

## **U.S. FDA Approves Supplemental New Drug Application Adding Overall Survival Data for XOSPATA<sup>®</sup> (gilteritinib)**

- *Phase 3 ADMIRAL trial showed patients treated with XOSPATA demonstrated longer Overall Survival than those who received salvage chemotherapy<sup>1</sup> -*
- *XOSPATA is the only FDA-approved targeted treatment for adult patients with relapsed or refractory FLT3 mutation-positive Acute Myeloid Leukemia<sup>1</sup> -*

**TOKYO – May 30, 2019** – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D. “Astellas”) today announced that the U.S. Food and Drug Administration (FDA) approved a supplemental New Drug Application (sNDA) to update the U.S. product labeling for XOSPATA<sup>®</sup> (gilteritinib) to include final analysis data from the ADMIRAL trial. The data demonstrated improvement in Overall Survival in those treated with gilteritinib monotherapy versus salvage chemotherapy in adult patients with relapsed (disease that has returned) or refractory (resistant to treatment) Acute Myeloid Leukemia (AML) with an FMS-like tyrosine kinase 3 (FLT3) mutation.

“The ADMIRAL trial’s Overall Survival (OS) findings are encouraging for patients and families impacted by relapsed/refractory FLT3 mutation-positive AML,” said Alexander Perl, M.D., Abramson Cancer Center, University of Pennsylvania. “The data underscore the importance of single-agent XOSPATA for this patient population that, until recently, had few remaining treatment options.”

Results from the ADMIRAL trial show the median OS for patients who received XOSPATA was 9.3 months compared to 5.6 months for patients who received salvage chemotherapy (Hazard Ratio = 0.64 (95% CI 0.49, 0.83), P=0.0004). The other co-primary endpoints of Complete Remission (CR)/Complete Remission with Partial Hematologic Recovery (CRh) in the XOSPATA arm at the interim analysis was 21% (95% CI: 14.5, 28.8).<sup>1</sup>

The safety profile of XOSPATA is based on 319 patients with relapsed or refractory AML in three clinical trials ([NCT02421939](#), [NCT02014558](#), and [NCT02181660](#)). Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These included cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (≥5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%). The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase

increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthralgia (7%), and fatigue/malaise (6%).

Please **see Important Safety Information including BOXED WARNING** at the end of this press release.

“Delivering innovation and value to address the unmet medical needs of patients is at the core of everything we do,” said Bernhardt G. Zeiher, M.D., Chief Medical Officer, Astellas. “The FDA’s approval of the sNDA based on Overall Survival data further highlights the strong potential XOSPATA has to help patients suffering from FLT3 mutation-positive AML, a life-threatening disease.”

The initial approval of XOSPATA in November 2018 by the FDA was based on an interim analysis of the following endpoints in the ADMIRAL clinical trial: the rate of complete remission (CR)/complete remission with partial hematologic recovery (CRh); the duration of CR/CRh (DOR); and the rate of conversion from transfusion dependence to transfusion independence.

The FDA reviewed the sNDA for XOSPATA under the Oncology Center of Excellence Real-Time Oncology Review pilot program, which aims to explore a more efficient review process by allowing the FDA to evaluate clinical data as soon as trial results become available.

XOSPATA was discovered through a research collaboration with Kotobuki Pharmaceutical Co., Ltd., and Astellas has exclusive global rights to develop, manufacture and commercialize XOSPATA.

XOSPATA was approved by the Japan Ministry of Health, Labor and Welfare (MHLW) for relapsed or refractory AML with FLT3 mutations and launched as XOSPATA<sup>®</sup> 40 mg Tablets in 2018.<sup>2</sup> In February 2019, the European Medicines Agency accepted a marketing authorization application (MAA) for regulatory review. The MAA is for the oral once-daily therapy XOSPATA for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation.<sup>3</sup>

Astellas is currently investigating gilteritinib in various FLT3 mutation-positive AML patient populations through several Phase 3 trials. Visit <http://www.clinicaltrials.gov> to learn more about ongoing gilteritinib clinical trials.

