (CHEST-2 and PATENT-2).

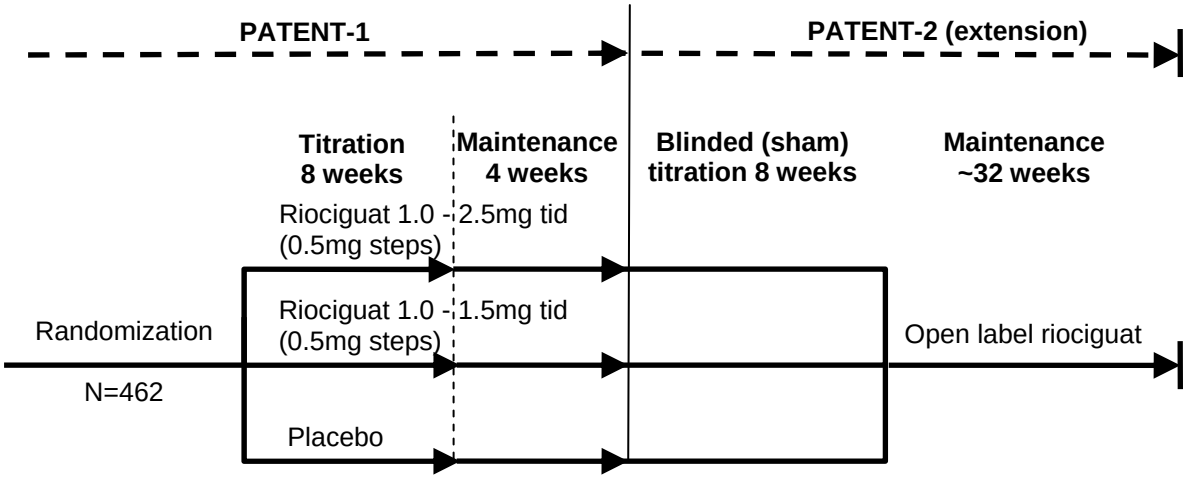
CHEST Study Design

In CHEST-1, inoperable CTEPH patients are randomised to receive either riociguat or placebo orally for 16 weeks. Those in the riociguat group are titrated, over a period of eight weeks and in 0.5 mg increments, to receive up to 1.5-2.5 mg riociguat three times a day (t.i.d.). After the titration phase, patients are followed for another eight weeks during the maintenance phase, to complete CHEST-1. Patients from both groups then have the option of participating in the 28-week open label extension study (CHEST-2), after completing an 8-week blinded (sham) titration (see diagram below).



PATENT Study Design

In PATENT-1, PAH patients are randomised to receive either placebo or two different doses of riociguat orally over a period of 12 weeks. As in CHEST-1, in PATENT-1, those patients receiving riociguat are titrated, over a period of eight weeks in 0.5 mg increments to receive up to either 1.5 mg or 2.5 mg three times daily (t.i.d.). Patients are then followed for another four weeks during the maintenance phase, to complete PATENT-1. Patients from all three groups then have the option of participating in the 32-week open label extension study (PATENT-2), after completing an eight-week blinded (sham) titration (see diagram below).



The primary outcome measure for both trials is a patient's exercise capacity, measured by the change from baseline in the 6-MWT. This is a standard test that measures the distance a patient can walk in six minutes (6-minute walking distance: 6-MWD), and has been used as a primary endpoint in previous pivotal clinical studies in patients with CTEPH and PAH. Secondary outcome measures include:

- Change from baseline in pulmonary vascular resistance (PVR)
- Change from baseline in WHO functional class
- Change from baseline in NT-pro BNP (N-terminal prohormone brain natriuretic peptide)
- Change from baseline in the Borg dyspnea scale
- Change from baseline in quality of life, measured by standard instruments called the EQ-5D and LPH-Q (Living with Pulmonary Hypertension Questionnaire)
- Time to clinical worsening
- Safety

Study Participants

CHEST-1 will include 270 patients with inoperable CTEPH or recurrent or persisting PH after surgical treatment. The principle investigator is Prof. Hossein Ardeschir Ghofrani from the University Lung Centre in Giessen, Germany. Recruitment began in February 2009 at the department of pneumology, Prof. Gert Höffken, University Dresden, Germany.

