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Investor News

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Bayer's Riociguat Meets Primary Endpoint in Pivotal Phase III Study in Patients with Pulmonary Arterial Hypertension

- Riociguat demonstrates a statistically significant improvement in the six-minute walk test (6MWT) in both treatment-naïve patients and in patients pre-treated with endothelin receptor antagonists (ERAs) or non-intravenous (non-iv) prostanoid monotherapy
- Riociguat was well tolerated with a good safety profile

Leverkusen, Germany, October 22, 2012 – Bayer HealthCare today announced positive data for riociguat from the pivotal Phase III study PATENT-1. The study met its primary endpoint by demonstrating a statistically significant improvement in the six-minute walk test (6MWT), a predictor of improved outcome in patients suffering from pulmonary arterial hypertension (PAH).[1,2] Patients treated with riociguat showed an improvement of 36 meters (95%-CI [20-52 meters] $p<0.0001$) from baseline after 12 weeks compared with placebo.[1] The data will be presented on October 23, 2012, in the late-breaking abstracts session at CHEST 2012, the annual meeting of the American College of Chest Physicians (ACCP) in Atlanta, USA.

Additionally, statistically significant improvements were observed across secondary endpoints, including pulmonary vascular resistance (PVR), N-terminal prohormone brain natriuretic peptide (NT-pro BNP), WHO functional class (FC), time to clinical worsening (TTCW) and Borg dyspnea score. A positive trend was observed in 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 as monotherapy or in combination with ERAs or non-iv prostanoid monotherapy in patients with PAH. The most frequent treatment emergent adverse events with riociguat were

headache, dizziness, peripheral edema, and gastrointestinal symptoms such as dyspepsia and nausea.

Pulmonary arterial hypertension is a severe, progressive and life-threatening disease, in which the pressure in the pulmonary arteries is significantly increased and which can lead to heart failure and death.[3] Despite the availability of several approved therapies, the prognosis for those who suffer from this disease remains poor.[3]

“The six-minute walk test is a key indicator for improved outcomes in patients with PAH and, therefore, the positive results of the PATENT-1 trial are encouraging,” said Professor Ardeschir Ghofrani, University Hospital Giessen and Marburg, Germany and Principal Investigator of the PATENT study. “The improvements were not limited to treatment naïve patients receiving riociguat monotherapy, but were also statistically significant for those who received combination treatment with an endothelin receptor antagonist or a non-iv prostanoid.”

“We are optimistic about the potential of riociguat to add a much needed treatment option for PAH,” said Kemal Malik, member of the Bayer HealthCare Executive Committee and Head of Global Development. “We look forward to working closely with regulatory authorities and healthcare professionals and plan to submit this novel treatment for marketing authorization during the first half of 2013.”

Riociguat is the first of a novel class of compounds, the stimulators of soluble guanylate cyclase (sGC). Riociguat restores the NO-sGC-cGMP (nitric oxide–sGC-cyclic guanosine monophosphate) pathway and leads to increased generation of cGMP, which plays an important role in regulating vascular tone, proliferation, fibrosis, and inflammation.[4] The ability of riociguat to directly stimulate sGC independent of NO while also increasing the sensitivity of sGC to NO is potentially important in PH.[5] Endothelial dysfunction associated with PH can be related to low levels of NO.[4]

“As PAH is associated with endothelial dysfunction, decreased NO levels and impaired sGC activity, this result with riociguat is a real step forward and gives us hope for a much-needed new treatment option for this serious and deadly disease,” said Professor Ardeschir Ghofrani.

About the PATENT Program

PATENT (**P**ulmonary **A**rterial Hyper**ten**sion sGC-Stimulator **T**rial) is a Phase III program to assess the efficacy and safety of oral riociguat in the treatment of treatment naïve and pre-treated patients with symptomatic PAH. PATENT is a multi-center, multi-national program with centers in 30 countries. The program included a randomized, double-blind, placebo-controlled pivotal trial phase (PATENT-1) and an open label extension trial phase (PATENT-2).

