Health Technology Briefing
February 2022

Rozanolixizumab for generalised myasthenia gravis

Company/Developer	UCB Pharma Ltd

☒New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 22732	NICE ID: 10273	UKPS ID: 653185

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Rozanolixizumab is in clinical development for the treatment of generalised myasthenia gravis (gMG). Myasthenia gravis (MG) is a long-term condition which causes certain muscles to become weak and tire easily. It is caused by a problem with the immune system. In MG patients, harmful IgG (immunoglobulin G) antibodies mistakenly attack healthy cells and tissues, causing weakness and fatigue of voluntary muscles, meaning that the muscles are unable to tighten (contract). Symptoms include drooping of the eyelids and double vision; swallowing, speaking and breathing difficulties when muscles in the mouth, throat and chest are affected. Many commonly used therapies in MG have important limitations such as late onset of action and various side effects including increased risk of infection; therefore, alternative therapeutic options are needed for gMG patients.

Rozanolixizumab is a monoclonal antibody (a type of protein) that is administered subcutaneously and designed to recognise and attach to FcRn receptor, a protein that keeps the IgG antibodies in the body for longer. By binding to and blocking FcRn, rozanolixizumab increases the removal of these antibodies leading to an improvement in muscle function. If licensed, rozanolixizumab could offer a novel alternative treatment for patients with gMG that targets a different pathway compared to many conventional treatments.

Proposed Indication

Rozanolixizumab is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who have a positive record of acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) autoantibodies and require additional therapy.[1]

Technology

Description

Rozanolixizumab (UCB7665) is a humanised, high affinity, anti-human neonatal Fc receptor (FcRn) monoclonal antibody that is designed to reduce the levels of pathogenic immunoglobulin G (IgG) autoantibodies in autoimmune and alloimmune diseases.[2]

In the phase III trials (NCT03971422, NCT04124965, NCT04650854), patients were randomised to receive rozanolixizumab subcutaneously at one of two different dosages and receive these assigned dosages at pre-specified time points during the treatment period.[1,3,4]

Key Innovation

Many commonly used non-targeted therapies for myasthenia gravis have important limitations such as various side effects and increased risk of infection; therefore, alternative therapeutic options are needed for patients. The treatment approach of blocking neonatal Fc receptor (FcRn) does not result in widespread immune suppression, in contrast to many therapies.[5] Current treatment for gMG does not include any anti-FcRn therapy so this would be a novel treatment for this indication targeting a different pathway to conventional treatments.[6]

If licensed, rozanolixizumab will provide an additional licensed treatment option for patients who are positive for AchR or MusK autoantibodies with gMG.[3]

Regulatory & Development Status

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

Rozanolixizumab is currently in phase II/III clinical trials for.[7]

- Chronic inflammatory demyelinating polyradiculoneuropathy
- Autoimmune Encephalitis
- Myelin oligodendrocyte glycoprotein antibody-associated Disease
- Primary immune thrombocytopenia

Rozanolixizumab was designated an orphan drug in the EU in 2020 for myasthenia gravis.[8]

Patient Group

Disease Area and Clinical Need

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease which causes certain muscles to become weak and tire easily. MG is caused by an error in the transmission of nerve impulses to muscles and occurs when normal communication between the nerve and muscle is interrupted at the

neuromuscular junction. In MG, antibodies block, alter, or destroy the receptors for acetylcholine at the neuromuscular junction, which prevents the muscle from contracting. This is most often caused by antibodies to the acetylcholine receptor itself, but antibodies to other proteins, such as MuSK (Muscle-Specific Kinase) protein, also can impair transmission at the neuromuscular junction. The muscles that control eye and eyelid movement are commonly affected first, which causes drooping of the eyelid and double vision. Muscles controlling facial expression, chewing, swallowing, speaking and, less commonly, breathing and neck and limb movements can also be affected.[9] When muscle groups other than the eye muscles are affected, the condition is known as generalised MG (gMG).[10] MG affects both men and women and occurs across all racial and ethnic groups. It most commonly impacts young adult women (under 40) and older men (over 60), but it can occur at any age, including childhood.[9,11] MG is not inherited nor is it contagious. Occasionally, the disease may occur in more than one member of the same family.[9]

The prevalence of MG in the UK is estimated at about 15 per 100,000 population.[12] Using mid-2020 population estimates, it is estimated that around 10,020 people have MG in the UK.[13] In England in 2020-2021, there were 3,321 hospital admissions with a primary diagnosis of MG (ICD-10 code G70.0), resulting in 4,191 finished consultant episodes (FCEs) and 11,097 FCE bed days.[14]

Recommended Treatment Options

Recommended treatments available for gMG are as follows:[6,15]

- Pyridostigmine is the first treatment offered,
- If gMG patients are still symptomatic, prednisolone (or another steroid) is offered,
- Immunosuppressants can be used if symptoms are not controlled by steroids. These include azathioprine, methotrexate, mycophenolate mofetil and ciclosporin.
- Surgery to remove the thymus gland (thymectomy) in some people with an unusually large thymus

