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Siltuximab Pivotal Trial Data Show Efficacy for Treatment of Patients with Multicentric Castleman's Disease

Siltuximab regulatory filing granted priority review by the United States Food and Drug Administration

RARITAN, NJ, December 8, 2013 - Janssen Research & Development, LLC ("Janssen") today announced positive results from a pivotal Phase 2 global registration study (MCD2001) suggesting siltuximab, an investigational compound, along with best supportive care (BSC), exhibited statistically significant efficacy and a tolerable safety profile compared with placebo and BSC in treating patients with the rare disorder Multicentric Castleman's Disease (MCD) who are HIV-negative and human herpes virus-8 (HHV-8)-negative.[1] MCD is a disorder in which lymphocytes, a certain type of white blood cells, are over-produced and lead to enlargement of lymph nodes.[2,3]

These data supported the recent regulatory filings of siltuximab in the United States and European Union. Interim findings from a separate Phase 2 study (MCD2002) reinforce the safety profile of siltuximab.[4] The studies were featured in an oral presentation (MCD2001) and poster presentation (MCD2002) at the 55th American Society of Hematology (ASH) Annual Meeting in New Orleans, USA.

"MCD is a devastating disease that weakens the immune system and may lead to life-threatening infections," said Raymond S. Wong, MBChB, M.D., Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong and lead study investigator. "These results are encouraging and from my perspective support the potential for siltuximab as a new treatment for these patients who previously had no approved treatment options."

Oral Presentation
The MCD2001 study found more than one-third of patients in the siltuximab arm had a durable tumor and symptomatic response to treatment, compared to none of the patients who received placebo plus BSC (34 percent versus 0 percent). The median time to treatment failure was not reached for patients who received siltuximab plus BSC versus 134 days for who received placebo plus BSC. In looking at the response rate to treat MCD-related symptoms, 25 percent of patients who received siltuximab plus BSC had durable complete symptom resolution, defined as 100 percent of reduction of baseline overall symptom scores for at least 18 weeks, compared to none of the patients who received placebo plus BSC.[1]

The safety profile, defined by frequencies of treatment-emergent adverse events (AEs), Grade 3 or higher AEs and serious adverse events (SAEs), was similar between siltuximab and placebo even with the duration of treatment being twice as long for those in the siltuximab arm. The most frequently reported Grade 3 or higher AEs with siltuximab were fatigue (9 percent), night sweats (8 percent), hyperkalemia (high levels of potassium in blood), hyperuricemia (high levels of uric acid in blood), localized edema (swelling at a specific site in the body), hyperhidrosis (excessive sweating), neutropenia (an abnormally low number of neutrophils, a type of white blood cell), thrombocytopenia (a decrease of platelets in the blood), hypertension (high blood pressure), and weight increase (4 percent each).[1]

Poster Presentation
In addition, an interim analysis of the Phase 2 study MCD2002 was presented on December 7 in a poster titled:

- An Open-Label, Phase 2, Multicenter Study Of The Safety Of Long-Term Treatment With Siltuximab (an Anti-Interleukin-6 Monoclonal Antibody) In Patients With Multicentric Castleman's Disease (Abstract #1806)

This ongoing extension study assessed the safety of long-term treatment with siltuximab in 19 patients with MCD whose disease was controlled for an extended period of time in a Phase 1 study. At the time of study analysis (January 2013), the patients had been treated with siltuximab for up to 7.2 years (median of 5.1 years) with no cumulative toxicity observed. At the data cutoff for this interim analysis of the extension study, all patients were alive and maintaining disease control. Findings suggest prolonged siltuximab treatment exhibited a tolerable side effect profile.[4]

During a median treatment duration of 5.1 (range 3.4-7.2) years, the most commonly reported AEs included upper respiratory tract infection (89 percent); nausea (63 percent); vomiting (58 percent); diarrhea (53 percent); hypercholesterolemia (high levels of cholesterol in blood) (47 percent); hypertriglyceridemia (high levels of triglycerides in blood), pain in arms and legs, headache, rash and abnormal liver function (each 42 percent). However, the majority of them were low grade. Two patients had at least one serious infection during the Phase 1 study, and none were reported during the Phase 2 extension study.[4]

These abstracts were also published online in the December 6 supplemental volume of *Blood*.

MCD2001 Study Design[1]
MCD2001 is a Phase 2 multi-national, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of siltuximab plus best supportive care (BSC) versus placebo plus BSC in 79 patients with MCD who are HIV-negative and HHV-8-negative. MCD2001 is the first randomized study in MCD. Patients were randomized 2:1 to receive either siltuximab plus BSC or placebo plus BSC until protocol-defined treatment failure, after which patients taking the placebo could cross over to un-blinded siltuximab. Half of the patients on placebo (13 out of 26) crossed over to siltuximab.

