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Investor News

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Pulmonary Arterial Hypertension (PAH):

Start of Phase IIIb Study with Bayer's Riociguat in PAH Patients Who Demonstrate an Insufficient Response to PDE-5 Inhibitors

Leverkusen, Germany, March 13, 2014 – Bayer HealthCare announced today the enrolment of the first patient in an open-label, multicentre, multinational Phase IIIb pilot study, RESPITE (Riociguat clinical Effects Studied in Patients with Insufficient Treatment response to PDE-5 inhibitors). The RESPITE study is designed to evaluate the clinical effects of riociguat in patients with pulmonary arterial hypertension (PAH) who demonstrate an insufficient response to treatment with phosphodiesterase-5 inhibitors (PDE-5i) either as monotherapy or in combination with an endothelin receptor antagonist (ERA).

"A large proportion of PAH patients treated with PDE-5 inhibitors does not reach or maintain specific treatment goals," said Dr. Joerg Moeller, Member of the Bayer HealthCare Executive Committee and Head of Global Development. "The exact scientific reason for this insufficient response to treatment is still unknown. However, riociguat potentially has an advantage over PDE-5 inhibitors as the soluble guanylate cyclase (sGC) stimulator works independently from endogenous nitric oxide (NO) levels. The RESPITE study may provide the first clinical evidence on the potential clinical benefits of switching these PAH patients to riociguat."

In the pivotal Phase III clinical trial PATENT-1, riociguat was shown to be the first oral treatment with robust efficacy across multiple clinically relevant endpoints in patients with PAH, either as a monotherapy or in combination with ERA or prostacyclin analogue (PCA) therapies. So far no other oral drugs, including PDE-5 inhibitors, have been able to show this. To date, there is no clinical data available to inform physicians if replacement of PDE-5 inhibitors with riociguat is safe and if it is associated with clinically relevant improvements in patients who are not at treatment goal with PDE-5 inhibitors. In the RESPITE study, approximately 60 PAH patients pre-treated with either sildenafil or

tadalafil for at least three months, and who demonstrate an insufficient clinical response to PDE-5 inhibitor therapy (defined as WHO Functional Class (FC) III, a six-minute walk distance (6MWD) of between 165 and 440m and a cardiac index of <2.5 L/min/m^2) will be treated with riociguat for 24 weeks after a wash-out phase. Outcome variables being assessed in this exploratory study include changes in 6MWD, cardiac index, Quality of Life, WHO FC, clinical worsening, and other disease-related parameters as well as nitric oxide biomarkers. The results of RESPITE are intended to be used as the basis for further investigations.

“In many guidelines and for many regulatory bodies worldwide, PDE-5 inhibitors are currently an established therapy for patients with PAH in WHO Functional Class II and III, and for many patients, they are a well-tolerated and effective treatment option,” said Principal Investigator Professor Marius Hoeper, Hannover University Medical School, Germany. “However, there is still a substantial number of PAH patients who do not reach treatment goals while receiving PDE-5 inhibitors. The RESPITE study is designed as a first step to provide important data on the clinical effects of riociguat in this particular patient population.”

Riociguat offers a new mode of action for the treatment of pulmonary hypertension (PH) that is different from that of PDE5-inhibitors, ERAs and PCAs. While ERAs and PCAs are effective synergistic therapies in combination with riociguat as they act on different therapeutic targets, concomitant use of the sGC-stimulator and PDE-5 inhibitors has to be avoided and is contraindicated as this may have an additive effect on systemic blood pressure.

