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Newcastle University

Health Technology Briefing
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Emicizumab for mild or moderate haemophilia A

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

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Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Emicizumab is currently in development for the treatment of congenital mild or moderate haemophilia A, without factor VIII inhibitors. Haemophilia A is a genetic bleeding disorder caused by insufficient levels of a blood clotting factor, called factor VIII (eight). This causes poor blood clotting, which results in difficulty in stopping the flow of blood from a wound, causing prolonged bleeding. There is currently no cure for haemophilia A. It is managed by lifelong prophylactic (preventative) treatment to prevent bleeding episodes from occurring. Bleeds can be prevented or reduced by injections of factor VIII into the vein. However, the half-life of factor VIII means >2 infusions per week are necessary; resulting in a substantial treatment burden, thus treatments with a high efficacy and reduced burden are needed

Emicizumab is a type of protein called an antibody; it is a bispecific antibody meaning it can bind two or more targets. Emicizumab bridges activated factor IX (nine) and factor X (ten) to restore the function of missing activated factor VIII, which brings those clotting factors near each other and activates the blood clotting system even if no factor VIII is present. Emicizumab will be administered subcutaneously (SC), which reduces frequency of venous access. If approved, emicizumab will provide an additional treatment option for congenital mild or moderate haemophilia A without factor VIII inhibitors.

Proposed Indication

Prophylaxis in patients with mild or moderate haemophilia A without factor VIII inhibitors.[1]

Technology

Description

Emicizumab (Hemlibra, RO5534262, RG6013, ACE910) is a humanised monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure. Emicizumab bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective haemostasis. Emicizumab has no structural relationship or sequence homology to factor VIII and, as such, does not induce or enhance the development of direct inhibitors to factor VIII.[2,3]

Emicizumab is currently in clinical development for the treatment of patients with mild or moderate congenital haemophilia A without FVIII inhibitors. In the phase III trial NCT04158648, emicizumab is administered as a SC injection at a dose of 3mg/kg once a week (QW) for 4 weeks, followed by patients preference of one of the following regimens: 1.5 mg/kg QW, 3 mg/kg once every 2 weeks (Q2W), or 6 mg/kg once every 4 weeks (Q4W).[2]

Key Innovation

There is currently no cure for haemophilia A; lifelong treatment is required. The aim of treatment for haemophilia A is to prevent bleeding episodes from occurring. Bleeds can be prevented or reduced by injections of factor VIII into the vein.[4] However, because of the half-life of factor VIII, more than two infusions per week are necessary for maintaining protective trough levels, which results in a substantial treatment burden, and an unsatisfactory level of care for persons who are unable to adhere to this strategy. Thus, treatments with a high efficacy and reduced burden are needed.[5] Emicizumab works by mimicking the action of factor VIII. Emicizumab binds to factor X and activated factor IX which brings those clotting factors near each other and activates the blood clotting system even if no factor VIII is present. Emicizumab is administered SC, greatly reducing the frequency of venous access.[4]

If approved, emicizumab would offer an additional treatment option for mild or moderate haemophilia A without FVIII Inhibitors.

Regulatory & Development Status

Emicizumab is currently licensed in the UK for the following indications in all ages: for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors, and severe haemophilia A (congenital factor VIII deficiency, Factor VIII < 1%) without factor VIII inhibitors.[3]

Emicizumab is currently in phase II and III trials for the treatment of haemophilia A, severe haemophilia A, haemophilia A with inhibitor, haemophilia A without inhibitors and acquired haemophilia A.[6]

Patient Group

Disease Area and Clinical Need

Haemophilia A, also known as classical haemophilia, is a genetic bleeding disorder caused by insufficient levels of a blood protein called factor VIII. Factor VIII is a clotting factor, which is essential for proper blood

clotting. Individuals with haemophilia A do not bleed faster or more profusely than healthy individuals, but because their blood clots poorly, they have difficulty stopping the flow of blood from a wound. Haemophilia A can be mild, moderate, or severe, depending on the baseline level of factor VIII made by that individual. In mild cases, prolonged bleeding episodes may only occur after surgery, dental procedures, or trauma. In more severely affected individuals, symptoms may include prolonged bleeding from minor wounds, painful swollen bruises, and unexplained (spontaneous) bleeding into vital organs as well as joints and muscles (internal bleeding). Haemophilia A is caused by disruptions or changes (mutations) to the Factor VIII gene located on the X chromosome. This mutation may be inherited or occur randomly with no previous family history of the disorder (spontaneously). Haemophilia A is mostly expressed in males but some females who carry the gene may have mild or, rarely, severe symptoms of bleeding.[7]

Haemophilia A is the most common X-linked recessive disorder and the second most common inherited clotting factor deficiency. Haemophilia A mostly affects males, but females can also be affected. Approximately 40% of individuals with haemophilia A have non-severe haemophilia.[7] In the UK, between April 2015 and March 2016, there was a total of 7,700 patients registered for congenital haemophilia A in the UK National Haemophilia Database, including 411 new haemophilia A registrations in the year and 3,267 patients being treated for haemophilia A.[8]

