Press Release

Astellas Receives Positive CHMP Opinion for Zolbetuximab in Combination with Chemotherapy for Treatment of Advanced Gastric and Gastroesophageal Junction Cancer

- *If approved by the European Commission, zolbetuximab would become the first and only CLDN18.2-targeted therapy approved in the European Union*

- *A decision on the EU marketing authorization is expected by October 2024*

TOKYO, July 26, 2024 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas") today announced that on July 26, 2024, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending the approval of zolbetuximab in the European Union. Zolbetuximab, a first-in-class claudin (CLDN) 18.2-targeted monoclonal antibody, is recommended in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are CLDN18.2 positive.[1] If approved, zolbetuximab would become the first and only CLDN18.2-targeted therapy available for patients in the European Union.

In Europe, gastric cancer is the sixth most common cause of cancer-related mortality, responsible for more than 95,000 deaths in 2022.[2,3] The disease is often diagnosed in the advanced or metastatic stage due to overlapping early-stage symptoms with other more common stomach conditions.[4] The average five-year survival rate for patients in Europe is 26% across all stages of the disease, driving the need for new therapeutic options that can slow progression and extend lives.[5]

Moitreyee Chatterjee-Kishore, Ph.D., M.B.A., Senior Vice President and Head of Immuno-Oncology Development, Astellas
"More than 135,000 new cases of gastric cancer were diagnosed in Europe in 2022, requiring new treatment options that can improve patient outcomes and address the considerable unmet needs associated with this life-limiting cancer. Zolbetuximab has the potential to become the first approved CLDN18.2 targeted treatment for patients with HER2 negative advanced gastric or GEJ cancers in the European Union, underscoring Astellas' ongoing dedication to delivering therapeutic advancements that drive value for patients."

The positive CHMP opinion is based on the results from the Phase 3 SPOTLIGHT and GLOW clinical trials which explored the efficacy and safety of first-line zolbetuximab treatment in adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive, published in *The Lancet* and *Nature Medicine* respectively.[6,7] CLDN18.2 positivity is

defined as ≥75% of tumor cells demonstrating moderate-to-strong membranous CLDN18 immunohistochemical staining, assessed and confirmed using an in-vitro companion diagnostic test or medical device.[6,7] Astellas collaborated with Roche on the VENTANA® CLDN18 (43-14A) RxDx Assay that, upon approval, is intended to be used by a pathologist or laboratory to identify patients eligible for targeted treatment with zolbetuximab.[8] This immunohistochemistry based companion diagnostic test is currently under review by the notified body.

The positive opinion will now be reviewed by the European Commission, which has the authority to approve medicines in all 27 European Union (EU) member states as well as Iceland, Liechtenstein, and Norway.[9]

Astellas has already reflected the impact from this result in its financial forecast for the current fiscal year ending March 31, 2025.

In addition to the EMA, Astellas has submitted applications to other regulatory agencies around the world with reviews of zolbetuximab ongoing. Zolbetuximab was approved in Japan by the Ministry of Health, Labour and Welfare (MHLW) in March 2024, the first and only CLDN18.2-targeted treatment approved by any regulatory agency in the world.[10] For more information, please see the press release "Astellas' VYLOY™ (zolbetuximab) Approved in Japan for Treatment of Gastric Cancer" issued on March 26, 2024.

CURRENT LEGAL STATUS: Zolbetuximab has not been approved in the EU for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are CLDN18.2 positive.

About Zolbetuximab

Zolbetuximab is a claudin 18.2-directed cytolytic antibody being investigated in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive. Eligible patients should have CLDN 18.2 positive tumor status defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining. In both the SPOTLIGHT and GLOW Phase 3 clinical trials, approximately 38% of patients screened had tumors that were CLDN18.2 positive.[6,7]

As an investigational first-in-class monoclonal antibody (mAb), zolbetuximab targets and binds to CLDN18.2, a transmembrane protein expressed on cancer cells. In pre-clinical studies, zolbetuximab reduced the number of CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, leading to tumor growth inhibition.[11]

About Locally Advanced Unresectable Metastatic Gastric and Gastroesophageal Junction Cancer

Across Europe, over 135,000 new cases of gastric cancer, also known as stomach cancer, were diagnosed in 2022.[3] Gastric cancer is the sixth most common cause of cancer-related mortality in Europe, responsible for 95,431 deaths in 2022.[2,3] Gastroesophageal junction (GEJ) adenocarcinomas start in the first two inches (5 cm) where the esophagus joins the stomach.[12]