PATENT-1

In the PATENT-1 study, 443 patients with symptomatic PAH were randomized and treated with either placebo or two different doses of riociguat orally over a period of 12 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 daily, or up to 1.5 mg in an exploratory arm. After the titration phase, patients were followed up for an additional four weeks to the completion of the study.

PATENT-1 met its primary end point by demonstrating a statistically significant improvement in the six-minute walk test (6MWT): Patients treated with riociguat showed an improvement of 36 meters (95%-CI [20-52 meters] p<0.0001) from baseline after 12 weeks compared with placebo. The PATENT-1 study included both treatment-naïve patients and those pre-treated with ERAs or non-iv prostanoid monotherapy. A statistically significant improvement in exercise capacity, as measured by the 6MWT, was seen in both groups of patients treated with riociguat monotherapy (38 meters from baseline [95%-CI 15-62 meters]) and patients on combination treatment (36 meters from baseline [95%-CI 15-56 meters]).[1]

Statistically significant improvements were also observed across secondary endpoints including pulmonary vascular resistance (PVR) (p<0.0001), N-terminal prohormone brain natriuretic peptide (NT-pro BNP) (p<0.0001), WHO functional class (FC) (p=0.0033), time to clinical worsening (TTCW) (p=0.0046) and Borg dyspnea score (p=0.0022). A positive trend was observed in European quality of life 5-dimensions questionnaire (EQ-5D) (p=0.0660) and living with pulmonary hypertension questionnaire (LPH) (p=0.0019).[11] The questionnaires results are 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.

The PATENT-1 study showed that riociguat was well tolerated with a good safety profile as monotherapy or in combination with ERAs or non-iv prostanoid monotherapy in patients with PAH. The ten most frequently reported treatment emergent adverse events with riociguat vs. placebo were: headache (27% vs. 20%), dyspepsia (19% vs. 8%), peripheral edema (17% vs. 11%), nausea (16% vs. 13%), dizziness (16% vs. 12%), diarrhea (14% vs. 10%), nasopharyngitis (10% vs. 11%), dyspnea (6% vs. 11%), cough (5% vs. 10%) and vomiting (10% vs. 9%).[1]

PATENT-2

Following PATENT-1, patients then had the option of participating in the open label extension study (PATENT-2) after completing an eight-week blinded sham titration. PATENT-2 is investigating the sustainability of the efficacy results, as well as longer-term safety aspects of riociguat. The results of PATENT-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.[6,7] 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.[8] Early diagnosis is essential as a delay in treatment initiation can have a negative impact on survival.[9] Continuous treatment monitoring is then vital to ensure that patients are receiving optimal care for their particular type and stage of disease.[7]

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 for the treatment of one of the five types of PH, pulmonary arterial

hypertension (PAH).[7] 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.[10]

About Pulmonary Arterial Hypertension (PAH)

PAH, one of the five types of PH, is a rare but life-threatening disease in which the pressure in the pulmonary arteries is above normal.[11] PAH is characterized by morphological changes to the endothelium of the arteries of the lungs causing remodelling of the tissue, vasoconstriction and thrombosis-in-situ. As a result of these changes, the blood vessels in the lungs are narrowed making it difficult for the heart to pump blood through to the lungs. PAH affects an estimated 52 people per million globally.[12] It is more prevalent in younger women than men. In most cases PAH has no known cause and, in some cases, it can be inherited.[11]

Despite the availability of several approved therapies, the prognosis for patients with PAH remains poor.[3]

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).[4] 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.[4]

Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of NO and insufficient stimulation of the NO-sGC-cGMP pathway.[4] Riociguat is believed to have a dual mode of action: sensitizing sGC to endogenous NO and also directly stimulating sGC independent of NO.[5] 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.

Riociguat is currently under investigation for other types of pulmonary hypertension, including CTEPH. The CHEST study is a Phase III trial assessing the efficacy and safety of oral riociguat in patients with CTEPH, a disease for which there are currently no approved pharmacological therapies. Data from the first phase of the study, CHEST-1, will also be presented at the “Late Breaking Abstracts” session at the CHEST Congress.

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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