Press Release

# European Medicines Agency Validates Type II Variation for Astellas' XTANDI® (enzalutamide) for Treatment of Non-Metastatic Hormone-Sensitive Prostate Cancer with High-Risk Biochemical Recurrence

*Application based on results from Phase 3 EMBARK trial, which showed XTANDI plus leuprolide reduced risk of metastasis or death by 58%*

**TOKYO, September 12, 2023** – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas") today announced that the European Medicines Agency (EMA) has validated its Type II variation for XTANDI® (enzalutamide) for the treatment of patients with non-metastatic hormone-sensitive prostate cancer (nmHSPC; also known as non-metastatic castration-sensitive prostate cancer or nmCSPC) with high-risk biochemical recurrence (BCR) who are unsuitable for salvage-radiotherapy.

**Ahsan Arozullah, MD, MPH, Senior Vice President and Head of Oncology Development, Astellas**
"As the most commonly diagnosed cancer in men in Europe, prostate cancer impacts hundreds of thousands of patients across the continent, and for those who have received initial curative treatment, a risk remains that their cancer may return in the form of biochemical recurrence. These patients, particularly those with rapidly rising PSA levels, need new therapeutic approaches. The validation of the Type II variation by the EMA marks an important step toward potentially making XTANDI, an existing standard of care for advanced prostate cancer in the E.U., available to patients with earlier stages of the disease who are at risk of their cancer spreading."

Submission to the EMA was supported by data from the international Phase 3 EMBARK trial, which evaluated the safety and efficacy of XTANDI in patients with nmHSPC with high-risk BCR across three study arms: XTANDI plus leuprolide (n=355), placebo plus leuprolide (n=358), or XTANDI monotherapy (n=355).

The EMBARK study met its primary endpoint of metastasis-free survival (MFS) for the XTANDI plus leuprolide arm, demonstrating a statistically significant reduction in the risk of metastasis or death over placebo plus leuprolide. Detailed results from the trial were presented as a plenary session during the 2023 American Urological Association Annual Meeting on April 29.

The overall safety profile was consistent with the known safety profile of each of the medicines. XTANDI, either in combination with leuprolide or as a monotherapy, has not been approved by any regulatory agency for the treatment of patients with nmHSPC with high-risk BCR.

The EMBARK data are being discussed with other regulatory authorities around the world, including the U.S. Food and Drug Administration (FDA), to support additional license applications for XTANDI in this indication in 2023 and beyond.

Astellas has already reflected the impact from this acceptance in its financial forecast of the current fiscal year ending March 31, 2024.

**About EMBARK**
The Astellas- and Pfizer-led Phase 3, randomized, double-blind, placebo-controlled, multi-national trial enrolled 1,068 patients with nmHSPC with high-risk BCR at sites in the U.S., Canada, Europe, South America, and the Asia-Pacific region. Patients who were considered to experience high-risk BCR had a prostate-specific antigen doubling time (PSA-DT) ≤ 9 months; serum testosterone ≥ 150 ng/dL (5.2 nmol/L); and screening PSA by the central laboratory ≥ 1 ng/mL if they had a radical prostatectomy (with or without radiotherapy) as primary treatment for prostate cancer, or at least 2 ng/mL above the nadir if they had radiotherapy only as primary treatment for prostate cancer. Patients in the EMBARK trial were randomized to receive enzalutamide 160 mg daily plus leuprolide (n=355), enzalutamide 160 mg as a monotherapy (n=355), or placebo plus leuprolide (n=358). Leuprolide 22.5 mg was administered every 12 weeks.

The primary endpoint of the trial was MFS for enzalutamide plus leuprolide versus placebo plus leuprolide. MFS is defined as the duration of time in months between randomization and the earliest objective evidence of radiographic progression by central imaging or death due to any cause, whichever occurred first. For more information on the EMBARK trial (NCT02319837), go to www.clinicaltrials.gov.

XTANDI, either in combination with leuprolide or as a monotherapy, has not been approved by any regulatory agency for the treatment of patients with nmHSPC with high-risk BCR.

**About Non-Metastatic Hormone-Sensitive Prostate Cancer with High-Risk Biochemical Recurrence**
In non-metastatic hormone- (or castration-) sensitive prostate cancer (nmHSPC or nmCSPC), no evidence of the cancer spreading to distant parts of the body (metastases) is detectable with conventional radiological methods (CT/MRI), and the cancer still responds to medical or surgical treatment designed to lower testosterone levels.[1,2] Of men who have undergone definitive prostate cancer treatment, including radical prostatectomy, radiotherapy, or both, an estimated 20-40% will experience a BCR within 10 years.[3] About 9 out of 10 men with high-risk BCR will develop metastatic disease, and 1 in 3 will die as a result of the recurrence.[4] The EMBARK trial focused on men with high-risk BCR. Per the EMBARK protocol, patients with nmHSPC and high-risk BCR are those initially treated by radical prostatectomy or radiotherapy, or both, with a PSA-DT ≤ 9 months. High-risk BCR patients with a PSA-DT of ≤ 9 months have a higher risk of metastases and death.[5]

**About XTANDI® (enzalutamide)**
XTANDI® (enzalutamide) is an androgen receptor signaling inhibitor. XTANDI is a standard of care and has received regulatory approvals in one or more countries around the world for use in men with metastatic hormone-sensitive prostate cancer (mHSPC; also known as metastatic castration-sensitive prostate cancer or mCSPC), metastatic castration-resistant prostate cancer (mCRPC), and non-metastatic castration-resistant prostate cancer (nmCRPC). XTANDI is currently approved for one or more of these indications in more than 90 countries, including in the U.S., European Union, and Japan. Over one million patients have been treated with XTANDI globally.[6]

**About XTANDI™ (enzalutamide) in the E.U.**
Enzalutamide is an androgen receptor signaling inhibitor indicated in the E.U. for the treatment of adult men with:

- Metastatic hormone-sensitive prostate cancer (mHSPC, also known as metastatic castration-sensitive prostate cancer or mCSPC) in combination with androgen deprivation therapy (ADT).
- High-risk non-metastatic castration-resistant prostate cancer (CRPC).
- Metastatic CRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. It is also indicated in adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

**Important Safety Information**
For important Safety Information for enzalutamide please see the full Summary of Product Characteristics at: https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf.

**Important Safety Information**
For Important Safety Information for enzalutamide please see the Package Insert.

**About Astellas**
Astellas Pharma Inc. is a pharmaceutical company conducting business in more than 70 countries around the world. We are promoting the Focus Area Approach that is designed to identify opportunities for the continuous creation of new drugs to address diseases with high unmet medical needs by focusing on Biology and Modality. Furthermore, we are also looking beyond our foundational Rx focus to create Rx+® healthcare solutions that

combine our expertise and knowledge with cutting-edge technology in different fields of external partners. Through these efforts, Astellas stands on the forefront of healthcare change to turn innovative science into VALUE for patients. For more information, please visit our website at https://www.astellas.com/eu.

**About the Pfizer/Astellas Collaboration**
In October 2009, Medivation, Inc., which is now part of Pfizer (NYSE:PFE), and Astellas (TSE: 4503) entered into a commercial agreement to jointly develop and commercialize XTANDI® (enzalutamide) in the United States, while Astellas has responsibility for manufacturing and all additional regulatory filings globally, as well as commercializing the product outside the United States.

**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.

Information about pharmaceutical products (including products currently in development) which is included in this press release is not intended to constitute an advertisement or medical advice.

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[6] Data on file. Northbrook, IL: Astellas Inc.