#### **About the ADMIRAL Trial<sup>4</sup>**

The Phase 3 ADMIRAL trial ([NCT02421939](https://clinicaltrials.gov/ct2/show/study/NCT02421939)) was an open-label, multicenter, randomized study of gilteritinib versus salvage chemotherapy in adult patients with FLT3 mutations who are refractory to, or have relapsed after, first-line AML therapy. The co-primary endpoints of the trial were Overall Survival and Complete Remission (CR)/Complete Remission with Partial Hematologic Recovery (CRh). The study enrolled 371 patients with relapsed or refractory AML and positive for FLT3 mutations present in bone marrow or whole blood. Subjects were randomized in a 2:1 ratio to receive gilteritinib (120 mg) or salvage chemotherapy.

### **About XOSPATA® (gilteritinib)**

XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory Acute Myeloid Leukemia (AML) with an FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.<sup>1</sup>

### **Important Safety Information**

#### **Contraindications**

XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

### **WARNING: DIFFERENTIATION SYNDROME**

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

### **Warnings and Precautions**

**Differentiation Syndrome (See BOXED WARNING)** 3% of 319 patients treated with XOSPATA in the clinical trials experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe.

**Posterior Reversible Encephalopathy Syndrome (PRES)** 1% of 319 patients treated with XOSPATA in the clinical trials experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

**Prolonged QT Interval** XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). 1% of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from

baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

**Pancreatitis** 4% of 319 patients treated with XOSPATA in the clinical trials experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

**Embryo-Fetal Toxicity** XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

## Adverse Reactions

Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These were cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent ( $\geq 5\%$ ) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

7% discontinued XOSPATA treatment permanently due to an adverse reaction. The most common ( $>1\%$ ) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

The most frequent ( $\geq 5\%$ ) grade  $\geq 3$  nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthralgia (7%), and fatigue/malaise (6%).

Other clinically significant adverse reactions occurring in  $\leq 10\%$  of patients included: electrocardiogram QT prolonged (9%), hypersensitivity (8%), pancreatitis (5%), cardiac failure (4%), pericardial effusion (4%), acute febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

**Lab Abnormalities** Shifts to grades 3-4 nonhematologic laboratory abnormalities in XOSPATA treated patients included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased (12%), aspartate aminotransferase increased (10%), calcium decreased (6%), creatine kinase increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

## **Drug Interactions**

**Combined P-gp and Strong CYP3A Inducers** Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases XOSPATA exposure which may decrease XOSPATA efficacy. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

**Strong CYP3A inhibitors** Concomitant use of XOSPATA with a strong CYP3A inhibitor increases XOSPATA exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity.

**Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor** Concomitant use of XOSPATA may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless their use is considered essential for the care of the patient.

## **Specific Populations**

**Lactation:** Advise women not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.

**Please see Full Prescribing Information including **BOXED WARNING** for additional safety information.**

## **About Astellas**

Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. For more information, please visit our website at [www.astellas.com/en](http://www.astellas.com/en).

## **Cautionary Notes**

In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

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**Contacts for inquiries or additional information:**

Astellas Pharma Inc.

Media and Investor Relations inquiries

TEL: +81-3-3244-3201 FAX: +81-3-5201-7473

United States:

Media inquiries: Marjorie Moeling

TEL: +1-224-205-5205 E-MAIL: [marjorie.moeling@astellas.com](mailto:marjorie.moeling@astellas.com)

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<sup>1</sup> XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc.

<sup>2</sup> Astellas Pharma Inc. Astellas Announces Approval in Japan for XOSPATA® 40 mg Tablets for the Treatment of FLT3mut+ Relapsed or Refractory AML (09-21-2018).

<https://www.astellas.com/en/news/14271>. Accessed 05-30-2019.

<sup>3</sup> Astellas Pharma Inc. Astellas Announces Acceptance of XOSPATA™ (gilteritinib) for Regulatory Review by the European Medicines Agency (02-28-2019). <https://www.astellas.com/us/news/14631>. Accessed 05-30-2019.

<sup>4</sup> ClinicalTrials.gov. A study of ASP2215 versus salvage chemotherapy in patients with relapsed refractory acute myeloid leukemia (AML) with FMS-like tyrosine kinase (FLT3) mutation (02-21-2019.) <https://clinicaltrials.gov/ct2/show/NCT02421939>. Accessed 05-30-2019.