Health Technology Briefing
March 2022

Ravulizumab for treatment of neuromyelitis optica spectrum disorder

Company/Developer	Alexion Pharmaceuticals

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29254	NICE ID: 10533	UKPS ID: 660228

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Ravulizumab is in clinical development for the treatment of neuromyelitis optica spectrum disorder (NMOSD). NMOSD is a rare autoimmune disease where the immune system attacks the nerves in the eyes and central nervous system (CNS), which can result in weakness, paralysis, pain, blindness, and premature death. The condition often has frequent relapses which can result in progressive disabilities for the patient. New treatment options could decrease frequency and intensity of relapses for patients, increasing overall survival for patients.

Ravulizumab is type of monoclonal antibody that blocks the immune system from targeting the patient's own cells. It has been created from the already licensed medicinal product, eculizumab, but has been designed to last longer so patients need less frequent treatments while still gaining the same benefits. Ravulizumab is administered intravenously. If licensed, ravulizumab will offer a new treatment option for patients with NMOSD.

Proposed Indication

Ravulizumab is in clinical development for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) and are anti-aquaporin-4 antibody positive (AQP4+), that have had at least one attack or relapsed in the past 12 months.[1]

Technology

Description

Ravulizumab (Ultomiris, ALXN-1210) is a recombinant IgG2/4 monoclonal antibody that inhibits terminal complement activation at the C5 protein, preventing initiation of the complement system.[2] The complement system often becomes overactivated in autoimmune conditions such as NMOSD where it causes neuronal destruction - blocking this can reduce symptoms of disease or incidence of relapse.[3,4] Ravulizumab has been developed from the licensed eculizumab to have a longer half-life for less frequent dosing, and only has a difference in four point mutations.[5]

Ravulizumab is in clinical development for the treatment of naive adult patients with NMOSD who are AQP4+, who have had at least one attack or relapse within the last 12 months.[1] In the phase III clinical trial (NCT04201262), ravulizumab will be administered intravenously (IV), with a weight based loading dose on day 1, followed by a weight-based maintenance dose on day 15, and then once every 8 weeks until the end of the study period.[1]

Key Innovation

Ravulizumab was developed to have the same mechanism of action and efficacy as the already licensed eculizumab but to have an extended half-life so that maintenance dosing can be delivered once every eight weeks compared to the current regimen of every two weeks.[5] The longer half-life of ravulizumab reduces the treatment burden on patients as they only require six infusions per year instead of 26, increasing quality of life, better treatment adherence and improved accessibility.[6] Studies have shown ravulizumab to be non-inferior to eculizumab in both safety and efficacy.[6] Eculizumab is licensed for use in the UK but its cost-effectiveness has not been assessed by NICE.[7] If licensed ravulizumab would provide a targeted treatment option for adult patients with AQP4+ NMOSD – the first treatment to target the pathophysiological mechanism of the disease that would be available to patients in the UK, giving an alternative to treatments that only treat acute episodes or individual symptom management.[8]

Regulatory & Development Status

Ravulizumab is licensed for the indications of paroxysmal nocturnal haemoglobinuria and atypical haemolytic syndrome.[2]

Ravulizumab is also in phase III clinical development for:[9]

- Myasthenia gravis
- Thrombotic microangiopathy
- Dermatomyositis

Patient Group

Disease Area and Clinical Need

Neuromyelitis optica (NMO), also known as Devic's disease, is a rare chronic autoimmune disease of the CNS where the immune system damages the spinal cord and the nerves of the eyes causing transverse myelitis and optic neuritis respectively.[8] NMO can present with an isolated incident or be relapsing, with frequent attacks which can result in permanent neurologic disabilties.[10] NMO is caused by a pathogenic serum IgG antibody against the water channel AQP4 in 70% of cases - it binds to AQP4 channels on astrocytes, triggering activation of the classical complement cascade, causing granulocyte, eosinophil, and lymphocyte infiltration, culminating in injury first to astrocyte, then oligodendrocytes followed by demyelination and neuronal loss.[8,11] NMOSD is a term used to encompass both NMO and limited phenotypes such as recurrent optic neuritis or myelitis.[12] Symptoms can include eye pain, loss of vision, weakness and pain in the limbs, increased sensitivity to temperature, and incontinence - these can range from mild to severe with full paralysis and blindness, with an increased risk of mortality.[4,10,13] Over 95% of patients with NMOSD have no relatives with the disease, but there is a strong association with a family history of autoimmune diseases (50% of cases).[4] NMOSD is seen in all races, genders and ages with incidence rates differing between groups but is most common in late middle-aged women.[4]

NMOSD is a rare disease with an annual incidence rate of 0.08 per 100,000 in the UK population (2013), with a range of 0.037-0.73 per 100,000 seen globally.[14,15] NMSOD has a high mortality rate if not diagnosed and treated appropriately, with 23% of patients having a median survival of three years from enrolling in studies and at five years from onset 50% of untreated patients require a wheelchair or have significant visual loss (registered blind) (UK, 2013).[11] In England (2020-21), there were 713 finished consultant episodes (FCE) for NMOSD (ICD-10 code: G36.0), with 562 hospital admissions that resulted in 347 day cases and 2784 FCE bed days.[16]

Recommended Treatment Options

Therapy for NMOSD should be started early with azathioprine suggested as first-line treatment, and immunosuppressive drugs such as methotrexate, mycophenolate mofetil and mitoxantrone suggested as second-line treatments.[17] Rituximab is recommended through specialist funding for select patients for one year after the failure of first-line treatments.[18] General standard-of-care for relapse prevention includes using a range of immunosuppressive therapies, B-cell targeting therapies, as well as new treatments that target AQP-4 (e.g. eculizumab or tocilizumab).[19]

Clinical Trial Information

Trial	NCT04201262, 2019-003352-37; A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients With Neuromyelitis Optica Spectrum Disorder (NMOSD) **Phase III –** Active, not recruiting **Location(s):** UK, USA, Australia and a number of EU and other countries **Primary completion date:** April 2022
Trial Design	Single group assignment, external placebo-controlled, open-label design

Population	N= 58; subjects with neuromyelitis optica spectrum disorder and who are AQP4+; aged 18 years and older.
Intervention(s)	Weight-based loading dose of ravulizumab via IV infusion on day 1, followed by weight-based maintenance doses on day 15, then once every 8 weeks until end of the Long-Term Extension Period.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Time to first adjudicated on-trial relapse [time frame: baseline, up to 2 years (end of the primary treatment period)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost of ravulizumab was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Inebilizumab for treating neuromyelitis optica spectrum disorders [ID1529] (GID-TA10522) Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Neuromyelitis Optica Service (Adults and Adolescents). D04/S(HSS)/b.

Other Guidance

- American Academy of Neurology. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. 2015.[20]
- Neuromyelitis Optica UK. Neuromyelitis Optica: a guide to the condition. 2012.[21]
- European Federation of Neurological Associations. EFNS guidelines on diagnosis and management of neuromyelitis optica. 2010.[22]

Additional Information

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