Jazz Pharmaceuticals Presents Positive Interim Phase 2/3 Results of Rylaze™ (asparaginase erwinia chrysanthemi (recombinant)-rywn) in Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma at ASH 2021 Annual Meeting

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Rylaze maintains clinically meaningful level of asparaginase activity throughout the entire duration of treatment
Initial observed and modeled data showed that ≥90% of patients achieved nadir serum asparaginase activity levels ≥0.1 IU/mL at both 48 and 72 hours when receiving 25 mg/m2 on Monday/Wednesday and 50 mg/m2 on Friday
Data will support the supplemental Biologics Licensing Application in early 2022 to be reviewed under the U.S. FDA's Real-Time Oncology Review program

DUBLIN, Dec. 12, 2021 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced initial positive results from a Phase 2/3 trial of intramuscular (IM) administration of Rylaze™ (asparaginase erwinia chrysanthemi (recombinant)-rywn) in adult and pediatric patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) who have developed hypersensitivity or silent inactivation to an *E. coli*-derived asparaginase. The study was developed and conducted in close collaboration with the Children's Oncology Group (COG). These initial results will be presented for the first time today at the 63rd American Society of Hematology (ASH) Annual Meeting.

Three cohorts with unique, IM administration dosing schedules were evaluated in the trial, demonstrating a safety profile consistent with other asparaginases. In Cohort 1c, a dosing regimen of *Rylaze* administered 25 mg/m^2 on Monday and Wednesday and 50 mg/m^2 on Friday demonstrated a positive benefit-to-risk profile, showing that *Rylaze* maintains a clinically meaningful level of nadir serum asparaginase activity (NSAA) ≥0.1 IU/mL at both 48 and 72 hours. *Rylaze* was approved by the U.S. Food and Drug Administration (FDA) on June 30, 2021 under the Real-Time Oncology Review (RTOR) program for use as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL or LBL in adult and pediatric patients one month and older who have developed hypersensitivity to *E. coli*-derived asparaginase. *Rylaze* was approved at the dosing schedule of 25 mg/m^2 every 48 hours based on data from Cohort 1a, in conjunction with data produced by a preliminary population pharmacokinetic (PPK) model.

These data will support additional regulatory filings for *Rylaze*, including a supplemental Biologics Licensing Application (sBLA) in early 2022 for a Monday/Wednesday/Friday (M/W/F) IM dosing schedule that will be reviewed under the FDA RTOR program. These data will also support regulatory submissions in Europe in mid-2022, with potential for approval in 2023.

"Asparaginase is an integral part of ALL therapy that is associated with improvement in survival rates. Following FDA approval earlier this year, *Rylaze* is already providing patients who have developed hypersensitivity to *E. coli*-derived asparaginase with a much-needed, effective therapeutic option with reliable supply and consistently high quality," said Rob Iannone, M.D., M.S.C.E., executive vice president, research and development and chief medical officer of Jazz Pharmaceuticals. "Rylaze is proof of Jazz's ability to take medicines from concept through development, approval and launch, and we look forward to working with the FDA through the sBLA submission with these additional data in early 2022 in support of a label expansion for M/W/F dosing."

"The results from the Phase 2/3 study for *Rylaze* help to expand our knowledge of its dosing and safety profile, and support Monday/Wednesday /Friday dosing, which is more in line with clinical practice," said primary study investigator Dr. Luke Maese, associate professor at the University of Utah, Primary Children's Hospital and Huntsman Cancer Institute. "The accelerated development and approval of *Rylaze* ensured that many patients with LBL and ALL – most of whom are children – who cannot tolerate *E. coli*-derived asparaginases have a new treatment option that maintains therapeutic levels of asparaginase activity throughout duration of treatment."

Interim Trial Results
Data presented at ASH 2021 include initial analyses from an ongoing Phase 2/3 open-label, multicenter, dose confirmation and pharmacokinetic (PK) study of *Rylaze* (also known as JZP458) in patients with ALL/LBL who developed hypersensitivity or silent inactivation to a long-acting *E. coli*-derived asparaginase. Preliminary data are from Part A of the study, which investigated three Cohorts via IM administration:

- Cohort 1a (n=33): studied a dose of 25 mg/m^2 Monday/Wednesday/Friday
- Cohort 1b (n=53): studied a dose of 37.5 mg/m^2 Monday/Wednesday/Friday
- Cohort 1c (n=52): studied a dose of 25 mg/m^2 on Monday and Wednesday and 50 mg/m^2 on Friday

Part B of the Phase 2/3 study remains active to further confirm the dose and schedule of the intravenous (IV) route of administration for *Rylaze*.