The primary efficacy endpoint of the study was durable tumor and symptomatic response, defined as partial response or complete response (Cheson criteria) by independent radiological review, and improvement/stabilization in MCD-related symptoms for at least 18 weeks. Secondary endpoints included additional predefined efficacy measures and safety. The primary analysis occurred after the last treated patient completed assessments at 48 weeks.

Baseline MCD symptoms included fatigue (86 percent), malaise (61 percent), night sweats (52 percent), peripheral sensory neuropathy (nerve damage in the peripheral nervous system) (38 percent), anorexia and pruritus (itching) (37 percent each). Median treatment duration was 375 days with siltuximab versus 152 days with placebo, with 64 percent versus 27 percent completing 48 weeks of treatment, respectively.

About Multicentric Castleman's Disease (MCD)
MCD is a rare disorder with high morbidity in which lymphocytes, a certain type of white blood cells, are over-produced and lead to enlargement of lymph nodes.[2,3] MCD can also affect lymphoid tissue of internal organs, causing the liver, spleen, or other organs to enlarge.[5] Signs and symptoms are driven by dysregulated Interleukin-6 (IL-6) production.[1,6] Many common symptoms include fever, weakness, fatigue, night sweats, weight loss, loss of appetite, nausea, vomiting and nerve damage that leads to numbness and weakness.[3] Some symptoms can be life threatening.[7,8] Infections, renal failure, and malignancies including malignant lymphoma and Kaposi's sarcoma are common causes of death in patients with MCD.[7,8] Currently, there are no approved treatments in the U.S. or EU for MCD.

Unlike "unicentric" Castleman's disease, which is localized and affects only a single area or group of lymph nodes,[6] patients with MCD have more than one group of lymph nodes in different anatomical areas that are affected.[9] Unicentric disease can be treated by surgically removing the diseased lymph node,[10] while multicentric disease is usually much more difficult to treat.[11] Currently, the focus of care is to reduce lymph node masses and to attempt to put the disease in remission through a combination of treatments, including corticosteroids, chemotherapy and immunotherapy.[7,8] While such treatments may initially help, the disease often returns.

Castleman's disease is formally diagnosed through a biopsy.[5] The number of people diagnosed with Castleman's disease is unknown, but the disease is known to be rare.[12]

About Siltuximab
Siltuximab is an investigational, anti Interleukin-6 (IL-6) chimeric monoclonal antibody that targets and binds to human IL-6. IL-6 is a multifunctional cytokine produced by various cells such as T cells, B cells, monocytes, fibroblasts and endothelial cells. Dysregulated, or imbalanced, overproduction of IL-6 from activated B cells in affected lymph nodes has been implicated in the pathogenesis of MCD.[6] Information about ongoing studies with siltuximab can be found on clinicaltrials.gov.

On September 3, 2013, Janssen announced simultaneous submissions of a Biologic License Application (BLA) to the United States Food and Drug Administration (U.S. FDA) and a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for siltuximab for the treatment of patients with MCD who are HIV-negative and HHV-8-negative. The U.S. FDA accepted the submission and granted siltuximab priority review, and the EMA has granted Accelerated Assessment of the MAA for siltuximab. Siltuximab has been granted orphan drug status in MCD in the U.S. and EU. With the regulatory submissions, a Named Patient Program (NPP) was made available in the U.S. for siltuximab to provide pre-approval treatment access to eligible patients with MCD.

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 healthcare solutions to help people throughout the world.

In oncology, our goal is to fundamentally alter the way cancer is understood, diagnosed, and managed, reinforcing our

commitment to the patients who inspire us. In looking to find innovative ways to address the cancer challenge, our primary efforts focus on several treatment and prevention solutions. These include disease area strongholds that focus on hematologic malignancies and prostate cancer; cancer interception with the goal of developing products that interrupt the carcinogenic process; biomarkers that may help guide targeted, individualized use of our therapies; as well as safe and effective identification and treatment of early changes in the tumor microenvironment. While we continually strive to find new real-life solutions for cancer patients, the Janssen Pharmaceutical Companies can provide a broad offering throughout the cancer journey - from prevention, diagnosis, and treatment - to the return to wellness.

Janssen Research & Development is part of the Janssen Pharmaceutical Companies. Please visit http://www.janssenrnd.com for more information.

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