NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
November 2022

Ravulizumab (subcutaneous formulation) for treating paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome

Company/Developer	Alexion Pharmaceuticals Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 35188	NICE ID: 11820	UKPS ID: 660226

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

The subcutaneous formulation of ravulizumab (ravulizumab SC) is in clinical development for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS). In PNH and aHUS, proteins known as the 'complement system', which is part of the immune system, become overactive and start to attack the body's own cells. This occurs due to a genetic fault in the complement system in aHUS, and an acquired mutation in a class of blood cell protective proteins in PNH. This results in the destruction of red blood cells in PNH, and the formation of blood clots in small blood vessels (thrombotic microangiopathy) in aHUS. PNH results in anaemia, thrombosis (blood clots in the blood vessels), pancytopenia (low blood cell counts) and dark urine. aHUS results in anaemia, thrombocytopenia (a decrease in the number of platelets, components that help the blood to clot) and kidney failure.

Ravulizumab, administered subcutaneously (SC), is a 'complement inhibitor'. It is a monoclonal antibody (a type of protein) designed to attach to the C5 protein, which is part of the complement system. By attaching to the C5 protein, the medicine blocks its effect and thereby reduces symptoms. The intravenous formulation of ravulizumab is already approved for the treatment of PNH and aHUS and is in use in the NHS. If licensed, ravulizumab SC would become the first on body device system treatment option for patients with PNH and aHUS and will provide additional choice for patients and clinicians on the method of administration of ravulizumab.

Proposed Indication

Paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS).[1-3]

Technology

Description

Ravulizumab (Ultomiris) is a monoclonal antibody IgG2/4K that specifically binds to the complement protein C5, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) and preventing the generation of the C5b-9. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.[4] Ravulizumab is a long-acting C5 inhibitor that achieves immediate, complete, and sustained inhibition of complement-mediated haemolysis with an extended dosing interval compared to eculizumab. It exhibits high-affinity binding to C5 and inhibits C5a and C5b formation, thereby preventing immune activation and haemolysis.[5]

Ravulizumab is currently in clinical development for the treatment of PNH. In the phase III clinical trial (NCT03748823; 2017-002370-39) patients are given ravulizumab as a subcutaneous (SC) infusion administered via an on-body delivery system.[6]

Key Innovation

Ravulizumab SC is delivered via a rapid, patient-friendly delivery device. Data from a phase III study of ravulizumab SC have shown that it may offer the same benefits of immediate, complete and sustained complement inhibition as the intravenous (IV) formulation, while also providing an additional treatment choice for those who would rather self-administer their medicine.[7]

If licensed, ravulizumab SC would offer a SC on-body delivery system treatment option for patients with PNH and aHUS.

Regulatory & Development Status

Ravulizumab SC does not currently have Marketing Authorisation in the EU/UK for any indication.

Ravulizumab IV infusion has Marketing Authorisation in the EU/UK for the treatment of PNH, aHUS and generalized myasthenia gravis (gMG).[4,8]

Ravulizumab SC is not currently in clinical development for any other indications.

Patient Group

Disease Area and Clinical Need

PNH is a rare condition that manifests with haemolytic anaemia, thrombosis, and peripheral blood cytopenias due to bone marrow failure.[9] PNH occurs due to a mutation in a gene called PIG-A within stem cells in the bone marrow. These stem cells give rise to red blood cells, white blood cells and platelets, therefore, when the PIG-A mutation occurs all cells derived from the affected stem cell carry the mutation. Mutated blood cells are deficient in a class of proteins called GPI-anchored proteins, which protect red blood cells from destruction. Many clinical PNH manifestations result from a deficiency in GPI-anchored

proteins.[10] The exact cause of PNH is not fully understood, but it is known that the PIG-A mutation is acquired and not present from birth.[11] It can occur at any age, but is usually diagnosed in young adulthood.[12] Signs and symptoms of PNH can show a large amount of variation. Some people exhibit no symptoms, yet others may be affected by a number of different symptoms and complications. Common signs and symptoms include: haemoglobinuria (dark or black urine due to haemoglobin in the urine), anaemia, breathlessness, difficulty swallowing, abdominal pain, erectile dysfunction in men, fatigue, jaundice, kidney damage and blood clots.[13] PNH can be potentially life-threatening and thrombosis is recognised as the leading cause of death in PNH patients.[14]

aHUS is a disease that causes abnormal blood clots to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow, including haemolytic anaemia, thrombocytopenia, and kidney failure. It can occur at any age and is often caused by a combination of environmental and genetic factors. Environmental factors that can trigger aHUS include certain medications, chronic diseases, viral or bacterial infections, cancers, organ transplantation, and pregnancy.[15] Symptoms include vague feelings of illness, fatigue, irritability, and lethargy that can potentially lead to hospitalisation.[16]

