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Investor News

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Bayer's Riociguat First Drug to Demonstrate Efficacy in Patients with Chronic Thromboembolic Pulmonary Hypertension

- Phase III CHEST-1 study met its primary endpoint, demonstrating a statistically significant improvement in the six-minute walk test (6MWT) in patients with inoperable or residual chronic thromboembolic pulmonary hypertension (CTEPH) treated with riociguat
- Riociguat was well tolerated with a good safety profile

Leverkusen, Germany, October 23, 2012 – Bayer HealthCare today announced positive data from the pivotal Phase III CHEST-1 trial, which investigated riociguat in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or with persistent or recurrent pulmonary hypertension after surgery. The results, presented as a late breaker at CHEST 2012, the annual meeting of the American College of Chest Physicians (ACCP) in Atlanta, USA, showed that the CHEST-1 study met its primary endpoint, demonstrating a statistically significant improvement in the six-minute walk test (6MWT). Patients treated with riociguat showed an improvement of 46 meters (95%-CI [25-67 meters] $p<0.0001$) from baseline after 16 weeks compared with placebo.[1]

In the CHEST-1 trial, riociguat also showed statistically significant improvements in secondary endpoints including pulmonary vascular resistance (PVR), N-terminal prohormone brain natriuretic peptide (NT-proBNP) and WHO functional class (FC). A positive trend was observed in time to clinical worsening (TTCW), Borg dyspnea score, European quality of life 5-dimensions questionnaire (EQ-5D) and living with pulmonary hypertension questionnaire (LPH).[1]

The study also showed that riociguat was well tolerated with a good safety profile in patients with CTEPH. The most frequent treatment emergent adverse events with riociguat were headache, dizziness, peripheral edema, and gastrointestinal symptoms such as dyspepsia and nausea.[1]

CTEPH is a life-threatening disease in which thromboembolic occlusion (blood clots) of the pulmonary vessels gradually lead to an increased pressure in the pulmonary arteries.[2] The recommended standard treatment is a surgical procedure known as pulmonary endarterectomy (PEA),[2] but it is estimated that only a quarter of all patients worldwide receive a surgical assessment. Furthermore, CTEPH is inoperable in an estimated 20 to 40 percent of patients, and in some cases the disease persists or reoccurs after surgery.[2] To date, no approved pharmacological therapy exists for CTEPH and, hence, there is an urgent unmet medical need for patients who are unable to undergo surgery, or who have persistent or recurrent PH after surgery.

“These study results with riociguat are encouraging because it is the first drug treatment which has demonstrated in a Phase III trial such improvements in inoperable CTEPH or in difficult to treat patients with persistent or recurrent pulmonary hypertension after surgery,” said Principal Investigator, Professor Ardeschir Ghofrani, University Hospital Giessen and Marburg, Germany. “The positive clinical results seen in people with both pulmonary arterial hypertension and CTEPH provide evidence that restoring the NO-sGC-cGMP pathway may prove to be central to successful PH management.”

“Riociguat is the first drug which has demonstrated efficacy in two potentially fatal pulmonary hypertension indications, namely CTEPH and pulmonary arterial hypertension,” said Kemal Malik, member of the Bayer HealthCare Executive Committee and Head of Global Development. “We plan to submit an application for marketing authorization during the first half of 2013 with the hope of bringing this new treatment option to patients as quickly as possible”.

About the CHEST Program

CHEST (**Ch**ronic Thrombo**e**mbolic Pulmonary Hypertension sGC-**S**timulator **T**rial) is a Phase III program to assess the efficacy and safety of oral riociguat in the treatment of patients with either inoperable chronic thromboembolic pulmonary hypertension or pulmonary hypertension which had persisted or reoccurred after pulmonary endarterectomy. CHEST is a multi-center, multi-national program with centers in 26 countries. The program included a randomized, double-blinded, placebo-controlled pivotal trial phase (CHEST-1) and an open label extension trial phase (CHEST-2).

CHEST-1

In the CHEST-1 study, 261 patients with inoperable CTEPH or with persistent or recurrent pulmonary hypertension after surgery were randomized and treated with either riociguat or placebo orally for 16 weeks. Riociguat was titrated, over a period of eight weeks in 0.5 mg increments, from 1.0 mg up to 2.5 mg, three times a day. After the titration phase, patients were followed up for another eight weeks to the completion of the study.

The CHEST-1 study met its primary endpoint by demonstrating a statistically significant improvement in the six-minute walk test (6MWT): Patients treated with riociguat showed an improvement of 46 meters (95%-CI [25-67 meters] p<0.0001) from baseline after 16 weeks compared with placebo. In the CHEST-1 trial, riociguat also showed statistically significant improvements in secondary endpoints including pulmonary vascular resistance (PVR) (p<0.0001), N-terminal prohormone brain natriuretic peptide (NT-proBNP) (p<0.0001) and WHO functional class (FC) (p=0.0026). A positive trend was observed in time to clinical worsening (TTCW) (p=0.1724)*, Borg dyspnea score (p=0.0035)*, European quality of life 5-dimensions questionnaire (EQ-5D) (p<0.0001)* and living with pulmonary hypertension questionnaire (LPH) (p=0.1220)*.[1]

The CHEST-1 study showed that riociguat was well tolerated with a good safety profile in patients with CTEPH.[1] The ten most frequently reported treatment emergent adverse events with riociguat vs. placebo were: headache (25% vs. 14%), dizziness (23% vs. 13%), peripheral edema (16% vs. 21%), cough (5% vs. 18%), dyspepsia (18% vs. 8%), nasopharyngitis (15% vs. 9%), dyspnea (5% vs. 14%), nausea (11% vs. 8%), diarrhea (10% vs. 5%) and vomiting (10% vs. 3%).[1]

* based on hierarchical testing: a sequential testing procedure was performed for the secondary efficacy variables, strictly in the order: PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg dyspnea score, EQ-5D, and LPH questionnaires.

