Jazz Pharmaceuticals Announces First Patient Enrolled in Phase 2 Clinical Trial Evaluating Defibrotide for the Prevention of CAR-T Associated Neurotoxicity

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DUBLIN, Oct. 10, 2019 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that the first patient has been enrolled in an exploratory Phase 2 clinical trial evaluating the ability of defibrotide to prevent neurotoxicity in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) receiving CAR T-cell therapy. The prospective, multicenter, open-label, single-arm study will evaluate the safety and efficacy of defibrotide in the prevention of CAR T-cell associated neurotoxicity in patients with relapsed or refractory DLBCL receiving axicabtagene ciloleucel.

"The introduction of CAR-T therapies to the oncology treatment landscape is groundbreaking but can be associated with serious complications such as neurotoxicity," said Robert Iannone, M.D., M.S.C.E., executive vice president, research and development of Jazz Pharmaceuticals. "At Jazz, we strive to improve outcomes for patients, and we are committed through our development program to explore the potential of defibrotide, including as a preventative treatment for neurotoxicity in patients receiving CAR-T therapy."

Patients may experience neurotoxicity after CD19 targeted CAR-T therapy,[1] and while the exact cause is unknown, research suggests that endothelial cell damage may play a role.[1,2] Some researchers hypothesize that the damage caused by cytokine release after CAR-T therapy may compromise the ability of endothelial cells to protect the central nervous system (CNS), causing neurotoxicity.[3] This study will explore whether defibrotide could help prevent CNS endothelial cell damage, thereby protecting the CNS and minimizing neurotoxicity.

This study will be conducted in two parts, with the first part evaluating the safety of a 2.5 mg/kg/dose and a 6.25 mg/kg/dose of defibrotide based on a standard 3+3 design. Part two will evaluate the safety and efficacy of defibrotide at the recommended dose for the prevention of CAR-T-associated neurotoxicity. The primary endpoint is the incidence of CAR-T-associated neurotoxicity (any grade, defined by Common Terminology Criteria for Adverse Events [CTCAE] v5.0) by CAR-T Day +30.

Approximately 35 eligible patients will be enrolled at six medical centers across the United States. Additional information about the trial, including eligibility criteria and a list of clinical trial sites, can be found at: https://clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT03954106).

About Defitelio® (defibrotide sodium)

In the U.S., Defitelio® (defibrotide sodium) injection 80mg/mL received U.S. FDA marketing approval on March 30, 2016 for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT) and is the first and only FDA-approved therapy for patients with this rare, potentially fatal complication. Defitelio is not approved for the treatment or prevention of CAR T-cell associated neurotoxicity. Defitelio is contraindicated in patients currently taking anticoagulants or fibrinolytics and in patients who are allergic to Defitelio or any of its ingredients. Defitelio may increase the risk of bleeding and should be withheld or stopped if significant bleeding occurs. Patients should be monitored for allergic reactions, especially if there is a history of previous exposure to Defitelio. The most common side effects of Defitelio are decreased blood pressure, diarrhea, vomiting, nausea and nose bleeds.

Please see full Prescribing Information for Defitelio.

In Europe, defibrotide is marketed under the name Defitelio® ▼ (defibrotide). In October 2013, the European Commission granted marketing authorization to Defitelio under exceptional circumstances for the treatment of severe VOD in patients undergoing HSCT therapy. It is the first and only approved treatment in Europe for severe VOD. In Europe, Defitelio is indicated in patients over one month of age. It is not indicated in patients with hypersensitivity to defibrotide or any of its excipients or with concomitant use of thrombolytic therapy.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system found under section 4.8 of the **SmPC**. (http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/002393/human_med_001646.jsp)

About CAR-T Associated Neurotoxicity

Chimeric antigen receptor (CAR) T-cell therapy is an emerging immunotherapy approach for the treatment of hematologic malignancies. [4] The two primary toxicities associated with CAR T-cell therapy include cytokine release syndrome (CRS) and neurotoxicity.[4] Many patients experience neurotoxicity after CD19 targeted CAR-T therapy,[1] and while the exact cause is unknown, research suggests that endothelial cell damage may play a role.[1,2] The damage caused by CAR-T therapy may compromise the ability of endothelial cells to protect the central nervous system (CNS), causing neurotoxicity.[3]

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (Nasdaq: JAZZ), a global biopharmaceutical company, is dedicated to developing life-changing medicines for people with limited or no options. As a leader in sleep medicine and with a growing hematology/oncology portfolio, Jazz has a diverse portfolio of products and product candidates in development, and is focused on transforming biopharmaceutical discoveries into novel medicines. Jazz Pharmaceuticals markets Sunosi® (solriamfetol), Xyrem® (sodium oxybate) oral solution, Defitelio® (defibrotide sodium), Erwinaze® (asparaginase *Erwinia chrysanthemi*) and Vyxeos® (daunorubicin and cytarabine) liposome for injection in the U.S. and markets Defitelio® (defibrotide), Erwinase® and Vyxeos® liposomal 44 mg/100 mg powder for concentrate for solution for infusion in countries outside the U.S. For country-specific product information, please visit www.jazzpharmaceuticals.com/medicines. For more information, please visit www.jazzpharmaceuticals.com and follow us on

Twitter at @JazzPharma.

References:

1. Gust J, Taraseviciute A and Turtle CJ. Neurotoxicity Associated with CD19-Targeted CAR-T Cell Therapies. CNS Drugs November 2018 (32) 1091–1101.

2. Santomasso BD, et al. Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia. Cancer Discov August 2018 (8) (8) 958-971.

3. Mackall C and Miklos D. CNS Endothelial Cell Activation Emerges as a Driver of CAR T Cell–Associated Neurotoxicity. Cancer Discov December 2017 (7) (12) 1371-1373.

4. Hunter BD and Jacobson CA. CAR T-Cell Associated Neurotoxicity: Mechanisms, Clinicopathologic Correlates, and Future Directions. JNCI: Journal of the National Cancer Institute July 2019 (111) (7) 646–654.

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