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FDA Accepts Application for Chugai's Crovalimab for the Treatment of PNH, a Rare Life-Threatening Blood Condition

- Acceptance based on the phase III COMMODORE 2 study which demonstrated that crovalimab achieved disease control and was well-tolerated in people with paroxysmal nocturnal haemoglobinuria (PNH)
- If approved, crovalimab will be the first monthly subcutaneous treatment for PNH with the option to self-administer at home, in the US
- Filing applications have also been accepted in Japan, China, and EU, and submissions to other regulatory authorities around the world are ongoing

TOKYO, September 6, 2023 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced today that the US Food and Drug Administration (FDA) has accepted the Biologics License Application (BLA) for crovalimab, an investigational, novel anti-C5 recycling monoclonal antibody, for the treatment of paroxysmal nocturnal haemoglobinuria (PNH). The acceptance was based on results from the pivotal phase III COMMODORE 2 study which demonstrated that crovalimab achieved disease control and was well-tolerated in people with PNH.[1] Results from the phase III COMMODORE 1 study, demonstrating the consistent benefit-risk profile of crovalimab, also supported the application.[2]

"We are very pleased that the application of crovalimab, created using our company's expertise in antibody engineering, was accepted for filing in the United States, in addition to Japan, China and Europe," said Chugai's President and CEO, Dr. Osamu Okuda. "Crovalimab aims to become a treatment that can be self-administered at home by subcutaneous injection every 4 weeks. In PNH, which requires long-term treatment, the availability of more flexible treatment options to meet the needs of patients and their caregivers is significant. We are committed to collaborating with Roche, to offer crovalimab's values to patients with PNH worldwide."

PNH is a rare and life-threatening blood condition, which affects approximately 20,000 people worldwide.[3] In PNH, red blood cells are destroyed by the complement system – part of the innate immune system. This causes symptoms such as anaemia, fatigue and blood clots, and can lead to kidney disease.[4] C5 inhibitors – treatments that block the complement system cascade – have been shown to be effective in treating PNH.[5] Crovalimab is a novel C5 inhibitor that is recycled within the bloodstream, enabling sustained complement inhibition through low dose, subcutaneous (SC) administration every four weeks.[6,7]

The BLA was based on results from the phase III COMMODORE 2 study in people with PNH who have not been previously treated with complement inhibitors. Results from the study demonstrated that crovalimab, administered as SC injections every four weeks, achieved disease control and was non-inferior with comparable safety to eculizumab, a current standard of care, given intravenously every two weeks.[1]

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Adverse events (AE) in the study occurred in 78% of participants treated with crovalimab and 80% treated with eculizumab, with the most common AE being an infusion-related reaction.[1] The application also included data from the phase III COMMODORE 1 study, which supported the favourable benefit-risk profile of crovalimab in people with PNH switching from currently approved C5 inhibitors.[2] Data from the COMMODORE 1 and 2 studies were recently presented at the European Hematology Association 2023 Hybrid Congress.[1,2]

The submission of the global phase III data from the COMMODORE 1 and 2 studies are ongoing around the world, and filing applications has been accepted in Japan and EU. Positive data from a single arm study evaluating crovalimab in PNH, the COMMODORE 3 study in China, have been submitted via China's Centre for Drug Evaluation Breakthrough Therapy Designation pathway and crovalimab has been accepted for consideration for approval under Priority Review by China's National Medical Products Administration. The data were presented at the American Society of Hematology 2022 Annual Meeting.[8]

Crovalimab is being investigated in a broad clinical development programme, including five ongoing phase III studies and three earlier phase studies in PNH and other complement mediated diseases.[1,2,8,9,10]

[Reference Information]

Chugai Files New Drug Application in Japan for Crovalimab for Paroxysmal Nocturnal Hemoglobinuria (Press release issued on June 14, 2023)
https://www.chugai-pharm.co.jp/english/news/detail/20230614153000_993.html

