News Release

Janssen Collaborates for Continued Evaluation of Multidrug-Resistant Tuberculosis Treatment Regimens with SIRTURO® (bedaquiline)

RARITAN, N.J., Nov. 6, 2014 /PRNewswire/ -- Janssen Research & Development, LLC (Janssen) today announced a collaboration with the International Union Against Tuberculosis and Lung Disease (The Union) to include SIRTURO® (bedaquiline) in the STREAM study. The STREAM study is an ongoing, multi-center international randomized controlled trial to evaluate a standardized treatment regimen of anti-tuberculosis drugs for patients with multidrug-resistant tuberculosis (MDR-TB).[i]

Janssen is working with The Union, the sponsor of the study, and the study's principal investigators from the United Kingdom Medical Research Council (MRC) on an amendment to their current protocol to include two bedaquiline-containing treatment arms to further assess safety and efficacy in adult patients with pulmonary MDR-TB and also to evaluate a new treatment regimen, including an all-oral option. The amendment, which will include the two bedaquiline-containing treatment arms, will be known as STREAM Stage 2. STREAM Stage 2 is part of the post-approval requirements for bedaquiline from both the United States (U.S.) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and is accepted by both health authorities as an alternative to the initially planned Phase 3 trial of SIRTURO®.

Bedaquiline is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (>/= 18 years) with pulmonary MDR-TB. Use of bedaquiline should be reserved for when an effective treatment regimen cannot otherwise be provided. Bedaquiline should be administered by directly observed therapy (DOT). The indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary MDR-TB. The safety and efficacy of bedaquiline for the treatment of drug-sensitive TB, latent infection due to *Mycobacterium tuberculosis* and for the treatment of infections caused by non-tuberculous mycobacteria (NTM) have not been established. In addition, there are no data on the treatment with bedaquiline of extrapulmonary TB (e.g., central nervous system). Therefore, use of bedaquiline in these settings is not recommended.

The U.S. prescribing information for bedaquiline includes Boxed Warnings regarding increased risk of death and occurrence of QT prolongation. The Warnings and Precautions section provides additional information regarding these risks and includes risk of hepatic-related adverse drug reactions, drug interactions, use in HIV-TB co-infected patients and treatment failure. The most common adverse drug reactions were nausea, arthralgia and headache. Additional adverse events include hemoptysis and chest pain. Please see Important Safety Information below for additional details.

STREAM opened for recruitment in July 2012, with Stage 1 results estimated in 2017. Details of the STREAM Stage 2 study protocol, which will include bedaquiline, are being finalized. The study sponsors are eager to begin STREAM Stage 2 and plan to begin immediately after all requisite approvals are in place. The Union, through a grant from The United States Agency for International Development (USAID), is currently funding STREAM Stage 1 with additional support from the UK MRC and the UK Department for International Development (DFID).

To date, SIRTURO® has received accelerated approval in the U.S., conditional approval in the European Union (E.U.), approval in South Korea, South Africa and the Philippines, and is registered in the Russian Federation through a partner for the Russian Federation and CIS countries, JSC Pharmstandard. Regulatory filings have been submitted in China, Colombia, India, Peru, Thailand and Vietnam. Janssen is prioritizing registration in high MDR-TB burden countries to facilitate access to bedaquiline as soon as possible.

INDICATIONS AND USAGE

SIRTURO® (bedaquiline) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (>/= 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO® for use when an effective treatment regimen cannot otherwise be provided. SIRTURO® should be administered by directly observed therapy (DOT).

This indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary MDR-TB.

Limitations of Use:

The safety and efficacy of SIRTURO® for the treatment of latent infection due to Mycobacterium tuberculosis have not been established. The safety and efficacy of SIRTURO® for the treatment of drug-sensitive TB have not been established. In addition, there are no data on the treatment with SIRTURO® of extra-pulmonary TB (e.g., central nervous system). The safety and efficacy of SIRTURO® for the treatment of infections caused by non-tuberculous mycobacteria (NTM) have not been established. Therefore, use of SIRTURO® in these settings is not recommended.

