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Investor News

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Bayer Submits Riociguat for the Treatment of Pulmonary Arterial Hypertension in Japan

Leverkusen, Germany, April 23, 2014 – Bayer HealthCare has filed riociguat for the treatment of pulmonary arterial hypertension (PAH) for regulatory approval in Japan. PAH is a progressive and life-threatening form of pulmonary hypertension in which the blood pressure in the pulmonary arteries is significantly increased due to vasoconstriction and which can lead to heart failure and death. In January 2014, the MHLW in Japan had approved riociguat under the trade name Adempas® in another life-threatening form of pulmonary hypertension, namely chronic thromboembolic pulmonary hypertension (CTEPH).

“In the pivotal Phase III clinical trial, PAH patients who received riociguat observed rapid and significant improvements with regard to the severity of their disease and to their symptoms,” said Dr. Jörg Möller, Member of the Bayer HealthCare Executive Committee and Head of Global Development. “Moreover, these improvements were sustained over the long-term. Effective therapeutic options are needed in the treatment of a progressive disease where mortality remains high in spite of several drugs already available, so we hope to be able to bring riociguat to PAH patients and their treating physicians in Japan soon.”

Riociguat is the first oral treatment to show early, significant and sustained clinical efficacy in Phase III clinical trials across multiple clinically relevant endpoints in patients with PAH, either as a monotherapy or in combination with certain other medicines used to treat PAH, such as endothelin receptor antagonists (ERAs) or non-intravenous prostacyclin analogue (PCA) therapies. So far no other oral drugs, including PDE5-inhibitors, have been able to show this. Riociguat significantly improved the patient’s ability to walk farther, helping the heart and lungs work better and making breathing easier when performing everyday basic tasks. Consequently, PAH patients who received

riociguat observed reductions in disease severity and these improvements are sustained over long-term.

The submission of riociguat in PAH in Japan is based on results from the randomized, double-blind, placebo-controlled, global Phase III study PATENT-1 as well as long-term data from PATENT-2 available at the time. These assessed the efficacy and safety of oral riociguat in the treatment of PAH. The PATENT-1 study met its primary endpoint by demonstrating a statistically significant improvement ($p<0.0001$) from baseline in the six-minute walk test (6MWT), a marker of disease severity and predictor of survival, after 12 weeks compared with placebo. Additionally, statistically significant improvements were observed across a broad range of clinically relevant secondary endpoints, including WHO functional class (FC), time to clinical worsening (TTCW), Borg dyspnea score, haemodynamic parameters (cardiac output, pulmonary vascular resistance (PVR), mPAP) and a disease-related biomarker, N-terminal prohormone brain natriuretic peptide (NT-pro BNP), PATENT-1 included both treatment naïve symptomatic PAH patients and those pre-treated with ERAs or non-iv prostanoid. Results of the PATENT-1 study were published in the New England Journal of Medicine (NEJM) in July 2013.

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 Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

CTEPH is a progressive and life-threatening disease and a type of PH, in which it is believed that thromboembolic occlusion (organized blood clots) of pulmonary vessels gradually lead to an increased blood pressure in the pulmonary arteries, resulting in an overload of the right heart. CTEPH is a rare disease and is comparable in terms of population size to PAH, as it affects an estimated 8-40 people per million globally. CTEPH may evolve after prior episodes of acute pulmonary embolism, but the pathogenesis is not yet completely understood. The standard and potentially curative 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. However, a considerable number of patients with CTEPH (20%-40%) are not operable and in up to 35% of patients, the disease persists or reoccurs after PEA. These patients need an effective pharmacological treatment.

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 nitric oxide (NO) dependence, and is the first drug which has shown clinical benefits in CTEPH, where until the approval of riociguat no pharmacological treatment was available.

The riociguat development program across different forms of PH demonstrates Bayer's ongoing commitment to understanding this severe and life-threatening condition, with high unmet medical need, to improve the lives of people with PH.

Riociguat was approved under the name Adempas® in the US for use in 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 the EU, riociguat was approved by the European Medicines Agency (EMA) in March 2014 under the name Adempas® for use in CTEPH and PAH.

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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