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Newcastle University

Health Technology Briefing
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Crovalimab for treatment of paroxysmal nocturnal haemoglobinuria

Company/Developer	Roche Products Ltd.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30101	NICE ID: 10622	UKPS ID: 658241

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Crovalimab is currently in clinical development for patients with paroxysmal nocturnal haemoglobinuria (PNH). PNH is a rare, acquired, life-threatening disease of the blood. The disease is characterised by destruction of red blood cells, blood clots, and impaired bone marrow function. It is a blood condition where blood cells are prone to be attacked by part of the body's immune system. The process where the red blood cells are destroyed is called "haemolysis" and it is responsible for many of the symptoms of the disease. The condition is caused by a mutation (DNA change) that results in a lack of certain proteins being present on the surface of red blood cells that normally protect them from being destroyed by complement proteins. Symptoms of PNH can include anaemia, breathlessness, difficulty swallowing, fatigue, blood clots and kidney damage.

Crovalimab is an antibody that binds to the human C5, a complement protein with capacity to start an inflammatory reaction in humans resulting in the destruction of blood cells. It is a unique treatment option that allows for subcutaneous injections once every 4 weeks that can be self-administered. Additionally, crovalimab can also bind to variants. If licensed, crovalimab has the potential to be a novel subcutaneous therapy for patients with PNH and offers the opportunity to enhance efficacy and binding to C5 mutational variants.

Proposed Indication

Crovalimab is indicated for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH).[1]

Technology

Description

Crovalimab (RG-6107) is a novel anti-C5 sequential monoclonal antibody recycling technology (SMART) antibody that combines isoelectric point, neonatal Fc receptor, and pH dependent affinity engineering. This results in efficient C5 binding, enhanced uptake of C5 bound crovalimab by endothelial cells, disposal of C5 in the endosome and efficient neonatal Fc receptor mediated recycling of crovalimab. Crovalimab binds to the C5 β-chain and prevents cleavage of the wildtype and single nucleotide polymorphism (SNP) C5 by the C5 convertase. In addition, crovalimab uniquely inhibits C5b6 deposition on membranes, further limiting membrane attack complex-mediated tissue damage.[2]

Crovalimab is currently in clinical development for patients with PNH. In the COMMODORE 1-3 phase III clinical studies (NCT04432584, NCT04434092, NCT04654468) crovalimab is administered as follows:

- Loading dose: one intravenous (IV) dose (Day 1) of either 1000mg (for participants with body weight greater than 40kg but less than 100kg) or 1500mg (for participants with body weight >=100kg) followed by an subcutaneous (SC) doses (Day 2, 8, 15, 22) starting at 340mg and escalating to maintenance dose.
- Maintenance dose: SC dose every 4 weeks Q4W) of up to 1020mg depending on the patient's body weight.[3-5]

Key Innovation

Crovalimab is unique in that its properties allow for subcutaneous injections once every 4 weeks (Q4W) that can be self-administered. Additionally, crovalimab binds to C5 mutational variants with adequate efficacy in patients. Promising results were obtained in the Phase I/II trial (NCT03157635) conducted in patients with PNH, with or without prior anti-C5 treatment.[6] If licensed, crovalimab has the potential to be a novel subcutaneous therapy for patients (ages 12 and older) with PNH, and offers the opportunity to enhance efficacy and binding to C5 mutational variants.[2,6]

Regulatory & Development Status

Crovalimab does not currently have Marketing Authorization in the EU/UK for any indication.

Crovalimab is also currently in phase II/III clinical development for the following indications:[7]

- Atypical Hemolytic Uremic Syndrome
- Sickle Cell Disease

Patient Group

Disease Area and Clinical Need

Paroxysmal nocturnal haemoglobinuria (PNH) is a life-threatening syndrome with sudden onset of haematuria, anaemia, and thrombosis.[2] It is a rare blood disease that causes red blood cells to break apart in a process known as haemolysis. It happens because the surface of a person's blood cells are missing a

protein that protects them from the body's immune system. When red blood cells break apart, the haemoglobin inside is released. The release of haemoglobin causes many of the PNH symptoms.[8] The haemoglobin is excreted from the body in the urine, resulting in the dark-coloured or blood coloured urine (haemoglobinuria) that is characteristic of this disorder. Haemolysis is ongoing, but may worsen (i.e., a person may have a haemolytic episode) during periods of infection, trauma or stress. Mild haemolysis can cause fatigue, rapid heartbeat, headaches, chest pain and difficulty breathing when exercising. If haemolysis is severe, additional symptoms can develop, including disabling fatigue, difficulty swallowing (dysphagia) and painful contractions that affect the abdomen, the oesophagus (oesophageal spasms) and, in men, can cause erectile dysfunction and impotence. Chronic haemolysis can also lead to the development of blood clots and some affected individuals may develop acute and chronic kidney (renal) disease.[9]

