

HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

Zilucoplan for treating generalised myasthenia gravis

NIHRIO ID	20625	NICE ID	10634
Developer/Company	UCB Pharma Ltd	UKPS ID	660961

Licensing and market availability plans	Zilucoplan is in phase III clinical trials for treatment of generalised Myasthenia Gravis (gMG).
--	--

SUMMARY

Zilucoplan is currently in clinical development for adult patients with class II-IV generalized Myasthenia Gravis (gMG) who are Acetylcholine Receptor (AChR) antibody positive. Myasthenia gravis (MG) is a rare and chronic autoimmune disease. MG results from an abnormal immune reaction in which the body's natural immune defences (i.e., antibodies) inappropriately attack certain receptors in muscles, causing debilitating and potentially life-threatening muscle weakness. Currently there are no medicinal products recommended by NICE specifically for the treatment of gMG, and medicines that are used can take a long time to work and result in side-effects.

Zilucoplan is a synthetic peptide that works by attaching to and blocking the C5 complement protein, one of the proteins of the 'complement system', which is part of the body's defence system. By blocking the C5 complement protein, zilucoplan is expected to prevent the complement system from damaging the blood cells, thereby helping to relieve the symptoms of the disease. Zilucoplan is administered via subcutaneous (SC) injection. If licenced, zilucoplan will provide a treatment option for those with gMG who are AChR antibody positive, reducing the treatment and disease burden in these patients.

PROPOSED INDICATION

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

Zilucoplan is being developed for class II-IV gMG in adult patients who are AChR antibody positive.¹

TECHNOLOGY

DESCRIPTION

Zilucoplan is a small 15- amino acid peptide that binds to complement component 5 (C5) with high affinity and specificity. This prevents the cleavage of C5 into complement components C5a and C5b. Zilucoplan binds to the domain of C5 that corresponds to C5b and thereby blocks binding of C5b to complement component C6. This dual mechanism of action prevents activation of the terminal complement pathway and prevents assembly of the terminal complement complex which is a large hydrophilic pore that can damage and destroy the postsynaptic membrane, and impair neuromuscular transmission.²

Zilucoplan is being evaluated for adult patients with class II-IV gMG who are acetylcholine receptor (AChR) autoantibody positive. In the phase III trial (NCT04115293), zilucoplan (0.3 mg/kg) will be administered daily by subcutaneous (SC) injection over 12 weeks.³

INNOVATION AND/OR ADVANTAGES

The National Institute for Health and Care Excellence (NICE) currently do not have specific guidance for treating gMG.⁴ Current treatment approaches often involve the use of the drug pyridostigmine, steroids and immunosuppression medication. However, many of these treatments are associated with long term side-effects, often intolerable for patients and can take several months to become effective.^{5,6} These treatments non-specifically inhibit aspects of the immune system and do not directly address the causal mechanisms of tissue damage.⁷

In contrast to existing therapies, zilucoplan offers a targeted approach toward addressing the main mechanism of tissue damage in gMG.² The subcutaneous (SC) peptide C5 inhibitor zilucoplan met the prespecified primary efficacy end point and demonstrated a favourable safety and tolerability profile in the phase 2 clinical trial (NCT03315130), assessing a broad spectrum of patients with moderate to severe gMG regardless of their treatment history.^{1,2}

Many patients with gMG have substantial clinical disability, persistent disease burden, and adverse effects attributable to chronic immunosuppression. Therefore, there is a significant need for targeted, well-tolerated therapies with the potential to improve disease control and enhance quality of life.²

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Zilucoplan is currently in phase II/III clinical development for Amyotrophic Lateral Sclerosis and COVID-19^{8,9}

In 2020, zilucoplan received orphan drug designation by the U.S. Food and Drug Administration (FDA) for treatment of MG.¹⁰