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.[17] It is estimated that there are about 650 people in England with PNH.[18] In England (2021/22), there were 620 hospital admissions with primary diagnosis of PNH (ICD-10 code D59.5), and 631 finished consultant episodes (FCEs), resulting in 70 FCE bed days and 589 day cases.[19]

aHUS is an ultra-rare disease. The UK incidence is estimated at 0.4 per million per year and presents at all ages.[20] aHUS accounts for approximately 5-10% of all cases of haemolytic uremic syndrome.[16] In England (2021/22), there were 872 hospital admissions with primary diagnosis of haemolytic-uraemic syndrome (ICD-10 code D59.3), and 958 finished consultant episodes (FCEs), resulting in 878 FCE bed days and 692 day cases.[19]

Recommended Treatment Options

For treating PNH in adults the National Institute for Health and Care Excellence (NICE) currently recommends the following treatment options:[21-23]

- Ravulizumab IV
- Pegcetacoplan

Eculizumab is commissioned for PNH by NHS England through the national PNH highly specialised service.[24,25]

For treating aHUS NICE currently recommends the following treatment options:[26,27]

- Eculizumab
- Ravulizumab IV

Clinical Trial Information

Trial	NCT03748823; 2017-002370-39; A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label, Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients With Paroxysmal Nocturnal Haemoglobinuria Currently Treated With Eculizumab

	Phase III – Ongoing **Locations:** 10 EU countries, UK, USA, Canada and other countries **Primary completion date:** April 2020
Trial Design	Randomised, parallel assignment, open-label
Population	N=136 (actual); documented diagnosis of PNH confirmed by high-sensitivity flow cytometry evaluation; treated with eculizumab according to the labelled dosing recommendation for PNH (900 mg every 14 days ± 2 days) for at least 3 months prior to study entry; aged 18 and older
Intervention(s)	Ravulizumab (SC administered via an on-body delivery system)
Comparator(s)	Ravulizumab (IV)
Outcome(s)	**Primary outcome:** • To evaluate PK noninferiority of ravulizumab SC versus ravulizumab IV in adult patients with PNH See trial record for full list of other outcomes.
Results (efficacy)	Efficacy endpoints remained stable: mean (standard deviation, SD) lactate dehydrogenase (LDH) percentage change was 0.9% (20.5%); breakthrough hemolysis (BTH) events, 5/128 patients (3.9%); 83.6% achieved transfusion avoidance; 79.7% achieved stabilised haemoglobin. Total Treatment Administration Satisfaction Questionnaire (TASQ) score showed improved satisfaction with SUBQ ravulizumab compared with IV eculizumab (mean [SD] change at SUBQ day 351, – 69.3 [80.1]).[28]
Results (safety)	The most common AEs during SUBQ treatment (excluding ADEs) were headache (14.1%), COVID-19 (14.1%), and pyrexia (10.9%); the most common ADE unrelated to a device product issue was injection site reaction (4.7%).[28]

Estimated Cost

Cost of ravulizumab SC was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria (TA778). March 2022.
- NICE technology appraisal. Ravulizumab for treating atypical haemolytic uraemic syndrome (TA710). June 2021.
- NICE technology appraisal. Ravulizumab for treating paroxysmal nocturnal haemoglobinuria (TA698). May 2021.
- NICE highly specialised technologies 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
- NHS England. Service specification: Atypical haemolytic uraemic syndrome (aHUS) (all ages). May 2017.

Other Guidance

- BMJ Best Practice. Haemolytic uraemic syndrome – Guidelines. 2022.[29]
- PNH Education and Study Group. PESG PNH diagnosis, follow-up and treatment guidelines. 2016.[30]

Additional Information

References

1 Alexion Pharmaceuticals Inc. *Alexion Announces Phase 3 Study of Weekly Subcutaneous ULTOMIRIS® (ravulizumab-cwvz) Met Primary Endpoint.* 2020. Available from: https://media.alexion.com/news-releases/news-release-details/alexion-announces-phase-3-study-weekly-subcutaneous-ultomirisr [Accessed 29 November 2022].

2 Alexion Pharmaceuticals Inc. *Pipeline.* Available from: https://alexion.com/our-research/pipeline [Accessed 29 November 2022].

3 Clinicaltrials.gov. *A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label, Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab*. *Trial ID: NCT03748823*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03748823 [Accessed 29 November 2022].

4 Electronic Medicines Compendium. *Ultomiris 1,100 mg/11 mL concentrate for solution for infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/11945/smpc [Accessed 7 October 2022].

5 Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, Pessoa V, Gualandro S, Füreder W, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 2019;133(6):530-9. Available from: https://doi.org/10.1182/blood-2018-09-876136.

6 EU Clinical Trials Register. *A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label, Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab*. *Trial ID: 2017-002370-39*. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-002370-39 [Accessed 7 October 2022].

