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Japan Grants Global-First Approval To Zolbetuximab, 15 Other New Drugs

Half In Rare Diseases

by Lisa Takagi

Astellas's first-in class CLDN18.2-targeting antibody receives its first approval worldwide, while crovalimab and a number of drugs for rare diseases also receive nods from regulators and are now awaiting reimbursement price-listing.

Japan announced its latest batch of drug approvals on 26 March, including a global-first approval for *Astellas Pharma, Inc.*'s Vyloy (zolbetuximab), a first-in-class anti-claudin (CLDN) 18.2 antibody, for the treatment of gastric cancer.

The 30 new approvals included 16 drugs new to the Japanese market, along with multiple new indications and line extensions (*see table below*). *Chugai Pharmaceutical Co., Ltd.*/*Roche Holding AG*'s C5-inhibiting recycling monoclonal antibody Piasky (crovalimab) obtained its second approval globally after China in February, for paroxysmal nocturnal hemoglobinuria (PNH). (Also see "*Crovalimab Gets First Nod In China For PNH, Fiercer Global Competition Awaits*" - Scrip, 13 Feb, 2024.)

Following the official approvals, the new drugs must now move through the process of price listing for reimbursement under Japan's national health insurance scheme, which should be finalized by the end of May or June at the latest and will allow national launches.

Astellas' Zolbetuximab Approval Timeline Unclear After Manufacturing Issues Prompt CRL

By Lisa Takagi

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Global-First Approval For Zolbetuximab

Zolbetuximab received its first approval anywhere, as Vyloy, for use with chemotherapy in patients with HER2-negative, CLDN18.2-positive unresectable advanced or recurrent gastric cancer, following a Japanese submission (also the first worldwide) in early June 2023. The CLDN18.2-targeted antibody also becomes the first in its class to be approved anywhere.

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After a US FDA site inspection raised questions about the contract manufacturer of the potential first-in-class Claudin 18.2 inhibitor that could not be answered by the original January PDUFA date, Astellas will need to refile the application, but has not committed to when that might be.

Read the full article here

The approval based on the Phase III SPOTLIGHT and GLOW trials in the first-line setting, which both showed statistically significant improvements in the primary endpoint of progression-free survival, as well as against the secondary endpoint of overall survival, versus placebo plus chemotherapy. Around 38% of screened participants in both trials had CLDN18.2-positive tumors. (Also see "*Astellas Reports Second Phase III Win With Zolbetuximab In Stomach Cancer*" - Scrip, 16 Dec, 2022.)

Astellas noted there were around 127,000 cases of gastric cancer diagnosed in Japan in 2022 and nearly 44,000 deaths the same year, making it the third-deadliest malignancy in the country and among the highest incidences globally. Testing for CLDN18.2 will be done using the also newly approved Ventana CLDN18 RxDx Assay immunohistochemistry companion diagnostic from *Roche Diagnostics Corp.*

Zoletuximab is also awaiting approval for gastric cancer in other major markets including the US, although a Complete Response Letter was issued by the Food and Drug Administration early this year. This was in relation to manufacturing issues, rather than efficacy or safety concerns. (Also see "*Astellas' Zolbetuximab Approval Timeline Unclear After Manufacturing Issues Prompt CRL*" - Pink Sheet, 10 Jan, 2024.)

The antibody is also in an expanded Phase II trial for metastatic pancreatic cancer, but is facing an increasingly crowded CLDN18.2 field, where multiple firms - including a number from China - are developing potential rival same-class molecules. (Also see "*Japan Zolbetuximab Filing Heats Up CLDN18.2 Competition*" - Scrip, 21 Jun, 2023.)

Rare Disease Therapeutics

Many of the other approvals were drugs for rare diseases.

Takeda Pharmaceutical Co. Ltd. had three products in the group, including two with orphan designation: Adzynma (apadamtase alfa/cinaxadamtase alfa) for patients older than 12 with congenital thrombotic thrombocytopenic purpura; and Obizur (sustocog alfa) for bleeding control in adults with acquired haemophilia A.

Obizur will compete with Chugai/Roche's Hemlibra (emicizumab), which has been approved for the same indication in the country since June 2022. (Also see "*Japan-Specific Approval For Hemlibra In Acquired Hemophilia A*" - Scrip, 20 Jul, 2022.)

Among three new approvals for Japanese rare disease-focused firm *Nobelpharma Co., Ltd.* was Sargmalin (sargramostim), an inhaled recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF), which received its global first indication for autoimmune pulmonary alveolar proteinosis (aPAP). The rare disorder is characterized by myeloid cell dysfunction, abnormal pulmonary surfactant accumulation, hypoxaemia, dyspnoea and innate immune deficiency, which in some cases can lead to death.

Sargramostin has been approved in the US since 1991 as an injectable product for neutrophil recovery following induction chemotherapy and myeloid cell recovery following peripheral stem-cell transplantation in patients with acute myeloid leukemia, but never previously for "for aPAP nor as an inhalation," noted Nobelpharma.

First Approval For Aceneuramic Acid For Distal Myopathy

Another global-first approval went to Nobelpharma's Acenovel (aceneuramic acid) for distal myopathy (also known as distal muscular dystrophy), a rare disease characterised by reduced synthesis of sialic acid derived from pathogenic variants in the GNE gene. The disease is estimated to affect only 400 people in Japan with no fundamental treatments approved, noted Nobelpharma.

The firm has been developing N-acetylneuraminic acid for the indication since 2009 with government funding following requests from the Patient Association for Distal Myopathies and Japan's National Center of Neurology and Psychiatry (NCNP). Investigator-initiated local Phase II/III studies and a long-term administration study were supported by numerous national organizations including the NCNP and Tohoku University Graduate School of Medicine.

The firm originally planned to file for approval in both Japan and the US in 2015. However, as a US Phase II/III study with a larger number of patients compared to those in Japan failed to show efficacy and safety, the firm changed its plan to include the result from the long-term administration study, in addition to the Japanese Phase II/III results, to support the Japanese submission.

The Japanese Phase II/III trial had 16 patients in the treatment group and four receiving placebo

and showed a mean value change in upper limb muscle strength shown in upper extremity composite (UEC) score (95% CI) at 48 weeks of -0.1kg (-2.1 to 2.0 in UEC score) in the treatment group and -5.1kg (-10.4 to 0.3) for placebo, show results published in the *Journal of Neuromuscular Diseases* in October 2023.

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(With contributions from Ian Haydock in Tokyo.)