Trial in Progress: Phase III, Randomised, Open-Label, Multicentre COMMODORE 2 Study Evaluating Efficacy and Safety of Crovalimab vs Eculizumab in Adult/Adolescent Patients With PNH Without Prior Complement Inhibitor Therapy

Background

Paroxysmal nocturnal haemoglobinuria and CS Complement Inhibition

- Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, clonal, haemolytic, stem cell disorder, which causes haemolytic anaemia and thrombosis.
- The current standard of care for PNH is treatment with a C5 inhibitor.
- Eculizumab and ravulizumab are CS inhibitors currently approved for the treatment of patients with PNH, yet treatment limitations remain.
- Lack of sustained CS inhibition in some patients, resulting in the requirement for increased or more frequent dosing to prevent breakthrough haemolysis (BTH).
- Current therapies must be administered intravenously, often requiring a visit to a hospital or clinic, contributing to treatment burden.
- Crovalimab is a novel anti-complement CS antibody, engineered to bind optimally to CS in plasma, through affinity maturation.
- Crovalimab is engineered to have a significantly extended half-life, enabling subcutaneous (SC) self-administration once every 4 weeks (q4w), reducing the treatment burden on patients with PNH.
- The detailed mechanism of action of crovalimab is shown in Figure 1.

Study Design

The COMMODORE 2 study (NCT04443092) is a phase III, randomised, open-label, active-controlled, multicentre study evaluating the efficacy and safety of crovalimab compared with eculizumab in patients aged ≥12 years with PNH, not previously treated with complement inhibitors.

Methods

Patients with PNH aged ≥12 years not previously treated with complement inhibitors N = 200

- The Phase II/III COMPOSER (NCT03157635) study assessed the safety and efficacy of crovalimab in healthy volunteers, CS inhibitor treatment-naive patients with PNH and patients with PNH who were switched from eculizumab.
- Sustained terminal complement pathway inhibition in both CS-inhibitor treatment-naive and CS-inhibitor pretreated patients was observed with crovalimab.
- Treatment-naive patients demonstrated immediate and sustained reduction in haemolysis, decreased transfusion rates and increased haemoglobin levels.
- An acceptable safety profile was maintained in both CS-inhibitor-naive patients and those switched from eculizumab, and no meningococcal infections were reported during the study.

Key Objectives

- Co-primary Efficacy Objectives:
  - Proportion of patients who achieve transfusion avoidance, defined as patients who are packed red blood cell transfusion-free and do not require transfusion per protocol-specified guidelines, from baseline through Week 25.
  - Proportion of patients with haemolysis control, measured by LDH ≤ 1.5 x ULN from Week 5 through Week 25.

- Secondary Efficacy Objectives:
  - Proportion of patients with BTH, defined as ≥ 1 worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [haemoglobin ≤ 10 g/dL], a major adverse vascular event [MAVE, including thrombosis], dysphagia or erectile dysfunction) in the presence of elevated LDH ≥ 2 x ULN after prior reduction of LDH to ≤ 1.5 x ULN on treatment, from baseline to Week 25.
  - Proportion of patients with stabilization of haemoglobinuria, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline, in the absence of transfusion.
  - Change from baseline to Week 25 in fatigue, as assessed by the Functional Assessment of Chronic Illness Therapy – Fatigue for adults aged ≥18 years.

Other Objectives:

- Total number of units of packed red blood cells transfused per patient by Week 25.
- Proportion of patients who experienced a MAVE from baseline through Week 25.
- Proportion of patients who reached a haemoglobin level of ≥ 10 g/dL, without subsequent decrease below 9 g/dL, from baseline to Week 25.
- Mean change from baseline to Week 25 in the EORTC QLQ C30, and select disease-related symptoms (abdominal pain, headaches, dyspnoea, dysphagia, chest pain, and erectile dysfunction) of the EORTC Item Library (for adults aged ≥18 years).
- Mean change from baseline to Week 25 in the Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale, and the Physical Functioning scale of the PedsQL Core (for adolescents aged 12-17 years).
- Key safety objectives: Incidence and severity of adverse events, injection-site reactions, infusion-related reactions, hypersensitivity and infections (including meningococcal meningitis).
- Key pharmacokinetics objective: Serum concentrations of crovalimab and eculizumab over time.
- Key immunogenicity objective: Proliferation of anti-drug antibodies (ADA) at baseline and incidence of ADAs during the study.

For additional information, please visit https://clinicaltrials.gov/ct2/show/NCT04443092

Contact: www.roche.com/about_roche/roche_worldwide.htm

Acknowledgements

The COMMODORE 2 study plans to enrol patients from 108 study locations (Figure 3).

References


Disclosures

Austin Kulaeskaranraj has served as a consultant for Celgene, Novartis, Amgen, Ra Pharma, Alexion, Akebia, Apellis, Hoffman-La Roche, received research funding from Celgene, received honoraria from Celgene, Novartis, Amgen, Ra Pharma, Alexion, Akebia, Biocryst, Akari, Hoffman-La Roche and served as a speaker for Celgene, Novartis, Amgen, Ra Pharma, Alexion, Akebia, Biocryst, Akari, Hoffman-La Roche.

Table 2. Key Inclusion and Exclusion Criteria for the COMMODORE 2 Study

- **Inclusion Criteria**
  - Body weight ≥ 60 kg
  - Age ≥ 12 years
  - Confirmed diagnosis of PNH, with granulocyte or monocyte clone size ≥ 10%
  - Presence or one of more PNH-related signs or symptoms within 3 months prior to screening
  - LDH ≤ 2 x ULN
  - Vaccination against Neisseria meningitidis, Haemophilus influenzae type B and Streptococcus pneumoniae

- **Exclusion Criteria**
  - Current or previous treatment with a complement inhibitor
  - Platelet count < 300,000/mm³
  - Absolute neutrophil count < 500/μL
  - History of allogenic bone marrow transplantation
  - Known or suspected immune deficiency or suspected hereditary complement deficiency
  - Active systemic bacterial, viral or fungal infection ≤ 14 days before Day 1
  - Positive for hepatitis B surface antigen or hepatitis C antibody at screening