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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)

- The COMMODORE 2 study demonstrated that subcutaneous crovalimab every four weeks (maintenance dosing) was non-inferior in disease control to intravenous eculizumab every two weeks, with comparable safety, in people new to C5 inhibitors
- The COMMODORE 1 study in people switching from currently approved C5 inhibitors supported the consistent benefit-risk profile of crovalimab, as seen in the COMMODORE 2 study
- Monthly self-administration of subcutaneous crovalimab has the potential to address the high burden of a disease that requires lifelong treatment, including in settings where access to current C5 inhibitors is limited

TOKYO, June 12, 2023 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced that positive results from the global phase III COMMODORE 1 and 2 studies, evaluating the efficacy and safety of crovalimab, an investigational, novel anti-C5 recycling monoclonal antibody, compared to eculizumab, one of the current standard of care in paroxysmal nocturnal hemoglobinuria (PNH) were presented at the European Hematology Association (EHA) Hybrid Congress, taking place in Frankfurt, Germany on 8-11 June 2023.

"Crovalimab, which is administered subcutaneously every four weeks, is expected to decrease the treatment burden of patients with PNH, possibly reducing dosing time and bringing the option of self-administration at home," said Chugai's President and CEO, Dr. Osamu Okuda. "We will continue to work with Roche towards global filing for this drug so that the benefits of crovalimab can be delivered as soon as possible to patients and caregivers who are waiting for this new treatment."

PNH is a rare and life-threatening blood condition in which red blood cells are destroyed by the complement system — part of the innate immune system — causing symptoms such as anemia, fatigue, blood clots, and kidney disease.[1] C5 inhibitors are known to be effective in treating the condition.[2] Chugai's Recycling Antibody® technology has been applied to crovalimab and re-engineered to be recycled within the bloodstream, enabling sustained complement inhibition through low-dose subcutaneous administration every four weeks.[3,4]

In the COMMODORE 2 study, 79.3% (95% CI: 72.9, 84.5) of participants treated with crovalimab achieved hemolysis control from week five to week 25 compared with 79.0% (95% CI: 69.7, 86.0) with eculizumab. Additionally, 65.7% (95% CI: 56.9, 73.5) achieved transfusion avoidance (TA) from baseline to week 25 with crovalimab and 68.1% (95% CI: 55.7, 78.5) with eculizumab. TA is defined as people who

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become concentrated red blood cell transfusion-free and do not require transfusion per protocol-specified guidelines. Blood transfusion requirements are important clinical measures of hemolysis caused by complement dysregulation in PNH. A clinically meaningful improvement in FACIT-Fatigue score (improvement of over 5 points), which is a patient-reported scale to measure fatigue, from baseline to week 25 occurred in both arms, with an adjusted mean change of 7.8 (95% Cl: 6.5, 9.1) with crovalimab, and 5.2 (95% Cl: 3.4, 6.9) with eculizumab.[5]

Adverse events (AEs) occurred in 78% of participants treated with crovalimab and 80% treated with eculizumab in the COMMODORE 2 study. Serious infections occurred in 3% of participants treated with crovalimab and 7% with eculizumab, with no meningococcal infections. The most common AE that occurred in 16% of people treated with crovalimab and 13% of those treated with eculizumab was an infusion-related reaction. One participant in each arm experienced an AE that led to treatment discontinuation.[5]

The results from the COMMODORE 1 study indicate that crovalimab maintained disease control in people switching from currently approved complement inhibitors.[6] The data supports the consistent benefit-risk profile of crovalimab, as well as subcutaneous administration with the option to self-administer, as seen in the COMMODORE 2 study.

Roche also presented preliminary data from the COMMODORE Burden of Illness study. The data suggest that despite currently available C5 inhibitor treatments, people with PNH continue experiencing a diminished quality of life and considerable costs, and they may benefit from new treatment options.[7]

Global phase III data from the COMMODORE 1 and 2 studies in PNH will be submitted to regulatory authorities around the world. Positive data from a third phase III study evaluating crovalimab in PNH, the COMMODORE 3 study in China, were presented at the American Society of Hematology (ASH) Annual Meeting and Exposition on 10 December 2022. Data from the COMMODORE 3 study have been submitted via China's Centre for Drug Evaluation Breakthrough Therapy Designation pathway. This submission has been accepted under Priority Review for approval consideration by China's National Medical Products Administration.

About the COMMODORE 1 and 2 studies

The COMMODORE 2 study is a phase III, randomized, open-label study evaluating the efficacy and safety of crovalimab versus eculizumab in people with paroxysmal nocturnal hemoglobinuria (PNH) who have not been treated previously with C5 inhibitors. The 204 adults* enrolled in the study were randomized in a 2:1 ratio to be treated with either subcutaneous (SC) crovalimab every four weeks or intravenous (IV) eculizumab every two weeks. The six participants under 18 years old were included in a descriptive arm to be treated with SC crovalimab every four weeks.[8]

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

The COMMODORE 1 study is a phase III, randomized, open-label study evaluating the safety of crovalimab in people with PNH switching from currently approved C5 inhibitors. The study included 89 people (18 years of age or older) currently treated with eculizumab, randomized in a 1:1 ratio to be treated

with either SC crovalimab every four weeks or IV eculizumab every two weeks. In a non-randomized arm, the study also included pediatrics (<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.[9]

About the COMMODORE Burden of Illness Study

The COMMODORE Burden of Illness (BOI) study will quantify the direct medical costs (e.g., treatment and hospitalization), direct nonmedical costs (e.g., travel), and indirect costs (e.g., impact on work productivity and family burden) associated with PNH for patients and care providers and determine the impact of PNH on health-related quality of life (HRQoL), in U.K., France, and Germany.[10]

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.[3,11]

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.[12] 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.[13]

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