Efficacy Findings
The primary efficacy endpoints of the trial were the proportion of patients with a last 72-hour (from Friday to Monday) NSAA levels of ≥0.1 IU/mL during the first treatment course, in addition to safety and tolerability of *Rylaze* in patients with ALL/LBL.

The key secondary endpoint included the proportion of patients achieving the last 48-hour NSAA ≥0.1 IU/mL during the first treatment course.

The proportion of patients with observed NSAA levels ≥0.1 IU/mL with a 95% CI during Course 1 from these initial results is as follows (primary and key secondary endpoints):

	Cohort 1a	**Cohort 1b**	**Cohort 1c**
At 48 hours	97% (CI: 91%, 100%)	98% (CI: 95%, 100%)	96% (CI: 90%, 100%)
At 72 hours	66% (CI: 48%, 83%)	80% (CI: 70%, 91%)	90% (CI:81%, 98%)

Based on a PPK modeling and simulation analysis versus observed data for Cohort 1c, the proportion of patients predicted to achieve NSAA levels ≥0.1 IU/mL with a 95% CI from these initial results is as follows:

	Observed	Model Prediction
At 48 hours	96% (CI: 90%, 100%)	93% (CI: 92%, 94%)
At 72 hours	90% (CI:81%, 98%)	91% (CI: 90%, 92%)

The mean serum asparaginase activity (SAA) levels were also determined: mean SAA levels (95% CIs) from the initial data in Cohorts 1a, 1b and 1c at 48 hrs were 0.45 IU/mL (0.37, 0.53), 0.84 IU/mL (0.68, 0.99), and 0.66 IU/mL (0.54, 0.77); and at 72 hrs were 0.15 IU/mL (0.12, 0.19), 0.30IU/mL (0.23, 0.37), and 0.46 IU/mL (0.34, 0.58), respectively. These results reflect the higher dose on Friday from Cohort 1c.

Safety Findings

Grade 3/4 treatment-emergent adverse events (TEAEs), regardless of causality, occurred in 78/137 (57%) patients. There were no treatment-related TEAEs leading to death. The most commonly reported non-hematologic TEAEs (in ≥20% in any cohort) regardless of causality included: vomiting, nausea, fatigue, decreased appetite, pyrexia, abdominal pain, alanine aminotransferase (ALT) increased, febrile neutropenia, back pain, headache, sinus tachycardia, stomatitis, pain in extremity, aspartate aminotransferase (AST) increased and hyperglycemia. Treatment-related TEAEs leading to study drug discontinuation occurred in 6/137 (4%) of patients.

Overall, the safety profile of *Rylaze* was consistent with the reported safety information for patients with ALL/LBL receiving asparaginase with combination chemotherapy.

Further study analyses (including PK and safety analyses) are ongoing, and full study results will be reported at a later date.

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) and lymphoblastic lymphoma (LBL) in adult and pediatric patients one month or 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 (RTOR) 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: **https://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 Acute Lymphoblastic Leukemia (ALL)

ALL is a cancer of the blood and bone marrow that can progress quickly if not treated.[1] Leukemia is the most common cancer in children, and about three out of four of these cases are ALL.[2] 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.[3,4] Adults can also develop ALL, and about four of every 10 cases of ALL diagnosed are in adults.[4] The American Cancer Society estimates that almost 6,000 new cases of ALL will be diagnosed in the United States in 2021.[4] Asparaginase is

a core component of multi-agent chemotherapeutic regimens in ALL.[5] However, asparaginase treatments derived from *E. coli* are associated with the potential for development of hypersensitivity reactions.[6]

About Lymphoblastic Lymphoma (LBL)

LBL is a rare, fast-growing, aggressive subtype of Non-Hodgkin's lymphoma, most often seen in teenagers and young adults.[6] 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.[7],[8]

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. Within these therapeutic areas, we are identifying new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science. 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.

Caution Concerning Forward-Looking Statements

This press release contains forward-looking statements, including, but not limited to, statements related to Jazz Pharmaceuticals' expectations for additional regulatory filings for *Rylaze*, including the submission of a supplemental Biologics Licensing Application (sBLA) in early 2022 and regulatory filings in Europe in mid-2022, with potential for approval in 2023, its belief in the potential of *Rylaze* to provide a reliable therapeutic option for adult and pediatric patients, 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, pharmaceutical product development; the regulatory approval process; 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' Quarterly Report on Form 10-Q for the quarter ended September 30, 2021 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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