New Data Presented at EHA Show Chugai's Subcutaneously Administered Crovalimab Achieved Disease Control and was Well-Tolerated in People with Paroxysmal Nocturnal Hemoglobinuria (PNH) (Press release issued on June 12, 2023)
https://www.chugai-pharm.co.jp/english/news/detail/20230612170001_992.html

Roche's subcutaneous crovalimab given every four weeks achieves disease control in people with PNH, a life-threatening blood condition (Press release issued by Roche on December 11, 2022)
https://www.roche.com/media/releases/med-cor-2022-12-11

About the COMMODORE 1 and 2 studies

The COMMODORE 2 study is a phase III, randomised, open-label study evaluating the efficacy and safety of crovalimab versus eculizumab in people with paroxysmal nocturnal haemoglobinuria (PNH) who have not been treated previously with C5 inhibitors. The study's co-primary efficacy endpoints measure transfusion avoidance and control of haemolysis (the ongoing destruction of red blood cells measured by lactate dehydrogenase levels). The adults* enrolled in the study were randomised in a 2:1 ratio to be treated with either SC crovalimab every four weeks or intravenous (IV) eculizumab every two weeks. The participants who were less than 18 years old were included in a non-randomised treatment arm and were treated with SC crovalimab every four weeks.[11]

*Including two patients aged less than 18 years old enrolled before the revision of the protocol

The COMMODORE 1 study is a phase III, randomised, open-label study evaluating the safety of crovalimab in people with PNH switching from currently approved C5 inhibitors. The study's outcome

measures evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic properties of crovalimab. The study included people (18 years of age or older) currently treated with eculizumab. In a non-randomised arm, the study also included paediatrics (<18 years of age) currently treated with eculizumab, people currently treated with ravulizumab, people currently treated with off-label doses of eculizumab (higher than the approved dose for PNH: more than 900mg per dose and/or more frequently than every two weeks), or people with known mutations in the C5 gene who do not respond to current therapies.[12]

About crovalimab

Crovalimab is an anti-C5 recycling antibody created with Chugai's Recycling Antibody® technology. Recycling antibodies are designed to achieve pH-dependent antigen binding so that a single antibody molecule can bind with the antigen multiple times, enabling a longer efficacy compared with a conventional antibody. Crovalimab is designed to target C5, a key component of the complement system, and is expected to control complement activity. It is also expected to reduce the treatment burden for patients and their caregivers through subcutaneous administration. Since crovalimab binds to complement C5 at a different site from existing antibody drugs, it can be an effective treatment option for patients with a specific C5 gene mutation (appears in approximately 3.2% of Japanese patients with PNH), which causes existing antibody drugs not to bind to C5.[6,13]

In addition to PNH, clinical trials are ongoing for atypical hemolytic uremic syndrome (aHUS). Overseas, Roche is conducting trials for sickle cell disease (SCD) and lupus nephritis.

About paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematopoietic stem cell disorder characterized by intravascular hemolysis due to complement activation. It is caused by the clonal expansion of hematopoietic stem cells, driven by acquired mutations in the *PIG-A* gene.[14] While symptoms may vary in each individual, there are typically two types. One is symptoms attributed to the characteristic hemolysis in PNH, such as hemoglobinuria and thrombosis. The other is hematopoietic failures similar to those associated with aplastic anemia. PNH may cause complications, including chronic kidney disease and pulmonary hypertension. In Japan, PNH is a rare disease that is listed as one of the designated intractable diseases (designated intractable disease 62). 959 individuals have been granted the medical care recipient certificate for PNH as of the end of 2021.[15]

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2. Scheinberg P, et al. Phase III Randomised, Multicentre, Open-Label COMMODORE 1 Trial: Comparison of Crovalimab Vs Eculizumab in Complement Inhibitor-Experienced Patients with Paroxysmal Nocturnal Hemogobinuria (PNH). Presentation at European Hematology Association (EHA) Annual Congress; 2023 June 08-13. Abstract #S183.

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