The incidence of PNH in Great Britain has been estimated as approximately 1 in 770,000 each year, with a predicted prevalence of approximately 1 in 62,500. It is estimated that there are about 650 to 900 people in England with PNH.[10] In England, 2020-21, there were 445 finished consultant episodes (FCEs) and 431 admissions for PNH (ICD-10 code D59.5) which resulted in 390 day cases and 104 FCE bed days.[11]

Recommended Treatment Options

NICE currently recommends the following treatment options for PNH:[12]

- Ravulizumab
- Pegceracoplan
- Eculizumab

Clinical Trial Information

Trial	**COMPOSER**, NCT03157635, 2016-002128-10, An Adaptive Phase I/II Study to Assess Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Crovalimab in Healthy Volunteers and Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) **Phase I/II:** Active, not recruiting **Location(s):** 5 EU countries **Primary completion date:** October, 2030
Trial Design	Randomized, sequential assignment, quadruple masking
Population	N=59, male or female participants with PNH between 18 and 75 years of age, Neisseria meningitidis vaccination in accordance with most current local guidelines or standard of care (SOC) for participants at increased risk for meningococcal disease
Intervention(s)	Crovalimab administered IV infusion on different schedules across several study arms
Comparator(s)	Healthy participants will receive a single dose of crovalimab matching placebo
Outcome(s)	Primary outcomes: • Percentage of Participants with Dose-Limiting Events (DLEs) [Time frame: Baseline up to approximately 3 months]

	• Percentage of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time frame: Baseline up to approximately 3 months] • Terminal complement activity in serum as assessed by ex vivo liposome immunoassay (LIA) [Time frame: Baseline up to day 224] • OLE: Percentage of participants with AEs and SAEs [Time frame: OLE: week 21 up to week 545] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**COMMODORE 1,** NCT04432584, 2020-000597-26, A Phase III, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated With Complement Inhibitors. **Phase III:** Recruiting **Location(s):** 15 EU countries, UK, US, Canada and other countries **Primary completion date:** July 2022
Trial Design	Randomized, parallel assignment, open label
Population	N=250 (estimated), child, adult and older adult, body weight >= 40 kg at screening, treated with eculizumab or ravulizumab for PNH for at least 3 months prior to day 1, documented diagnosis of PNH, vaccination against Neisseria meningitides.
Intervention(s)	Participants will receive a loading series of crovalimab comprised of an (IV dose on day 1, followed by weekly crovalimab SC doses for 4 weeks.
Comparator(s)	Eculizumab will be administered at a dose of 900 mg every 2 weeks, as per the dosing schedule described above.
Outcome(s)	Primary outcomes: • Mean percentage change in lactate dehydrogenase (LDH) levels [Time frame: Baseline, week 21, week 23 and week 25] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**COMMODORE 2,** NCT04434092, 2019-004931-21, A Phase III, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Not Previously Treated With Complement Inhibitors. **Phase III:** Recruiting **Location(s):** 15 EU countries, UK, US, Canada and other countries **Primary completion date:** July 2022
Trial Design	Randomized, parallel assignment, open label
Population	N=200 (estimated), child, adult and older adult, body weight >= 40 kg at screening, documented diagnosis of PNH, vaccination against Neisseria meningitides, naïve to complement therapy
Intervention(s)	Adult Participants will receive an initial intravenous (IV) loading dose on Week 1 Day 1, followed by 4 weekly crovalimab subcutaneous (SC) doses.
Comparator(s)	Eculizumab will be administered at a dose of 600 mg for the first 4 weeks, followed by maintenance doses of 900 mg starting on Week 5, as per the prescribed dosing schedule
Outcome(s)	Primary outcomes: • Percentage of Participants who achieve Transfusion Avoidance (TA) [Time Frame: Baseline through Week 25] • Percentage of Participants with hemolysis control [Time Frame: Week 5 through Week 25] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**COMMODORE 3,** NCT04654468, A Phase III, Multicenter, Single Arm Study Evaluating the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Crovalimab in Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Not Previously Treated With Complement Inhibition. **Phase III:** Recruiting **Location(s):** China **Primary completion date:** December 2022