7 Business Wire. *Alexion Announces Phase 3 Study of Weekly Subcutaneous ULTOMIRIS® (ravulizumab-cwvz) Met Primary Endpoint.* 2020. Available from: https://www.businesswire.com/news/home/20200624005487/en/Alexion-Announces-Phase-3-Study-Weekly-Subcutaneous [Accessed 20 October 2022].

8 National Institute for Health and Care Excellence. *Ravulizumab.* Available from: https://bnf.nice.org.uk/drugs/ravulizumab/ [Accessed 20 October 2022].

9 Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804-11. Available from: https://doi.org/10.1182/blood-2014-02-522128.
10 MedlinePlus. *Paroxysmal nocturnal hemoglobinuria.* 2022. Available from: https://medlineplus.gov/genetics/condition/paroxysmal-nocturnal-hemoglobinuria/#description [Accessed 13 October 2022].
11 PNH National Service. *What causes PNH?* Available from: https://pnhserviceuk.co.uk/patient-information/what-is-pnh/what-causes-pnh/ [Accessed 24 November 2022].
12 National Centre for Advancing Translational Sciences. *Paroxysmal nocturnal hemoglobinuria.* 2011. Available from: https://rarediseases.info.nih.gov/diseases/7337/paroxysmal-nocturnal-hemoglobinuria [Accessed 13 October 2022].
13 PNH Support. *Signs and Symptoms.* Available from: https://pnhuk.org/what-is-pnh/signs-and-symptoms/ [Accessed 4 November 2022].
14 Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121(25):4985-96. Available from: https://doi.org/10.1182/blood-2012-09-311381.
15 Genetic and Rare Diseases Information Center. *Atypical hemolytic uremic syndrome.* 2021. Available from: https://rarediseases.info.nih.gov/diseases/8702/atypical-hemolytic-uremic-syndrome [Accessed 20 October 2022].
16 National Organisation of Rare Diseases. *Atypical Hemolytic Uremic Syndrome.* 2016. Available from: https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome/ [Accessed 20 October 2022].
17 Orphanet. *Paroxysmal nocturnal hemoglobinuria.* 2017. Available from: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=21&Disease_Disease_Search_diseaseGroup=paroxysmal-nocturnal-haemoglobinuria&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Paroxysmal-nocturnal-hemoglobinuria&title=Paroxysmal-nocturnal-hemoglobinuria&search=Disease_Search_Simple [Accessed 24 November 2022].
18 NHS England. *Highly Specialised Services 2018.* 2018. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/12/Highly-Specialised-Services-2018-v2.pdf [Accessed 24 November 2022].
19 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22.* 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 15 November 2022].
20 National Renal Complement Therapeutics Centre. *What is aHUS?* Available from: http://www.atypicalhus.co.uk/ahus/what-is-ahus/ [Accessed 20 October 2022].
21 National Institute for Health and Care Excellence. *Ravulizumab for treating paroxysmal nocturnal haemoglobinuria* (*TA698)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/TA698 [Accessed 24 November 2022].
22 National Institute for Health and Care Excellence. *Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria* (*TA778)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta778 [Accessed 24 November 2022].
23 Electronic Medicines Compendium. *Soliris.* 2022. Available from: https://www.medicines.org.uk/emc/product/362/smpc [Accessed 17 November 2022].
24 NHS England. *2013/14 NHS Standard Contract for Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents).* 2013. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-parox-haem-serv.pdf [Accessed 24 November 2022].
25 National Institute for Health and Care Excellence. *Highly Specialised Technologies Evaluation: Ravulizumab for treating paroxysmal nocturnal haemoglobinuria.* 2020. Available from: https://www.nice.org.uk/guidance/ta698/documents/final-scope [Accessed 24 November 2022].

26 National Institute for Health and Care Excellence. *Eculizumab for treating atypical haemolytic uraemic syndrome* (*HST1)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/hst1 [Accessed 20 October 2022].

27 National Institute for Health and Care Excellence. *Ravulizumab for treating atypical haemolytic uraemic syndrome* (*TA710)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta710 [Accessed 20 October 2022].

28 Yenerel MN, Sicre de Fontbrune F, Piatek C, Sahin F, Füreder W, Ortiz S, et al. Phase 3 Study of Subcutaneous Versus Intravenous Ravulizumab in Eculizumab-Experienced Adult Patients with PNH: Primary Analysis and 1-Year Follow-Up. *Adv Ther*. 2022:1-22. Available from: https://doi.org/10.1007/s12325-022-02339-3.

29 BMJ Best Practice. *Haemolytic uraemic syndrome.* 2022. Available from: https://bestpractice.bmj.com/topics/en-gb/470 [Accessed 20 October 2022].

30 Sahin F, Akay OM, Ayer M, Dal MS, Ertop S, Ilhan O, et al. *Pesg PNH diagnosis, follow-up and treatment guidelines.* 2016. Available from: http://europepmc.org/abstract/MED/27570707 [Accessed 24 November 2022].

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.