Journal of Clinical Oncology publishes pivotal Phase 3 data for Jazz Pharmaceuticals' Vyxeos® (daunorubicin and cytarabine) Liposome for Injection

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DUBLIN, July 19, 2018 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) announced today that data from the pivotal Phase 3 study of Vyxeos® (daunorubicin and cytarabine) liposome for injection compared to standard of care cytarabine and daunorubicin (7+3) were published online in the *Journal of Clinical Oncology*. The study evaluated the efficacy and safety of *Vyxeos* compared to 7+3 in 309 patients who were between 60 to 75 years of age with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC), a rapidly progressing and life-threatening blood cancer.

The study met its primary endpoint as *Vyxeos* demonstrated a superior improvement in overall survival compared to the 7+3 treatment regimen. The median overall survival for the *Vyxeos* treatment group was 9.6 months compared with 5.9 months for the 7+3 treatment group (2-sided p value = 0.005; HR [95% confidence interval] = 0.69 [0.52, 0.90]). *Vyxeos* was also associated with a significantly higher remission rate than 7+3 with a complete response rate of 38% versus 26%; p=0.036. In addition, the overall rate of hematopoietic stem cell transplant (HSCT) was 34% in the *Vyxeos* arm and 25% in the 7+3 arm. The reported adverse reactions with *Vyxeos* were generally consistent with the known safety profile of cytarabine and daunorubicin therapy.

Vyxeos was approved by the U.S. Food and Drug Administration (FDA) in August 2017, and is the first FDA-approved treatment specifically indicated for adults with newly-diagnosed t-AML or AML-MRC. Data from the study formed the basis of the FDA application and the Marketing Authorization Application (MAA) to the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).

"We are encouraged by the positive response to *Vyxeos* from U.S. health care professionals who had been waiting for an advancement in the treatment of these two types of patients with AML," said Allen Yang, M.D., Ph.D., vice president and acting chief medical officer of Jazz Pharmaceuticals. "At Jazz we are keenly aware that every clinical trial result advances the science to help patients and we are committed to helping as many people as possible with *Vyxeos*."

Designed with Jazz's CombiPlex® proprietary technology, *Vyxeos* is a unique liposomal formulation that delivers a fixed-ratio of daunorubicin and cytarabine to the bone marrow that has been shown to have synergistic effects at killing leukemia cells in vitro and in animal models.

"*Vyxeos* is the first agent to significantly improve survival in older, fit AML patients with secondary AML," said Jeffrey E. Lancet, MD, Chair of the Department of Malignant Hematology at Moffitt Cancer Center and lead author of the publication. "Collectively, the Phase 3 clinical data support the adoption of *Vyxeos* for the treatment of adults with newly-diagnosed t-AML or AML-MRC."

***Vyxeos* has different dosage recommendations from other medications that contain daunorubicin and/or cytarabine. Do not substitute *Vyxeos* for other daunorubicin- and/or cytarabine- containing products.**

In the Phase 3 study, patients in the *Vyxeos* arm received 44mg/100mg per m^2 (daunorubicin and cytarabine) liposome intravenously via a 90 minute infusion on days 1, 3 and 5 of induction (days 1 and 3 if a second induction was needed) and 29mg/65mg per m^2 (daunorubicin and cytarabine) liposome on days 1 and 3 for consolidation. Patients in the 7+3 arm received induction with cytarabine 100mg/m^2/day on days 1-7 by continuous infusion and daunorubicin 60mg/m^2/day on days 1-3. For consolidation, cytarabine was dosed on days 1-5 and daunorubicin on days 1-2. Patients could receive up to 2 cycles of induction and 2 cycles of consolidation in each arm. Subsequent induction was recommended for patients who did not achieve a response and was mandatory for patients achieving >50% reduction in percent blasts.

For the primary endpoint of overall survival, *Vyxeos* demonstrated an improvement that was superior to the 7+3 treatment regimen. The median overall survival for the *Vyxeos* treatment group was 9.6 months compared with 5.9 months for the 7+3 treatment group (2-sided p value = 0.005; HR [95% confidence interval] = 0.69 [0.52, 0.90]). *Vyxeos* also was associated with a significantly higher remission rate than 7+3 with a complete response rate of 38% versus 26%; p=0.036. In addition, the overall rate of hematopoietic stem cell transplant (HSCT) was 34% in the *Vyxeos* arm and 25% in the 7+3 arm. The overall, all-cause 30-day mortality was 6% in the *Vyxeos* arm and 11% in the 7+3 arm. During the first 60 days of the study, 14% (21/153) of patients died in the Vyxeos arm vs. 21% (32/151) of patients in the 7+3 treatment group.