Recommended Treatment Options

The recommended treatment plan for haemophilia depends on how severe it is. There are two main approaches to treatment. One is preventative treatment, where medicine is used to prevent bleeding and subsequent joint and muscle damage. The other is on-demand treatment, where medicine is used to treat prolonged bleeding. Severe haemophilia needs preventative treatment, which involves regular injections of clotting factor medicines.[9]

Preventative treatment for haemophilia A involves regular injections of a medicine called octocog alfa. Injections every 48 hours are often recommended. In mild or moderate cases, haemophilia A can be treated on-demand with injections of octocog alfa or a medicine called desmopressin. Some people who take blood clotting factor medicine develop inhibitors in their immune system, which make the medicine less effective. People with mild or moderate haemophilia A who develop inhibitors may be offered either bypass therapy or immunosuppressants.[9]

Clinical Trial Information

Trial	**HAVEN 6**; NCT04158648; 2019-002179-32; A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Emicizumab in Patients With Mild or Moderate Hemophilia A Without FVIII Inhibitors. **Phase III:** Active, not recruiting **Location:** 6 countries in EU, UK, USA, Canada and South Africa **Study completion date:** October 2021
Trial Design	Single group assignment, open label
Population	N = 73 (actual); mild moderate congenital Haemophilia A without FVIII inhibitors; Child, adult, older adult

Intervention(s)	Emicizumab, 3mg/kg QW for 4 weeks, then 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W, SC injection.
Comparator(s)	No comparator
Outcome(s)	• Model-Based Annualized Bleeding Rate for Treated Bleeds [Time Frame: Bleed data collected every week and on days of bleed from Baseline until Study Completion/Discontinuation Visit (after at least 52 weeks of emicizumab treatment in the study or 24 weeks after final dose of emicizumab; up to approximately 30 months)] • Median Calculated Annualized Bleeding Rate for Treated Bleeds [Time Frame: Bleed data collected every week and on days of bleed from Baseline until Study Completion/Discontinuation Visit (after at least 52 weeks of emicizumab treatment in the study or 24 weeks after final dose of emicizumab; up to approximately 30 months)] • Mean Calculated Annualized Bleeding Rate for Treated Bleeds [Time Frame: Bleed data collected every week and on days of bleed from Baseline until Study Completion/Discontinuation Visit (after at least 52 weeks of emicizumab treatment in the study or 24 weeks after final dose of emicizumab; up to approximately 30 months)] For full list of outcomes, see trial registry
Results (efficacy)	A mean (standard deviation) improvement in HJHS total score from baseline of −1.77 (2.94) was observed at Week 25 (n=47). The trend for improvement from baseline in the treatment burden domain for CATCH was consistent across age groups (8–17 and >18 years). Except for a small improvement in 'social activity risk perception' among adolescents, the remaining CATCH domains were stable. Improvements were observed in 'treatment burden' and 'preoccupation' domains among caregivers, but due to small sample number, trends should be interpreted with caution. Overall, 48/50 (96.0%) EmiPref respondents preferred emicizumab over their previous HA therapy.[1] Nearly half (46.5%) of the participants have so far been bleed-free, and more than four out of every five (80.3%) have had no bleeds that required treatment. Over 90% have had no joint bleeds that required treatment, and a marked improvement in joint health over the course of treatment was observed.[10]
Results (safety)	Data at the IA of the HAVEN 6 study indicate that emicizumab has a favourable safety profile. Forty-nine participants (69.0%) had ≥1 AE (Table 2); headache was the most common (14.1%). The majority of AEs (84.5%) were not emicizumab-related. Local injection-site reactions were reported for nine participants (12.7%); all were emicizumab-related. One participant (1.4%) experienced two Grade ≥3 AEs, neither emicizumab-related. Four participants (5.6%) reported a total of six SAEs; none were considered emicizumab-related by the investigator. There were no deaths, AEs leading to treatment withdrawal/modification/interruption, TEs, or TMAs.[1]

Estimated Cost

The NHS indicative price of 30mg/1ml vial of emcizumab is £2415.30, for 105mg/0.7ml vial it is £8453.55, for 150mg/1ml vial it is £12076.50, for 60mg/0.4ml vial it is £4830.60.[11]

Relevant Guidance

NICE Guidance

No relevant guidance.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors (all ages). 170134P. August 2019.
- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages). 170067/P. July 2018.
- NHS England. 2013/14 NHS Standard Contract for Haemophilia A (all ages). B05/S/a.

Other Guidance

- NHSGGC Paediatrics for Health Professionals. Haemophilia protocol. November 2020.[12]
- World Federation of Hemophilia. WFH Guidelines for the Management of Hemophilia, 3rd edition. August 2020.[13]
- British Society for Haematology. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. May 2020.[14]
- United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO). Laboratory coagulation tests and emicizumab treatment A United Kingdom Haemophilia Centre Doctors' Organisation guideline. January 2020.[15]
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Additional Information

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