PATIENT GROUP

DISEASE BACKGROUND

Myasthenia gravis (MG) is a rare and chronic autoimmune disease.¹¹ MG results from an abnormal immune reaction in which the body's natural immune defenses (i.e., antibodies) inappropriately attack acetylcholine receptors in muscles that receive nerve impulses.¹² These IgG antibodies disrupt communication between nerves and muscles, causing debilitating and potentially life-threatening muscle weakness.¹³ The exact cause of this antibody-mediated autoimmune response is unknown, but some cases have been linked to tumours in the thymus, and those with a family history or genetic predisposition to autoimmune disorders are at greater risk.¹⁴ Although the disorder may become apparent at any age, symptom onset typically starts in adulthood; in women under 40 and men over 60.^{12,15} Peak incidence rates occur in the third decade of life in women and sixth or seventh decade in men.¹⁶

The hallmark of MG is weakness of skeletal muscles that worsens after periods of activity and improves after periods of rest.¹⁷ The condition can vary in severity and distribution of muscle weakness between individuals. MG may be restricted to muscles in the eyes or it may be more generalised (gMG), where multiple muscle groups are involved.¹² More than 85% of people with ocular MG progress to gMG within 18 months, where muscles throughout the body may be affected, resulting in extreme fatigue and difficulties with facial expression, speech, swallowing and mobility making routine activities of daily living challenging.^{13,15} Around 10% of patients may develop potentially life-threatening complications due to severe involvement of muscles used during breathing, which is known as a myasthenic crisis.¹²

CLINICAL NEED AND BURDEN OF DISEASE

MG is a rare disease, affecting around 15 in every 100,000 people in the UK.¹¹ Using the 2020 mid-year population estimates, this equates to around 10,062 patients of any age in the UK with MG.¹⁸

In England (2019/20) there were 4,607 finished consultant episodes (FCE) where myasthenia gravis (ICD-10 code G70.0) was recorded as the primary diagnosis which resulted in 3,537 admissions, 2,041 day cases and 16,060 FCE bed days.¹⁹

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatments for gMG involve trying to keep the symptoms under control so the patient is able to live a largely normal life, these include: ²⁰

- medicines that help to reduce muscle weakness
- avoiding triggers (tiredness, stress, infections, certain medications which trigger symptoms)

In patients with an unusually large thyroid gland, surgery to remove the thymus gland (thymectomy) may sometimes be recommended.²⁰

CURRENT TREATMENT OPTIONS

There are currently no treatment options approved by NICE for the treatment of gMG.⁴

The following medicines are sometimes given to control symptoms of the disease:^{20,21}

- pyridostigmine
- steroids (such as prednisolone)
- immunosuppressants (azathioprine and methotrexate).
- Eculizumab²²
- Rituximab²³

PLACE OF TECHNOLOGY

If licenced, zilucoplan would offer a treatment option for adults with class II-IV gMG who are acetylcholine receptor (AChR) positive.

CLINICAL TRIAL INFORMATION

Trial	RAISE; NCT04115293; A Phase 3, Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Confirm the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects With Generalized Myasthenia Gravis Phase III - Recruiting Locations: 6 EU countries, UK, USA, Canada and Japan. Study completion date: November 2021	RAISE-XT; NCT04225871; A Phase 3, Multicenter, Open-Label Extension Study of Zilucoplan in Subjects With Generalized Myasthenia Gravis Phase III - Enrolling by invitation Locations: 5 EU countries, USA, Canada and Japan. Study Completion Date: December 2023
Trial design	Randomized, parallel assignment, quadruple-blinded	Single group assignment, open label
Population	N = 144 adults aged 18 to 74 with a diagnosis of gMG [Myasthenia Gravis Foundation of America (MGFA) Class II-IV] at Screening, and positive serology for acetylcholine receptor (AChR) autoantibodies.	N = 200 (estimated) adults with gMG who have previously participated in a qualifying Ra Pharmaceuticals sponsored zilucoplan study
Intervention(s)	0.3 mg/kg zilucoplan via daily subcutaneous (SC) injection	0.3 mg/kg zilucoplan via subcutaneous (SC) injection
Comparator(s)	Matched placebo	N/A
Outcome(s)	Primary Outcome Measure: <ul style="list-style-type: none"> • Change from Baseline in the MG-ADL Score Time Frame: From Baseline (Day 1) to Week 12 	Primary Outcome Measure: <ul style="list-style-type: none"> • Incidence of treatment-emergent adverse events (TEAEs) [Time Frame: From Baseline (Day 1) to Safety