Trial Design	Single group assignment, open label
Population	N=51, ages 12 years and older, body weight >= 40 kg at screening, documented diagnosis of PNH, Lactate Dehydrogenase Levels >= 2x the upper limit of normal (ULN), participants who have at least four transfusions during 12 months prior to screening vaccination against Neisseria meningitides, Vaccination against Haemophilius influenzae type B and Streptococcus pneumonia, naïve to previous complement inhibitor therapy
Intervention(s)	Crovalimab will be administered at a dose of 1000 mg IV (for participants with body weight between 40 and 100kg) or 1500 mg IV (for participants with body weight >=100kg) on Week 1 Day 1. On week 1 day 2 and on weeks 2, 3 and 4, it will be administered at a dose of 340 mg SC. For week 5 and Q4W thereafter, it will be administered at a dose of 680 mg SC (for participants with body weight between 40 and 100kg) or 1020 mg SC (for participants with body weight >=100kg).
Comparator(s)	N/A
Outcome(s)	Primary outcomes: • Mean Percentage of Participants with Hemolysis Control [Time Frame: Week 5 through Week 25] • Change from Baseline to Week 25 in Percentage of Participants who achieve Transfusion Avoidance (TA) [Time Frame: Baseline, Week 25] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost of crovalimab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Danicopan with a C5 inhibitor for treating paroxysmal nocturnal haemoglobinuria in people with extravascular haemolysis (GID-TA10980). Expected date of issue to be confirmed.
- NICE technology appraisal. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria (TA778). March 2022.

- NICE technology appraisal. Ravulizumab for treating paroxysmal nocturnal haemoglobinuria (TA698). May 2021.
- NICE highly specialised technology guidance. Eculizumab for treating atypical haemolytic uraemic syndrome (HST1). January 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents). B05/S(HSS)/a.

Other Guidance

- PNH Education and Study Group (PESG). PESG PNH diagnosis, follow-up and treatment guidelines. 2016.[13]

Additional Information

References

1 Clinicaltrials.gov. *Study to Assess Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Crovalimab in Healthy Volunteers and Participants With Paroxysmal Nocturnal Hemoglobinuria*. *Trial ID: NCT03157635*. 2017. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03157635 [Accessed 8th April 2022].

2 Röth A, Nishimura J-I, Nagy Z, Gaàl-Weisinger J, Panse J, Yoon S-S, et al. The complement C5 inhibitor crovalimab in paroxysmal nocturnal hemoglobinuria. *Blood*. 2020;135(12):912-20. Available from: https://doi.org/10.1182/blood.2019003399.

3 Clinicaltrials.gov. *A Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated With Complement Inhibitors. (COMMODORE 1)*. *Trial ID: NCT04432584*. 2020. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04432584 [Accessed 22nd April 2022].

4 Clinicaltrials.gov. *A Phase III Study Evaluating The Efficacy And Safety Of Crovalimab Versus Eculizumab In Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH) Not Previously Treated With Complement Inhibitors. (COMMODORE 2)*. *Trial ID: NCT04434092*. 2020. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/study/NCT04434092 [Accessed 22nd April 2022].

5 Clinicaltrials.gov. *A Study Evaluating the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Crovalimab in Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH) Not Previously Treated With Complement Inhibition (COMMODORE 3)*. *Trial ID: NCT04654468*. 2020. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04654468 [Accessed 22nd April 2022].

6 Kulasekararaj AG, Risitano A, Roeth A, He G, Pu J, Wright L, et al. Two Currently Recruiting Randomized Phase III Trials: COMMODORE 1 and 2 Evaluating Crovalimab Vs Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria with or without Current Anti-Complement Therapy. *Blood*. 2021;138:4313. Available from: https://doi.org/https://doi.org/10.1182/blood-2021-152306.

7 Clinicaltrials.gov. *Search: Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | crovalimab | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=crovalimab&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 8th April 2022].

8 The Aplastic Anemia and MDS International Foundation. *PNH - Paroxysmal Nocturnal Hemoglobinuria*. Available from: https://www.aamds.org/diseases/pnh [Accessed 8th April 2022].

9 National Organization for Rare Disorders (NORD). *Paroxysmal Nocturnal Hemoglobinuria*. Available from: https://rarediseases.org/rare-diseases/paroxysmal-nocturnal-hemoglobinuria/ [Accessed 8th April 2022].

10 National Institute for Health and Care Excellence (NICE). *Health Technology Appraisal - Pegcetacoplan for previously treated paroxysmal nocturnal haemoglobinuria*. 2020. Available from: https://www.nice.org.uk/guidance/ta778/documents/draft-scope-post-referral [Accessed 8th April 2022].

11 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 8th April 2022].

12 National Institute for Health and Care Excellence (NICE). *Search: paroxysmal nocturnal haemoglobinuria*. Available from: paroxysmal nocturnal haemoglobinuria | Search results | NICE [Accessed 8th April 2022].

13 Sahin F, Akay OM, Ayer M, Dal MS, Ertop S, Ilhan O, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. *American journal of blood research*. 2016;6(2):19-27. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981648/

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