Important Safety Information

BOXED WARNINGS:

- **An increased risk of death was seen in the SIRTURO® treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO® when an effective treatment regimen cannot otherwise be provided.**
- **QT prolongation can occur with SIRTURO®. Use with drugs that prolong the QT interval may cause additive QT prolongation.**

Warnings and Precautions

Increased Mortality: An increased risk of death was seen in the SIRTURO® treatment group. The imbalance in deaths is unexplained.

QT Prolongation: SIRTURO® prolongs the QT interval. An electrocardiogram (ECG) should be obtained before initiation of treatment, and at least 2, 12, and 24 weeks after starting treatment with SIRTURO®. Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Discontinue SIRTURO® and all other QT prolonging drugs if the patient develops clinically significant ventricular arrhythmia or a QTcF interval of >500 ms (confirmed by repeat ECG).

The following may increase the risk for QT prolongation when patients are receiving SIRTURO®, and therefore ECGs should be monitored closely: use with other QT-prolonging drugs including fluoroquinolones and macrolide antibacterial drugs and the antimycobacterial drug, clofazimine; a history of Torsade de Pointes; a history of congenital long QT syndrome; a history of hypothyroidism and bradyarrhythmias; a history of uncompensated heart failure; serum calcium, magnesium, or potassium levels below the lower limits of normal.

SIRTURO® has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

Hepatic-related Adverse Drug Reactions: More hepatic-related adverse drug reactions were reported with the use of SIRTURO® plus other drugs to treat TB compared to other drugs used to treat TB without the addition of SIRTURO®. Alcohol and other hepatotoxic drugs should be avoided while on SIRTURO®, especially in patients with diminished hepatic reserve. Monitor symptoms and liver-related laboratory tests. Discontinue SIRTURO® if aminotransferase elevations are accompanied by total bilirubin elevation >2X ULN; aminotransferase elevations are >8x ULN; or aminotransferase elevations persist beyond 2 weeks.

Drug Interactions: Co-administration of strong systemic CYP3A4 inducers (e.g., rifamycins such as rifampin, rifapentine, and rifabutin) should be avoided. Co-administration with strong systemic CYP3A4 inhibitors for more than 14 consecutive days should be avoided. Appropriate clinical monitoring for SIRTURO®-related adverse reactions is recommended.

HIV-TB Co-infected Patients: There are no clinical data on the combined use of antiretroviral agents and SIRTURO® in HIV/MDR-TB co-infected patients, and only limited clinical data on the use in HIV/MDR-TB co-infected patients who were not receiving antiretroviral therapy.

Treatment Failure: SIRTURO® should be administered by directly observed therapy. SIRTURO® should only be administered in combination with at least 3 drugs active against the patient's TB isolate. Nonadherence to the treatment regimen could result in failure or resistance.

Adverse Reactions

The most common adverse drug reactions reported in greater than or equal to 10.0% of patients treated with SIRTURO® compared to the placebo treatment group were nausea (38.0% vs. 32.1%), arthralgia (32.9% vs. 22.2%), headache (27.8% vs. 12.3%), and additional adverse events reported in greater than or equal to 10.0% of patients and with a higher frequency than the placebo treatment group were hemoptysis (17.7% vs. 11.1%) and chest pain (11.4% vs. 7.4%).

Please see full Prescribing Information and Medication Guide for more details.

About Janssen Research & Development, LLC

At Janssen, we are dedicated to addressing and solving some of the most important unmet medical needs of our time in oncology, immunology, neuroscience, infectious diseases and vaccines, and cardiovascular and metabolic diseases. Driven by our commitment to patients, we develop innovative products, services and health care solutions to help people throughout the world. Janssen Research & Development, LLC is part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Please visit http://www.janssenrnd.com for more information.

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[i] Nunn AJ, Rusen ID, Deun AV, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. *Trials*. 2014;15:353.