	See trial record for full list of outcome measures	Follow-Up Visit (up to 36 months) See trial record for full list of outcome measures
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

The cost of zilucoplan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Rituximab bio-similar for the treatment of myasthenia gravis (adults). 170084P. September 2018
- NHS England. 2014/15 NHS Standard Contract for Neuromuscular Operational Delivery Network Specification. D04/ODN/a.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.

OTHER GUIDANCE

- American Academy of Neurology. International Consensus Guidance for Management of Myasthenia Gravis. 2020.²⁴
- Association of British Neurologists. Myasthenia gravis management guidelines. 2015.²⁵

ADDITIONAL INFORMATION

REFERENCES

- 1 Clinicaltrials.gov. *Safety and Efficacy Study of RA101495 in Subjects With Generalized Myasthenia Gravis*. Trial ID. 2017. Status: Available from: <https://clinicaltrials.gov/ct2/show/NCT03315130> [Accessed 13 August 2021].
- 2 Howard, J. F., Jr., Nowak R. J., Wolfe G. I., Freimer M. L., Vu T. H., Hinton J. L., et al. *Clinical Effects of the Self-administered Subcutaneous Complement Inhibitor Zilucoplan in Patients With Moderate to Severe Generalized Myasthenia Gravis: Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial*. *JAMA Neurology*. 2020;77(5):582-92. Available from: 10.1001/jamaneurol.2019.5125 <https://doi.org/10.1001/jamaneurol.2019.5125> 8/18/2021

