Jazz Pharmaceuticals Announces U.S. FDA Approval of Rylaze™ (asparaginase erwinia chrysanthemi (recombinant)-rywn) for the Treatment of Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

July 1, 2021

Approval under U.S. FDA's Real-Time Oncology Review program represents an important therapeutic advance for pediatric and adult patients who develop hypersensitivity to E. coli-derived asparaginase treatments

Rylaze is expected to become commercially available in the U.S. in mid-July

Company to host investor webcast in July; details to follow

DUBLIN, June 30, 2021 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced the U.S. Food and Drug Administration (FDA) approval of Rylaze ™ (asparaginase erwinia chrysanthemi (recombinant)-rywn) for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) in pediatric and adult patients one month and older who have developed hypersensitivity to *E. coli*-derived asparaginase.[1] *Rylaze* is the only recombinant erwinia asparaginase manufactured product that maintains a clinically meaningful level of asparaginase activity throughout the entire duration of treatment, and it was developed by Jazz to address the needs of patients and healthcare providers with an innovative, high-quality erwinia-derived asparaginase with reliable supply.

"We are excited to bring this important new treatment to patients who are in critical need, and we are grateful to FDA for the approval of *Rylaze* based on its established safety and efficacy profile. We are pleased *Rylaze* was approved before the trial is complete and are diligently working to advance additional clinical trial data. We are committed to quickly engaging with FDA to evolve the *Rylaze* product profile with additional dosing options and an IV route of administration," said Bruce Cozadd, chairman and CEO of Jazz Pharmaceuticals. "Thank you to our collaborators within the Children's Oncology Group, the clinical trial investigators, patients and their families, and all of the other stakeholders who helped us achieve this significant milestone."

Rylaze was granted orphan drug designation for the treatment of ALL/LBL by FDA in June 2021. The Biologics Licensing Application (BLA) approval followed review under the Real-Time Oncology Review (RTOR) program, an initiative of FDA's Oncology Center of Excellence designed for efficient delivery of safe and effective cancer treatments to patients.

The company expects *Rylaze* will be commercially available in mid-July.

"The accelerated development and approval of *Rylaze* marks an important step in bringing a meaningful new treatment option for many ALL patients – most of whom are children – who cannot tolerate *E. coli*-derived asparaginase medicine," said Dr. Luke Maese, assistant professor at the University of Utah, Primary Children's Hospital and Huntsman Cancer Institute. "Before the approval of *Rylaze,* there was a significant need for an effective asparaginase medicine that would allow patients to start and complete their prescribed treatment program with confidence in supply."

Recent data from a Children's Oncology Group retrospective analysis of over 8,000 patients found that patients who did not receive a full course of asparaginase treatment due to associated toxicity had significantly lower survival outcomes – regardless of whether those patients were high risk or standard risk, slow early responders.[2]

About Study JZP458-201

The FDA approval of *Rylaze*, also known as JZP458, is based on clinical data from an ongoing pivotal Phase 2/3 single-arm, open-label, multicenter, dose confirmation study evaluating pediatric and adult patients with ALL or LBL who have had an allergic reaction to *E. coli*-derived asparaginases and have not previously received asparaginase erwinia chrysanthemi. The study was designed to assess the safety, tolerability and efficacy of JZP458.

The determination of efficacy was measured by serum asparaginase activity (SAA) levels. The Phase 2/3 study is being conducted in two parts. The first part is investigating the intramuscular (IM) route of administration, including a Monday-Wednesday-Friday dosing schedule. The second part remains active to further confirm the dose and schedule for the intravenous (IV) route of administration.

The FDA approval of *Rylaze* was based on data from the first of three IM cohorts, which demonstrated the achievement and maintenance of nadir serum asparaginase activity (NSAA) greater than or equal to the level of 0.1 U/mL at 48 hours using IM doses of *Rylaze* 25 mg/m^2. The results of modeling and simulations showed that for a dosage of 25 mg/m^2 administered intramuscularly every 48 hours, the proportion of patients maintaining NSAA ≥ 0.1 U/mL at 48 hours after a dose of *Rylaze* was 93.6% (95% CI: 92.6%, 94.6%).[1]

The most common adverse reactions (incidence >15%) were abnormal liver test, nausea, musculoskeletal pain, fatigue, infection, headache, pyrexia, drug hypersensitivity, febrile neutropenia, decreased appetite, stomatitis, bleeding and hyperglycemia. In patients treated with the *Rylaze*, a fatal adverse reaction (infection) occurred in one patient and serious adverse reactions occurred in 55% of patients. The most frequent serious adverse reactions (in ≥5% of patients) were febrile neutropenia, dehydration, pyrexia, stomatitis, diarrhea, drug hypersensitivity, infection, nausea and viral infection. Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received *Rylaze*. Adverse reactions resulting in permanent discontinuation included hypersensitivity (6%) and infection (3%).[1]

The company will continue to work with FDA and plans to submit additional data from a completed cohort of patients evaluating 25mg/m^2 IM given on Monday and Wednesday, and 50 mg/m^2 given on Friday in support of a M/W/F dosing schedule. Part 2 of the study is evaluating IV administration and is ongoing. The company also plans to submit these data for presentation at a future medical meeting.

Investor Webcast
The company will host an investor webcast on the *Rylaze* approval in July. Details will be announced separately.

