Jazz Pharmaceuticals Stops Enrollment in Phase 3 Study Evaluating Defibrotide for the Prevention of Veno-Occlusive Disease

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DUBLIN, April 29, 2020 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that enrollment in the Phase 3 clinical study of defibrotide for the prevention of hepatic veno-occlusive disease (VOD) post-hematopoietic stem-cell transplantation (HSCT) in high-risk or very high-risk patients is being discontinued. Enrollment in the study was stopped early based on the recommendation from an Independent Data Monitoring Committee (IDMC), which concluded it would be highly unlikely to reach statistical significance for the primary endpoint of VOD-free survival at Day +30 post-HSCT in the final analysis if the study were to complete enrollment.

The IDMC recommendation was made after completion of a pre-planned interim analysis of the first 280 patients and where the study met the protocol-specified futility criteria. The study was conducted as part of a post-marketing requirement related to safety. The IDMC conducted multiple periodic safety analyses during the study and reported no new safety concerns.

"We are disappointed with this outcome, but wish to thank the patients and physicians involved in the program for their participation in the study," said Robert Iannone, M.D., M.S.C.E., executive vice president, research and development of Jazz Pharmaceuticals. "While enrollment has been discontinued, the trial will run to completion through the follow-up of the more than 370 patients enrolled. VOD is a rapidly progressive and devastating condition that can develop following stem-cell transplantation. As the only approved treatment with demonstrated efficacy based on survival at 100 days after HSCT, defibrotide is an important medicine for this patient population."

Jazz has notified relevant health authorities and study investigators of the decision to discontinue new enrollment to the study. Patients enrolled in the study will be allowed to continue participation if they and the investigator determine this would be in the patient's best interest. Patients will continue to be followed per protocol. The full data will be submitted to a future medical meeting for presentation.

This Phase 3 trial was not designed to further evaluate defibrotide for the treatment of VOD and does not impact the approved indication or other ongoing clinical studies. Defitelio® (defibrotide sodium) remains the only treatment approved for the treatment of adult and pediatric patients with hepatic VOD, also known as sinusoidal obstruction syndrome, with renal or pulmonary dysfunction following HSCT. Defibrotide is currently being investigated in two Phase 2 company-sponsored studies for the prevention of acute Graft-versus-Host-Disease and the prevention of neurotoxicity in patients with relapsed or refractory diffuse large B-cell lymphoma receiving CAR T-cell therapy.

About the Phase 3 Clinical Program
The Phase 3 study was a randomized, open-label, multi-center trial with an adaptive design comparing the efficacy of defibrotide versus best supportive care in the prevention of hepatic VOD, with a provision for patients enrolled on the control arm to receive treatment doses of defibrotide upon development of VOD. The study was initiated on the basis of prior studies suggesting there is a benefit to defibrotide in preventing VOD, the largest of which was a randomized trial in 356 pediatric patients.[1] The study was expected to enroll approximately 400 adult and pediatric patients undergoing HSCT who are at high risk or very high risk of developing VOD with the potential to increase to 600 patients based on an adaptive design. High-risk or very high-risk patients are identified based on the regimen required to prepare them for HSCT, as well as their prior medical history and concomitant disease. The adaptive design allowed for an interim analysis with pre-defined stopping points for early success or futility as well as the option to increase enrollment up to a maximum of 600 patients if needed to preserve the statistical power of the study.

For patients randomized to receive defibrotide prophylaxis, defibrotide was administered starting within 24 hours before the start of the conditioning regimen for a recommended minimum of 21 days and ending no later than Day +30 post HSCT.

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, 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. In 2016 the U.S. Centers for Medicare and Medicaid Services granted a New Technology Add-on Payment for Defitelio and it is included in the National Comprehensive Cancer Network guidelines for chemotherapy induced VOD. Defitelio is not approved for the prevention of VOD. 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 U.S. Prescribing Information for Defitelio.

In Europe, defibrotide is marketed under the name Defitelio® ▼ (defibrotide). In October 2013, the European Medicines Agency (EMA) 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 patients over one month of age. Defitelio is contraindicated 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 VOD

HSCT is an aggressive, potentially curative procedure to treat patients with malignant and non-cancerous hematologic disorders such as leukemia, lymphoma and aplastic anemia, and congenital immunodeficiency and autoimmune disorders.[2] VOD is a rare complication of HSCT, which occurs in approximately 9-14% of HSCT patients.[3,4] Hepatic VOD, also known as sinusoidal obstruction syndrome, is an early and potentially life-threatening complication affecting the sinusoidal endothelial cells of the liver, which can typically occur within the first 21 days following HSCT.[5,6] Hepatic VOD progresses to multi-organ dysfunction in approximately 30-50% of cases.[6] VOD with multi-organ dysfunction (MOD) is associated with an overall mortality (death) rate of 84%.[4] MOD is characterized by the presence of renal or pulmonary dysfunction.[7,8] VOD is often characterized by sudden weight gain, hepatomegaly (abnormally enlarged liver), and elevated bilirubin.[7,8]

About Jazz Pharmaceuticals plc
Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharmaceutical company dedicated to developing life-changing medicines for people with serious diseases — often with limited or no options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in key therapeutic areas. Our focus is in neuroscience, including sleep medicine and movement disorders, and in oncology, including hematologic and solid tumors. We actively explore new options for patients including novel compounds, small molecule advancements, biologics and innovative delivery technologies. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in more than 90 countries. For more information, please visit www.jazzpharmaceuticals.com and follow @JazzPharma on Twitter.

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References:

1. Corbacioglu, S. et al. (2012). Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. Lancet (London, England), [online] 379(9823), pp.1301–1309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22364685 [Accessed 29 Apr. 2020].
2. Defitelio (defibrotide sodium) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals; March 30, 2016.
3. Ikehara S. New strategies for BMT and organ transplantation. Int J Hematol. 2002;76(Suppl 1):161-4.
4. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010;16(2):157-168.
5. Tsirigotis PD, Resnick IB, Avni B, et al. Incidence and risk factors for moderate-to-severe veno-occlusive disease of the liver after allogeneic stem cell transplantation using a reduced intensity conditioning regimen. Bone Marrow Transplant. 2014;49(11):1389-1392.
6. Carreras E, Díaz-Beyá M, Rosiñol L, et al. The incidence of veno-occlusive disease following allogeneic hematopoietic stem cell transplantation has diminished and the outcome improved over the last decade. Biol Blood Marrow Transplant. 2011;17(11):1713-1720.
7. Carreras E. How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. Brit J Haematol. 2015 Feb.; 168 (4); 481-91.
8. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2015;50(6):781-789.

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