Because early-stage cancer symptoms frequently overlap with more common stomach-related conditions, gastric cancers are often diagnosed in the advanced or metastatic stage, or once they have spread from the tumor's origin to other body tissues or organs.[4]

Early signs and symptoms can include indigestion or heartburn, pain or discomfort in the abdomen,

nausea and vomiting, bloating of the stomach after meals, loss of appetite.[4,13] Signs of more advanced gastric cancer can include unexplained weight loss, weakness and fatigue, sensation of food getting stuck in the throat while eating, vomiting blood or having blood in the stool.[4,13,14] Risk factors associated with gastric and GEJ cancer can include older age, male gender, family history, *H. pylori* infection, smoking, and gastroesophageal reflux disease (GERD).[15,16]

INVESTIGATIONAL STUDIES

About SPOTLIGHT Phase 3 Clinical Trial
SPOTLIGHT is a Phase 3, global, multi-center, double-blind, randomized study, assessing the efficacy and safety of zolbetuximab plus mFOLFOX6 (a combination chemotherapy regimen that includes oxaliplatin, leucovorin, and fluorouracil) compared to placebo plus mFOLFOX6 as a first-line treatment in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive. The study enrolled 565 patients at 215 study locations in the U.S., Canada, United Kingdom, Australia, Europe, South America, and Asia. The primary endpoint is progression-free survival (PFS) of participants treated with the combination of zolbetuximab plus mFOLFOX6 compared to those treated with placebo plus mFOLFOX6. Secondary endpoints include overall survival (OS), objective response rate (ORR), duration of response (DOR), safety and tolerability, and quality-of-life parameters.[6]

Data from the SPOTLIGHT clinical trial were presented during the 2023 American Society of Clinical Oncology (ASCO) Gastrointestinal (GI) Cancers Symposium in an oral presentation on January 19, 2023, and were subsequently published in *The Lancet* on April 14, 2023.[6]

For more information, please visit clinicaltrials.gov under Identifier NCT03504397.

About GLOW Phase 3 Clinical Trial
GLOW is a Phase 3, global, multi-center, double-blind, randomized study, assessing the efficacy and safety of zolbetuximab plus CAPOX (a combination chemotherapy regimen that includes capecitabine and oxaliplatin) compared to placebo plus CAPOX as a first-line treatment in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive. The study enrolled 507 patients at 166 study locations in the U.S., Canada, United Kingdom, Europe, South America, and Asia, including Japan. The primary endpoint is PFS in participants treated with the combination of zolbetuximab plus CAPOX compared to those treated with placebo plus CAPOX. Secondary endpoints include OS, ORR, DOR, safety and tolerability, and quality-of-life parameters.[7]

Data from the GLOW study were initially presented at the March 2023 ASCO Plenary Series with an updated oral presentation at the 2023 ASCO Annual Meeting on June 3, 2023, and were subsequently published in *Nature Medicine* on July 31, 2023.[7]

For more information, please visit clinicaltrials.gov under Identifier NCT03653507.

Investigational Pipeline in CLDN18.2
An expanded Phase 2 trial of zolbetuximab in metastatic pancreatic adenocarcinoma is in progress and recruiting patients. The trial is a randomized, multi-center, open-label study, evaluating the safety and efficacy of investigational zolbetuximab in combination with gemcitabine plus nab-paclitaxel as a first-line treatment in patients with metastatic pancreatic adenocarcinoma with CLDN18.2 positive tumors (defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining based on a validated immunohistochemistry assay). For more information, please visit clinicaltrials.gov under Identifier NCT03816163.

In addition to zolbetuximab, ASP2138 is under development in our Primary Focus Immuno-Oncology area and is currently recruiting patients. ASP2138 is a bispecific monoclonal antibody that binds to CD3 and CLDN18.2, and it is currently in a Phase 1/1b study in participants with metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma or metastatic pancreatic adenocarcinoma whose tumors have CLDN18.2 expression. The safety and efficacy of the agent under investigation have not been established for the uses being considered. For more information, please visit clinicaltrials.gov under Identifier NCT05365581.

There is no guarantee that the agent(s) will receive regulatory approval and become commercially available for the uses being investigated.

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/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.

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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