Intravenous Immunoglobulin (IVIg) is also sometimes given when there is a need for a fast response such as whilst waiting for other medications to take effect or as a rescue treatment in the event of an acute relapse of symptoms.[16] Where a rapid response is needed in myasthenic crises and exacerbations, plasma exchange (PEX) can also be provided. During PEX, plasma containing anticholinesterase receptor (AChR) antibodies is separated from whole blood and replaced by albumin or fresh frozen plasma.[17]

Clinical Trial Information

Trial	**MG0003**; NCT03971422; 2019-000968-18; A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Efficacy and Safety of Rozanolixizumab in Adult Patients With Generalized Myasthenia Gravis **Phase III** - completed **Location(s):** 9 EU countries, UK, USA, Canada and other countries **Study completion date**: October 2021	**MG0004**; NCT04124965; 2019-000969-21; A Randomized, Open-Label Extension Study to Investigate the Long-Term Safety, Tolerability, and Efficacy of Rozanolixizumab in Adult Patients With Generalized Myasthenia Gravis **Phase III** – completed **Locations:** 7 EU countries, USA, Canada and other countries **Study completion date**: September 2021

Trial Design	Randomised, parallel assignment, quadruple-blinded, placebo- controlled	Randomised, single group assignment, open-label
Population	N=200; aged 18 years and older; Subjects with a diagnosis of gMG	N=71; aged 18 years and older; Subjects eligible for MG0003 at time of enrolment
Intervention(s)	Subcutaneous (SC) administration of rozanolixizumab	Subcutaneous (SC) administration of rozanolixizumab
Comparator(s)	Matched placebo	No comparator
Outcome(s)	Primary outcome measures: • Change from Baseline to Visit 10 in Myasthenia Gravis-Activities of Daily Living (MG-ADL) score [Time Frame: Baseline and Visit 10 (Day 43)] See trial record for full list of other outcomes	Primary outcome measures: • Percentage of participants with treatment-emergent adverse events (TEAEs) [Time Frame: From Baseline until Final Visit (up to Week 60)] • Percentage of participants with treatment-emergent adverse events (TEAEs) leading to permanent withdrawal of study medication [Time Frame: From Baseline until Final Visit (up to Week 60)] See trial record for full list of other outcomes
Results (efficacy)	• Trial met its primary endpoint, demonstrating a statistically significant and clinically meaningful change from baseline in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score at Day 43. • All secondary endpoints were also met with statistical significance.[18]	-
Results (safety)	• Rozanolixizumab was well tolerated and no new safety signals were identified.[18]	-

Trial	**MG0007**; NCT04650854; 2020-003230-20; An Open-Label Extension Study to Evaluate Rozanolixizumab in Study Participants With Generalized Myasthenia Gravis **Phase III** – Enrolling by invitation **Location(s):** 8 EU countries, USA, Canada and other countries **Primary completion date**: August 2023
Trial Design	Randomised, single-group assignment, open-label
Population	N=200 (estimated); aged 18 years and older; Subjects who completed MG0003 or MG0004
Intervention(s)	Subcutaneous (SC) administration of rozanolixizumab
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Percentage of participants with treatment-emergent adverse events (TEAEs) [Time frame: From Baseline (Day 1) to End of Study (average of 20 months)]. • Percentage of participants with TEAEs leading to withdrawal of investigational medicinal product (IMP) [Time frame: from Baseline (Day 1) to End of Study (average of 20 months)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**MG0002**; NCT03052751; 2016-002698-36; A Multicenter, Randomized, Investigator- and Subject-Blind, Placebo-Controlled, Treatment Sequence Study Evaluating the Safety, Tolerability, and Efficacy of UCB7665 in Subjects With Moderate to Severe Myasthenia Gravis **Phase II** - Completed **Location(s):** 5 EU countries, USA and Canada **Study completion date**: August 2018
Trial Design	Randomised, parallel assignment, quadruple blinded, placebo controlled
Population	N=43; aged 18 years and older; Subjects with a diagnosis of MG
Intervention(s)	Subcutaneous (SC) administration of Rozanolixizumab
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Change from Baseline in Quantitative Myasthenia Gravis (QMG) Score to Visit 9 [Time frame: From Baseline to Visit 9 (up to Day 29)]

	See trial record for full list of other outcomes
Results (efficacy)	• Least squares (LS) mean change from baseline to day 29 for rozanolixizumab vs placebo was as follows: Quantitative MG (LS mean -1.8 vs -1.2, difference -0.7, 95% upper confidence limit [UCL] 0.8; p = 0.221; not statistically significant), MG–Activities of Daily Living (LS mean -1.8 vs -0.4, difference -1.4, 95% UCL -0.4), and MG-Composite (LS mean -3.1 vs -1.2, difference -1.8, 95% UCL 0.4) scores. • Efficacy measures continued to improve with rozanolixizumab 7 mg/kg in period 2.[19]
Results (safety)	• The most common adverse event in period 1 was headache (rozanolixizumab 57%, placebo 14%).[19]

Estimated Cost

The cost of rozanolixizumab is not yet known.

Relevant Guidance

NICE Guidance

No relevant NICE guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults). 170084P. September 2018.
- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Rare Neuromuscular Disorders (All ages). D04/S(HSS)/a.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.

Other Guidance

- Association of British Neurologists. Management guidelines for myasthenia gravis. 2019.[6]

Additional Information

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