The incidences of nonhematologic adverse events were comparable between arms, despite a longer treatment phase and prolonged time to neutrophil and platelet count recovery with *Vyxeos*. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the *Vyxeos* arm and 0.7% of patients in the control arm. Six percent of patients in both the *Vyxeos* and control arm had a fatal adverse reaction on treatment or within 30 days of therapy that was not in the setting of progressive disease. The most common adverse reactions (incidence ≥ 25%) were bleeding events, fever, rash, swelling, nausea, sores in the mouth or throat, diarrhea, constipation, muscle pain, tiredness, stomach pain, difficulty breathing, headache, cough, decreased appetite, irregular heartbeat, pneumonia, blood infection, chills, sleep disorders and vomiting.

About Vyxeos®

Vyxeos® (daunorubicin and cytarabine) liposome for injection 44mg/100mg is a liposome formulation of a fixed combination of daunorubicin and cytarabine for intravenous infusion.[1] *Vyxeos* is indicated for the treatment of adults with newly-diagnosed t-AML or AML-MRC. For more information about *Vyxeos* in the United States, please visit https://vyxeos.com.

Important Safety Information

Vyxeos has different dosage recommendations from other medications that contain daunorubicin and/or cytarabine. Do not substitute Vyxeos for other daunorubicin- and/or cytarabine- containing products.

Vyxeos should not be given to patients who have a history of serious allergic reaction to daunorubicin, cytarabine or any of its ingredients.

Vyxeos can cause a severe decrease in blood cells (red and white blood cells and cells that prevent bleeding, called platelets) which can result in serious infection or bleeding and possibly lead to death. Your doctor will monitor your blood counts during treatment with Vyxeos. Patients should tell the doctor about new onset fever or symptoms of infection or if they notice signs of bruising or bleeding.

Vyxeos can cause heart-related side effects. Tell your doctor about any history of heart disease, radiation to the chest, or previous chemotherapy. Inform your doctor if you develop symptoms of heart failure such as:

- shortness of breath or trouble breathing
- swelling or fluid retention, especially in the feet, ankles or legs
- unusual tiredness

Vyxeos may cause allergic reactions including anaphylaxis. Seek immediate medical attention if you develop signs and symptoms of anaphylaxis such as:

- trouble breathing
- severe itching
- skin rash or hives
- swelling of the face, lips, mouth, or tongue

Vyxeos contains copper and may cause copper overload in patients with Wilson's disease or other copper-processing disorders.

Vyxeos can damage the skin if it leaks out of the vein. Tell your doctor right away if you experience symptoms of burning, stinging, or blisters and skin sores at the injection site.

Vyxeos can harm your unborn baby. Inform your doctor if you are pregnant, planning to become pregnant, or nursing. Do not breastfeed while receiving Vyxeos. Females and males of reproductive potential should use effective contraception during treatment and for 6 months following the last dose of Vyxeos.

The most common side effects were bleeding events, fever, rash, swelling, nausea, sores in the mouth or throat, diarrhea, constipation, muscle pain, tiredness, stomach pain, difficulty breathing, headache, cough, decreased appetite, irregular heartbeat, pneumonia, blood infection, chills, sleep disorders, and vomiting.

Please see full Prescribing Information for Vyxeos including BOXED Warning at: http://pp.jazzpharma.com/pi/vyxeos.en.USPI.pdf

About AML

Acute myeloid leukemia (AML) is a blood cancer that begins in the bone marrow, which produces most of the body's new blood cells.[2] AML cells crowd out healthy cells and move aggressively into the bloodstream to spread cancer to other parts of the body.[3] AML is a relatively rare disease representing 1.3 percent of all new cancer cases.[4] It is estimated that more than 19,500 people will be diagnosed with AML in the United States this year with the potential for nearly 11,000 people to die from the disease.[5] The median age at diagnosis is 68 years old,[4] with rising age associated with a progressively worsening prognosis.[6] There is also a reduced tolerance for intensive chemotherapy as patients age.[7] AML has the lowest survival rate of any other form of leukemia.[4] Patients with newly diagnosed t-AML or AML-MRC may have a particularly poor prognosis.[8-10] A hematopoietic stem cell transplant (HSCT) may be a curative treatment option for patients.[11]

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is an international biopharmaceutical company focused on improving patients' lives by identifying, developing and commercializing meaningful products that address unmet medical needs. The company has a diverse portfolio of products and product candidates with a focus in the areas of sleep and hematology/oncology. In these areas, Jazz Pharmaceuticals markets Xyrem®(sodium oxybate) oral solution, Erwinaze® (asparaginase *Erwinia chrysanthemi*), Defitelio® (defibrotide sodium) and Vyxeos® (daunorubicin and cytarabine) liposome for injection in the U.S. and markets Erwinase® and Defitelio® (defibrotide) in countries outside the U.S. For country-specific product information, please visit www.jazzpharmaceuticals.com/products. For more information, please visit www.jazzpharmaceuticals.com and follow us on Twitter at @JazzPharma.

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Jacqueline Kirby, Vice President, Corporate Affairs & Government Relations, Ireland +353 1 697 2141, U.S. +1 215 867 4910, Investor Contact: Kathee Littrell, Vice President, Investor Relations, Ireland +353 1 634 7887, U.S. +1 650 496 2717