Riociguat was approved under the name Adempas in the US as the first and only drug for use in two forms of PH, chronic thromboembolic pulmonary hypertension (CTEPH) and PAH in October 2013. In Canada, the approvals for CTEPH and PAH followed in September 2013 and March 2014 respectively. In Switzerland and Japan, riociguat was approved in the CTEPH indication in November 2013, and in January 2014 respectively. In January 2014, the European Committee for Medicinal Products for Human Use (CHMP) recommended approval for riociguat in CTEPH and PAH, and in February 2014, the European Committee for Orphan Medicinal Products (COMP) confirmed the significant benefit of riociguat over existing treatments. In the opinion of the COMP, riociguat demonstrated a clinically relevant benefit for PAH patients in monotherapy and in combination, thereby confirming the orphan drug designation for riociguat.

About Pulmonary Hypertension

Pulmonary hypertension (PH) is a severe, progressive, life-changing and life-threatening disorder of the heart and lungs in which the blood pressure in the pulmonary arteries is above normal, and which can lead to heart failure and death. Patients with PH develop a markedly decreased exercise capacity and a reduced quality of life. 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. Early diagnosis and accurate identification of the PH type are essential as a delay in treatment initiation can have a negative impact on survival. Continuous treatment monitoring is then vital to ensure that patients are receiving optimal care for their particular type and stage of disease.

There are five different types of PH; each can affect the patient in a different way and every patient may have a different etiology and manifestation of PH. For the best chance of success patients need to be treated at a PH specialist center.

About Pulmonary Arterial Hypertension (PAH)

PAH, one of the five types of pulmonary hypertension (PH), is a progressive and life-threatening disease in which the blood pressure in the pulmonary arteries is significantly increased due to vasoconstriction and which can lead to heart failure and death. PAH is characterized by morphological changes to the endothelium of the artery of the lungs causing remodeling 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 is a rare disease and affects an estimated 15-52 people per million globally. It is more prevalent in women than men. In most cases, PAH has no known cause and, in some cases, it can be inherited.

In spite of several pharmacological treatment options for PAH having been available for over a decade, the prognosis for these patients has remained poor and so new treatment options are needed. Currently, mortality of PAH patients remains high and is still 15% at 1 year and 32% at 3 years after diagnosis.

About Riociguat

Riociguat is a soluble guanylate cyclase (sGC) stimulator, the first member of a novel class of compounds, discovered and developed by Bayer as an oral treatment to target a key molecular mechanism underlying PH. Riociguat is being investigated as a new and specific approach to treat different types of PH. sGC is an enzyme found in the

cardiopulmonary system and the receptor for nitric oxide (NO). When NO binds to sGC, the enzyme enhances synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). cGMP plays an important role in regulating vascular tone, proliferation, fibrosis, and inflammation.

PH is associated with endothelial dysfunction, impaired synthesis of NO and insufficient stimulation of sGC. Riociguat has a novel mode of action – it sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO. Riociguat, as a stimulator of sGC, addresses the issue of NO deficiency by restoring the NO-sGC-cGMP pathway, leading to increased generation of cGMP.

With its novel mode of action, riociguat has the potential to overcome a number of limitations of currently approved PAH therapies, including NO dependence, and is the first drug which has shown clinical benefits in CTEPH, where no pharmacological treatment is approved.

About Riociguat and PDE-5 inhibitors

Although riociguat and PDE-5 inhibitors both affect cGMP levels, riociguat as the stimulator of sGC increases the production of cGMP even in the absence of NO, while PDE-5 inhibitors can only prevent cGMP degradation. Consequently, depletion of NO which reduces cGMP production, may restrict the effectiveness of PDE-5 inhibitors, whereas riociguat is thought to continue to exert benefit despite NO deficiency.

Although riociguat and PDE-5 inhibitors influence cGMP through different modes of action, concomitant use of the sGC-stimulator and PDE-5 inhibitors has to be avoided as an additive effect on systemic blood pressure might be anticipated.

As ERAs and PCAs act on different therapeutic targets they should be effective synergistic therapies when used in combination with riociguat, as shown in the PATENT clinical trial program.

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 18.9 billion (2013), 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 56,000 employees (Dec 31, 2013) and is represented in more than 100 countries. More information is available at www.healthcare.bayer.com.

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