

News release for medical media and pharma trade press

American Thoracic Society (ATS) congress, San Diego:

Bayer Schering Pharma presents positive results of phase II study with Riociguat

San Diego, USA/ Newbury, Berkshire, 19th May, 2009 – Positive data from a phase II trial with Bayer Schering Pharma’s oral agent riociguat for the treatment of two different forms of pulmonary hypertension (PH); chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH); were presented today at the American Thoracic Society (ATS) international conference in San Diego, USA. Riociguat is an orally available soluble guanylate cyclase (sGC) stimulator, and is the first of these compounds to be developed in PH¹.

Results from the multi-center, open-label, uncontrolled phase II trial, showed that riociguat significantly improved exercise capacity from baseline values in patients with CTEPH and PAH¹. Riociguat also demonstrated significant effects on pulmonary hemodynamics and improvement of symptoms in patients with CTEPH and PAH¹.

“Bayer Schering Pharma aims to lead the way in advancing cardio-pulmonary research to address the significant unmet medical need for innovative treatment options in this field,” said Kemal Malik, M.D., Head of Global Development and member of the Executive Committee of Bayer HealthCare. The data presented at the ATS meeting serves to further reinforce our expectations for riociguat in patients with CTEPH and PAH,” he added.

“Pulmonary hypertension is a severe and life-threatening disease that progresses rapidly and, despite advances in patient care over the last few years, there is still a real need for more efficient therapies,” said lead investigator Prof. Hossein Ardeschir Ghofrani, Head of the Pulmonary Hypertension Division, Department of Internal Medicine, University of Giessen, Germany.” These findings are a positive step towards improving treatment options for PH patients – the majority of whom are currently still without viable treatment options. This could result in a significant enhancement in the care physicians currently offer their patients.”

The data presented at ATS follows an earlier presentation of positive topline phase II findings at the Annual Congress of the European Respiratory Society (ERS) in October 2008. Based on these data, randomised, placebo-controlled phase III trials in CTEPH (CHEST-1, followed by an open-label extension trial, CHEST-2) and PAH (PATENT-1, followed by an open-label extension trial, PATENT-2) were initiated in December 2008, with first results from the study programme currently expected in 2011. In addition to the CHEST and PATENT trials, further phase II studies of riociguat in patients suffering from other forms of PH, such as PH secondary to interstitial lung disease (PH-ILD), are ongoing. First results from the PH-ILD study are currently expected in 2009.²

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Contact for further information:

Sophia Cadman
Bayer Schering Pharma
Tel: +44 (0)1635 563235
Mobile: +44 (0)7908 486844
Email: sophia.cadman@bayerhealthcare.com

Note to Editors

About the Riociguat Phase II Study in CTEPH and PAH¹

The phase II trial for riociguat was a 12-week, multi-center, open-label, uncontrolled study conducted in 75 patients suffering from CTEPH or PAH. Riociguat was given orally three times daily for 12 weeks. Doses were titrated at two week intervals and patients who completed the study were offered long-term treatment with riociguat. Patients' exercise capacity was measured by the "six-minute walk test" (6-MWT), a standard test that has been used as a primary endpoint in previous pivotal clinical studies in patients with pulmonary hypertension (PH).

Riociguat resulted in clinically relevant improvements in walking distance from baseline in the 6-MWT that were evident as early as 14 days after initiating treatment. Significant improvements occurred in PAH and CTEPH patients. Similar improvements were found in treatment-naive patients and patients also on an endothelin receptor antagonist (bosentan), at baseline. In addition, riociguat exerted significant effects on pulmonary hemodynamics, echocardiographic parameters and N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels. Improvements were also observed in World Health Organization (WHO) functional class and Borg dyspnea score. The study also demonstrated that riociguat was generally well tolerated. Three

patients discontinued riociguat because of adverse events. Only one serious adverse event occurred that was considered drug related. This was the case of a patient that developed pulmonary edema, which was thought to be related to the unmasking of pulmonary venous occlusive disease (PVOD). There were no indications of drug-induced abnormalities in any of the laboratory parameters.

About the Riociguat Phase III Studies in CTEPH and PAH²

The riociguat phase III programme in CTEPH and PAH consists of two trials per indication (one pivotal trial and one extension trial, respectively):

Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial (CHEST):

The randomised, placebo-controlled pivotal trial, CHEST-1, investigates 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 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.