PATENT-1 will include 462 patients with PAH who are either treatment-naïve or are being treated with an endothelin receptor antagonist or a prostacyclin analogue. The principle investigator is Prof. Hossein Ardeschir Ghofrani from the University Lung Centre in Giessen, Germany. Recruitment began in December 2008 at the University Lung Centre, Giessen, Germany.

Study Results

The first results from CHEST-1 and PATENT-1 are expected in 2011. Data from both pivotal trials and the extension trials will be relevant for regulatory submission.

RIOCIGUAT PHASE II TRIAL

Objective

A phase II trial evaluated the safety and tolerability of riociguat in patients with CTEPH or PAH (primary objective), and the effects of riociguat on hemodynamics, exercise capacity and functional class (secondary objectives).

Design

In the multicenter, open-label, uncontrolled trial, oral riociguat was given three times daily for 12 weeks. Doses were titrated at 2-week intervals from 1.0 mg three times daily to a maximum of 2.5 mg three times daily, based on the low point of peripheral systolic blood pressure (SBP) and tolerability: the dose was increased, maintained, or decreased if SBP was greater than 100 mm Hg, 90-100 mm Hg, or less than 90 mm Hg, respectively. If SBP was less than 90 mm Hg and the patient showed symptoms of hypotension, riociguat was discontinued for 1 day, then restarted at a reduced dose.

Patients who completed the 12-week study were offered long-term treatment with riociguat.

Safety analyses were based on all patients who received at least one dose of riociguat. Adverse events, vital signs, ECGs and laboratory values were assessed every second week throughout the study. Clinical adverse events were graded by severity (mild, moderate or severe), and it was also noted whether or not they were serious. Hemodynamics, exercise capacity (6-MWT) and functional class (WHO) were also assessed.

Study Participants

The phase II trial included 75 adult patients aged 18–75 years (42 with CTEPH and 33 with PAH) in World Health Organization (WHO) functional class II or III. Patients also had to have a mean PVR > 300 dyn•s/cm^5, and a mean pulmonary arterial pressure (PAP) >25 mmHg. They were either treatment-naïve or were being treated with an endothelin receptor antagonist (bosentan) at baseline.

Study Results

Final findings from the phase II trial were presented at the American Thoracic Society (ATS) International Conference, 15-20 May 2009, in San Diego, California, USA. Key findings included:

Riociguat resulted in clinically relevant and significant improvements from baseline in walked distance in the 6-MWT that were evident as early as 14 days after initiating treatment in PAH and CTEPH patients. Similar improvements were found in treatment-naïve patients and patients also on an endothelin receptor antagonist (bosentan), at baseline.

Riociguat also resulted in strong and significant improvements in pulmonary hemodynamics, echocardiographic parameters, NT-proBNP levels, WHO functional class, Borg dyspnea score, and patient heart failure stage according to a standard functional classification system established by the New York Heart Association (NYHA).

Riociguat was well tolerated and had a favorable safety profile. Three patients discontinued riociguat because of adverse events. Only one serious adverse event (pulmonary edema in a patient with pulmonary venoocclusive disease (PVOD) occurred that was considered drug related. No drug-induced changes in laboratory parameters were observed.

Study Conclusions

The phase II study showed that riociguat is a promising new treatment with a favorable safety profile that can improve symptoms, exercise capacity and hemodynamics in patients with CTEPH and PAH. Based on the results of this phase II trial, the CHEST and PATENT phase III trial program of riociguat in CTEPH and PAH has been initiated.

Further phase II studies of riociguat are underway in patients suffering from other forms of PH such as PH in patients with interstitial lung disease (PH-ILD) or PH in patients with chronic obstructive pulmonary disease (PH-COPD). First results from these studies are expected in 2009 and 2011, respectively.

REFERENCES

[1] Ghofrani HA. Soluble guanylate cyclase stimulation: an emerging option in pulmonary hypertension therapy. Oral presentation at: the European Respiratory Society Congress, Berlin, Germany, October 4-8, 2008 (slide 4).

[2] Ghofrani HA, Hoeper MM, Halank M, Weimann G, Grimminger F. Riociguat treatment in patients with chronic thromboembolic pulmonary hypertension (CTEPH) or pulmonary arterial hypertension (PAH). Poster presentation at: the American Thoracic Society International Conference, 15-20 May 2009, San Diego, California, USA.