About Rylaze ™ (asparaginase erwinia chrysanthemi (recombinant)-rywn)
Rylaze, also known as JZP458, is approved in the U.S. for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL) in pediatric and adult patients one month and older who have developed hypersensitivity to *E. coli*-derived asparaginase. *Rylaze* has orphan drug designation for the treatment of ALL/LBL in the United States. *Rylaze* is a recombinant erwinia asparaginase that uses a novel *Pseudomonas fluorescens* expression platform. JZP458 was granted Fast Track designation by the U.S. Food and Drug Administration (FDA) in October 2019 for the treatment of this patient population. *Rylaze* was approved as part of the Real-Time Oncology Review program, an initiative of the FDA's Oncology Center of Excellence designed for efficient delivery of safe and effective cancer treatments to patients.

The full U.S. Prescribing Information for *Rylaze* is available at: **<http://pp.jazzpharma.com/pi/rylaze.en.USPI.pdf>**

Important Safety Information

RYLAZE should not be given to people who have had:

- Serious allergic reactions to RYLAZE
- Serious swelling of the pancreas (stomach pain), serious blood clots, or serious bleeding during previous asparaginase treatment

RYLAZE may cause serious side effects, including:

- Allergic reactions (a feeling of tightness in your throat, unusual swelling/redness in your throat and/or tongue, or trouble breathing), some of which may be life-threatening
- Swelling of the pancreas (stomach pain)
- Blood clots (may have a headache or pain in leg, arm, or chest)
- Bleeding
- Liver problems

Contact your doctor immediately if any of these side effects occur.

Some of the most common side effects with RYLAZE include: liver problems, nausea, bone and muscle pain, tiredness, infection, headache, fever, allergic reactions, fever with low white blood cell count, decreased appetite, mouth swelling (sometimes with sores), bleeding, and too much sugar in the blood.

RYLAZE can harm your unborn baby. Inform your doctor if you are pregnant, planning to become pregnant, or nursing. Females of reproductive potential should use effective contraception (other than oral contraceptives) during treatment and for 3 months following the final dose. Do not breastfeed while receiving RYLAZE and for 1 week after the final dose.

Tell your healthcare provider if there are any side effects that are bothersome or that do not go away.

These are not all the possible side effects of RYLAZE. For more information, ask your healthcare provider.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088 (1-800-332-1088).

About ALL
ALL is a cancer of the blood and bone marrow that can progress quickly if not treated.[3] Leukemia is the most common cancer in children, and about three out of four of these cases are ALL.[4] Although it is one of the most common cancers in children, ALL is among the most curable of the pediatric malignancies due to recent advancements in treatment.[5,6] Adults can also develop ALL, and about four of every 10 cases of ALL diagnosed are in

adults.[7] The American Cancer Society estimates that almost 6,000 new cases of ALL will be diagnosed in the United States in 2021.[7] Asparaginase is a core component of multi-agent chemotherapeutic regimens in ALL.[8] However, asparaginase treatments derived from *E. coli* are associated with the potential for development of hypersensitivity reactions.[9]

About Lymphoblastic Lymphoma

LBL is a rare, fast-growing, aggressive subtype of Non-Hodgkin's lymphoma, most often seen in teenagers and young adults.[8] LBL is a very aggressive lymphoma – also called high-grade lymphoma – which means the lymphoma grows quickly with early spread to different parts of the body.[10,11]

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (NASDAQ: JAZZ) is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases – often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. We actively explore new options for patients including novel compounds, small molecules and biologics, and through cannabinoid science and innovative delivery technologies. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in nearly 75 countries. For more information, please visit www.jazzpharmaceuticals.com and follow @JazzPharma on Twitter.

About The Children's Oncology Group (COG)

COG (childrensoncologygroup.org), a member of the NCI National Clinical Trials Network (NCTN), is the world's largest organization devoted exclusively to childhood and adolescent cancer research. COG unites over 10,000 experts in childhood cancer at more than 200 leading children's hospitals, universities, and cancer centers across North America, Australia, and New Zealand in the fight against childhood cancer. Today, more than 90% of the 14,000 children and adolescents diagnosed with cancer each year in the United States are cared for at COG member institutions. Research performed by COG institutions over the past 50 years has transformed childhood cancer from a virtually incurable disease to one with a combined 5-year survival rate of 80%. COG's mission is to improve the cure rate and outcomes for all children with cancer.

Caution Concerning Forward-Looking Statements

This press release contains forward-looking statements, including, but not limited to, statements related to Jazz Pharmaceuticals' belief in the potential of *Rylaze* to provide a reliable therapeutic option for adult and pediatric patients to maximize their chance for a cure, plans for a mid-July 2021 launch of *Rylaze*, the availability of a reliable supply of *Rylaze* and other statements that are not historical facts. These forward-looking statements are based on Jazz Pharmaceuticals' current plans, objectives, estimates, expectations and intentions and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, effectively launching and commercializing new products; obtaining and maintaining adequate coverage and reimbursement for the company's products; delays or problems in the supply or manufacture of the company's products and other risks and uncertainties affecting the company, including those described from time to time under the caption "Risk Factors" and elsewhere in Jazz Pharmaceuticals' Securities and Exchange Commission filings and reports (Commission File No. 001-33500), including Jazz Pharmaceuticals' Annual Report on Form 10-K for the year ended December 31, 2020 and future filings and reports by Jazz Pharmaceuticals. Other risks and uncertainties of which Jazz Pharmaceuticals is not currently aware may also affect Jazz Pharmaceuticals' forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. The forward-looking statements herein are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by Jazz Pharmaceuticals on its website or otherwise. Jazz Pharmaceuticals undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.

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