Pulmonary Arterial Hypertension sGC-Stimulator Trial (PATENT):

The randomised, placebo-controlled pivotal trial, PATENT-1, investigates 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.

Recruitment for CHEST-1 and PATENT-1 is ongoing and will involve the participation of four hospitals in the UK. The lead investigator of both trials is Prof. Hossein Ardeschir Ghofrani, Head of the Pulmonary Hypertension Division at the University of Giessen, Germany.

About Pulmonary Hypertension

Pulmonary Hypertension (PH) is a condition in which there is high blood pressure in the lung arteries. The arteries become narrow and there is less room for the blood to flow. Over time, some of the arteries may stiffen and become completely blocked. The narrowing of the pulmonary arteries causes the right side of heart to work harder to pump blood through the lungs. Eventually, the heart muscle weakens and loses its ability to pump enough blood for the body's needs. The extra stress causes the heart to enlarge and become less flexible. Heart failure is one of the most common causes of death in people who have PH.³

Patients with PH have a markedly decreased exercise tolerance and quality of life. There are no specific signs in patients with PH. Symptoms that suggest PH include shortness of breath with physical exercise (exertional dyspnea), decline of physical performance, fatigue and weakness. Pulmonary arterial hypertension is a devastating disease that harbors a poor prognosis. Without sufficient treatment, the natural course of the disease is characterised by a high mortality rate and limited survival.⁴

According to the current PH classification (Venice, 2003), there are five different forms of PH. These are; pulmonary arterial hypertension (PAH), pulmonary hypertension with left heart disease, pulmonary hypertension associated with lung disease and/or hypoxemia, pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH) and a miscellaneous category that encompasses all types of PH not defined by the aforementioned groups. The only approved therapies currently available are for PAH. These consist of three pharmacological classes: endothelin receptor antagonists; prostacyclin analogues and phosphodiesterase type 5 inhibitors.⁴

About Riociguat

Riociguat (BAY 63-2521) is an oral agent that is currently being investigated in phase III clinical trials as a potentially new approach to treating CTEPH and PAH, two life-threatening types of PH. Riociguat is an orally available soluble guanylate cyclase (sGC) stimulator, and is the first of these compounds to be developed in pulmonary hypertension (PH)¹.

It works through the same signaling pathway as the body's own vasodilating substance, nitric oxide (NO). NO relaxes the musculature in the blood-vessel walls, lowering the pulmonary blood pressure and relieving the heart by modulating the activity of the enzyme sGC.

Riociguat has a dual mode of action: it sensitises sGC to the body's own NO while also directly stimulating sGC independently of NO. This is very important because the NO levels in the pulmonary circulation are decreased in patients with PH. Directly stimulating sGC may avoid the limitations of therapies that involve the use of organic nitrates and other NO donors, such as non-specific interactions of NO with various biomolecules⁵.

About Bayer Schering Pharma

Bayer Schering Pharma is a worldwide leading specialty pharmaceutical company. Its research and business activities are focused on the following areas: Diagnostic Imaging, General Medicine, Oncology, Specialty Medicine and Women's Healthcare. With innovative products, Bayer

Schering Pharma aims for leading positions in specialised markets worldwide. Using new ideas, Bayer Schering Pharma aims to make a contribution to medical progress and strives to improve the quality of patients' lives.

Further information can be found at www.bayerscheringpharma.co.uk

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References

¹ HA Ghofrani MD, MM Hoepfer MD, M Halank MD, G Weimann MD, F Grimminger MD PhD presentation on behalf of the study group. Riociguat Treatment in Patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH) or Pulmonary Arterial Hypertension (PAH). American Thoracic Society (ATS) conference, San Diego, May 2009. Poster Presentation.

² Riociguat data on file, May 2009

³ World Health Organization. Chronic Respiratory Diseases: Pulmonary Hypertension. Link: http://www.who.int/respiratory/other/Pulmonary_hypertension/en/ (last accessed in May 2009).

⁴ S. Rosenkranz. Pulmonary Hypertension: Current Diagnosis and Treatment. *Clin. Res. Cardiol.* 2007, 96:527-541

⁵ Oleg V. Evgenov, Pál Pacher, Peter M. Schmidt, György Haskó, Harald H. H. W. Schmidt, Johannes-Peter Stasch. NO-independent Stimulators and Activators of Soluble Guanylate Cyclase: Discovery and Therapeutic Potential. *Nature Reviews Drug Discovery*. Vol. 5, Sept. 2006, p. 755 – 769.