- 3 Clinicaltrials.gov. *Safety, Tolerability, and Efficacy of Zilucoplan in Subjects With Generalized Myasthenia Gravis (RAISE)*. Trial ID. 2019. Status: Available from: <https://clinicaltrials.gov/ct2/show/NCT04115293> [Accessed 17 August 2021].
- 4 National Institute for Health and Care Excellence (NICE). *Neurological conditions - everything NICE says in an interactive flowchart: Myasthenia gravis*. 2021. Available from: <https://pathways.nice.org.uk/pathways/neurological-conditions/neurological-conditions-overview#content=view-node%3Anodes-myasthenia-gravis> [Accessed 03 August 2021].
- 5 Menon, D., Barnett C., Bril V. *Novel Treatments in Myasthenia Gravis*. *Frontiers in neurology*. 2020;11:538-. Available from: <https://pubmed.ncbi.nlm.nih.gov/32714266>
- 6 Sussman, J., Farrugia M. E., Maddison P., Hill M., Leite M. I., Hilton-Jones D. *The Association of British Neurologists' myasthenia gravis guidelines*. *Annals of the New York Academy of Sciences*. 2018;1412(1):166-9. Available from: <https://nyaspubs.onlinelibrary.wiley.com/doi/abs/10.1111/nyas.13503>
- 7 Howard, J. F., Vissing J., Gilhus N. E., Leite M. I., Utsugisawa K., Duda P. W., et al. *Zilucoplan: An Investigational Complement C5 Inhibitor for the Treatment of Acetylcholine Receptor Autoantibody-Positive Generalized Myasthenia Gravis*. *Expert Opinion on Investigational Drugs*. 2021 2021/05/04;30(5):483-93. Available from: 10.1080/13543784.2021.1897567 <https://doi.org/10.1080/13543784.2021.1897567>
- 8 UCB's Global Corporate Website. *Zilucoplan (RA101495)*. 2020. Available from: <https://www.ucb.com/clinical-studies/Clinical-studies-index/Zilucoplan-RA101495> [Accessed 13 August 2021].
- 9 Clinicaltrials.gov. *Zilucoplan*. 2021. Available from: <https://clinicaltrials.gov/ct2/results?cond=&term=Zilucoplan&cntry=&state=&city=&dist=> [Accessed 13 August 2021].
- 10 AP News. *Ra Pharmaceuticals Announces Clearance of IND Application for the HEALEY ALS Platform Trial*. 2020. Available from: <https://apnews.com/press-release/pr-businesswire/c6260adccb3c4248ae1792a8a69ec0c4> [Accessed 17 August 2018].
- 11 Muscular Dystrophy UK. *Myasthenia Gravis Overview*. 2021. Available from: <https://www.muscular dystrophyuk.org/conditions/myasthenia-gravis> [Accessed 03 August 2021].
- 12 National Organisation for Rare Disorders (NORD). *Myasthenia Gravis*. 2021. Available from: <https://rarediseases.org/rare-diseases/myasthenia-gravis/> [Accessed 03 August 2021].
- 13 Agenx. *argenx Announces Positive Topline Phase 3 ADAPT Trial Results*. 2020. Available from: <https://www.argenx.com/news/argenx-announces-positive-topline-phase-3-adapt-trial-results> [Accessed 14 July 2021].
- 14 Genetic and Rare Diseases Information Centre. *Myasthenia Gravis*. 2018. Available from: <https://rarediseases.info.nih.gov/diseases/7122/myasthenia-gravis> [Accessed 03 August 2021].
- 15 National Health Service (NHS). *Myasthenia gravis*. 2020. Available from: <https://www.nhs.uk/conditions/myasthenia-gravis/> [Accessed 03 August 2021].
- 16 Patient. *Myasthenia Gravis*. 2017. Available from: <https://patient.info/doctor/myasthenia-gravis-pro> [Accessed 03 August 2021].
- 17 National Institute of Neurological Disorder and Stroke. *Myasthenia Gravis Fact Sheet*. 2020. Available from: <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet> [Accessed 14 July 2021].
- 18 Office for National Statistics (ONS). *Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland*. 2021. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland> [Accessed 18 August 2021].
- 19 NHS Digital. *Hospital Admitted Patient Care Activity 2019-20*. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20>
- 20 National Health Service (NHS). *Myasthenia Gravis: Treatment 2020*. Available from: <https://www.nhs.uk/conditions/myasthenia-gravis/treatment/> [Accessed 03 August 2021].
- 21 NHS Foundation Trust: South Devon Healthcare. *Myasthenia Gravis Patient Information*. 2013. Available from: <https://www.torbayandsouthdevon.nhs.uk/uploads/25053.pdf> [Accessed 03 August 2021].
- 22 Electronic medicines compendium (emc). *Soliris*. 2021. Available from: <https://www.medicines.org.uk/emc/product/362/smpc#gref> [Accessed 23 Sept 2021].

- 23 NHS England. *Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults)*. 2018. Available from: <https://www.england.nhs.uk/wp-content/uploads/2021/04/Rituximab-biosimilar-for-the-treatment-of-myasthenia-gravis-adults-v2.pdf> [Accessed 23 Sept 2021].
- 24 Narayanaswami, P., Sanders D. B., Wolfe G., Benatar M., Cea G., Evoli A., et al. *International Consensus Guidance for Management of Myasthenia Gravis*. *Neurology*. 2021;96(3):114-22. Available from: <https://dx.doi.org/10.1212/wnl.00000000000011124>
- 25 Sussman, J., Farrugia M. E., Maddison P., Hill M., Leite M. I., Hilton-Jones D. *Myasthenia gravis: Association of British Neurologists' management guidelines*. *Practical Neurology*. 2015;15(3):199. Available from: 10.1136/practneurol-2015-001126
<http://pn.bmj.com/content/15/3/199.abstract>

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