CHEST-2

Following CHEST-1, patients from both arms then had the option of participating in the open label extension study (CHEST-2) after completing an eight-week blinded sham titration. CHEST-2 is investigating the sustainability of the efficacy results as well as longer-term safety aspects of riociguat for CTEPH patients. The results of CHEST-2 will be presented at an upcoming scientific congress in 2013.

About Pulmonary Hypertension

Pulmonary hypertension (PH) is a severe, progressive and life-threatening disorder in which the pressure in the pulmonary arteries is significantly increased and which can lead to heart failure and death.[3] Patients with PH develop a markedly decreased exercise tolerance and reduced quality of life.[4,5] The most common symptoms of PH include shortness of breath, fatigue, dizziness and fainting, all of which are worsened by exertion. As the symptoms of PH are non-specific, diagnosis can be delayed by as much as two years.[6] Early diagnosis is essential as a delay in treatment initiation can have a negative impact on survival.[7] Continuous treatment monitoring is then vital to ensure that patients are receiving optimal care for their particular type and stage of disease.[5]

According to the clinical classification of PH (Dana Point), there are five different types of PH based on underlying causes which are: pulmonary arterial hypertension (PAH), pulmonary hypertension owing to left heart disease (e.g. PH-LVD), pulmonary hypertension owing to lung disease and/or hypoxemia (e.g. PH-COPD or PH-ILD), chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary hypertension with unclear multifactorial mechanisms. Currently available pharmacological treatments are only approved to treat one of the five types of PH, pulmonary arterial hypertension.[5] As a result there is a strong need for more research to improve understanding of how all five types of PH can be treated effectively.[8]

About Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

CTEPH is a life-threatening disease in which thromboembolic occlusion (blood clots) of pulmonary vessels gradually lead to an increased pressure in the pulmonary arteries.[2] CTEPH may evolve after prior episodes of acute pulmonary embolism, but the pathogenesis is not yet completely understood.[9] The standard treatment for CTEPH is pulmonary endarterectomy (PEA), a surgical procedure in which the blood vessels of the lungs are cleared of clot and scar material.[2] However, a considerable number of patients with CTEPH are not operable and in some patients the disease persists or reoccurs after PEA.[2] Currently, there are no approved pharmacological treatments available for CTEPH.

About Riociguat

Riociguat (BAY 63-2521) is an oral agent being investigated as a new approach to treating different types of pulmonary hypertension. Riociguat is the first member of a novel class of compounds, the stimulators of soluble guanylate cyclase (sGC).[10] sGC is an enzyme found in the cardiopulmonary system. When nitric oxide (NO) binds to sGC, the enzyme catalyzes synthesis of the signaling molecule cyclic guanosine

monophosphate (cGMP). cGMP plays an important role in regulating vascular tone, proliferation, fibrosis, and inflammation.[10]

Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of NO and thus insufficient stimulation of the NO-sGC-cGMP pathway.[10] Riociguat is believed to have a dual mode of action: sensitizing sGC to endogenous NO and also directly stimulating sGC independent of NO.[11] With its novel mode of action, riociguat holds promise for PAH and other forms of PH, such as chronic thromboembolic pulmonary hypertension, where no pharmacological treatment is approved.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, agriculture and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of EUR 17.2 billion (2011), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover, develop, manufacture and market products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 55,700 employees (Dec 31, 2011) and is represented in more than 100 countries. More information at www.healthcare.bayer.com.

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[1] Ghofrani, HA. e*t al*. Riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension: a randomized, double-blind, placebo-controlled study (CHEST-1). ACCP 2012, Atlanta, USA. Oral abstract.

[2] Mayer, E. Surgical and post-operative treatment of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2010;19(115):64-67.

[3] Galiè, N *et al.* A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J* 2009;30:394-403.

[4] McKenna, S *et al*. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): A measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res.* 2006;15:103-115.

[5] Galiè, N *et al*. Guidelines for the diagnosis and treatment of pulmonary hypertension. Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009;30:2493-2537.

[6] Peacock, A. Treatment of Pulmonary Hypertension. *BMJ* 2003;326;853-836.

[7] Vachiéry J-L, Yerly P and Huez S. How to detect disease progression in pulmonary arterial hypertension. *Eur Respir Rev* 2012;21:123,40-47.

[8] Galiè, N *et al*. Pulmonary hypertension and pulmonary arterial hypertension: a clarification is needed. *Eur Respir J* 2010 Nov;36(5):986-90.

[9] Pengo *et al* Incidence of chronic thromboembolic pulmonary hypertension after PE, *New Engl J Med* 2004, 350, 2257-2264.

[10] Ghofrani, HA. *et al*. Riociguat for pulmonary hypertension. Furture Cardiol. 2010;6(10):155-166.

[11] Schermuly, R *et al*. Riociguat for the treatment of pulmonary hypertension. *Expert Opin Investig Drugs*. 2011 Apr;20(4):567-76.