Health Technology Briefing
September 2024

Inebilizumab for treating myasthenia gravis

Company/Developer	Amgen Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30363	NICE ID: Not available	UKPS ID: 674921

Licensing and Market Availability Plans

Currently in phase 3 clinical development.

Summary

Inebilizumab is currently in clinical development for the treatment of adults with myasthenia gravis (MG). MG is a rare, long-term autoimmune disorder that leads to muscle weakness and fatigue, which can be seriously debilitating and life-threatening, affecting eye alignment, swallowing, speech, mobility, and respiratory function. These symptoms can significantly impair independence and quality of life. In extreme cases, patients can experience life threatening myasthenic crises, which can result in extreme respiratory muscle weakness necessitating mechanical ventilation and admission to intensive care facilities. MG is caused by the body's immune system producing self-reactive antibodies (immunoglobulin G (IgG) auto-antibodies) which target antigens within the neuromuscular junction — the place where nerve cells communicate with muscle cells. Current treatments have long-term side effects, which can be intolerable for patients, and can take several months to become effective.

Inebilizumab is a monoclonal antibody (type of protein) that attaches to immune cells called B cells and depletes them. In MG, B cells produce autoantibodies that impair the communication between nerves and muscle cells. By depleting B cells, inebilizumab may lessen the production of autoantibodies and, as such, decrease disease activity and the associated symptoms. If licensed, inebilizumab will provide a new treatment option for adults with MG.

Proposed Indication

Adults with acetylcholine receptor antibody positive [AChR-Ab+] or muscle-specific tyrosine kinase antibody positive [MuSK-Ab+] myasthenia gravis.[1]

Technology

Description

Inebilizumab (Uplinza)[2] is a humanised monoclonal antibody that specifically binds to CD19, a cell surface antigen expressed by B lineage cells. CD19 is expressed on a broader range of cells within the B cell lineage than the cell surface antigen CD20. CD20 is restricted to pre-B cells in the bone marrow and the circulating naïve, mature and memory B cells. CD19 is additionally expressed on the early pro-B cells and the majority of antibody producing plasma cells in blood and secondary lymphoid organs and about half of the plasma cells in the bone marrow. The predominant mechanism of B cell depletion is through antibody dependent cell-mediated cytotoxicity.[3]

Inebilizumab is currently in phase III (MINT, NCT04524273) clinical development for the treatment of adults with myasthenia gravis (MG). Participants will receive intravenous (IV) administered inebilizumab at a dose of 300mg on days 1, 15 and 183 of the trial or a matched placebo.[1,3]

Key Innovation

Despite being one of the best studied immune diseases, there are clear unmet needs in MG therapy. Conventional therapies in MG induce remission in 70–80%, but very few attain sustained stable remission off therapy. This imposes the risk of long-term exposure to immunotherapies with cumulative toxicities including opportunistic infections, malignancies, and systemic organ dysfunction. A primary reason for such toxicity is the non-specificity of immune targets for the standard medications.[3] In MG, B cells produce self-reactive antibodies, called autoantibodies, that impair the communication between nerves and muscle cells. Most notably, these autoantibodies target proteins called acetylcholine receptor (AChR) and muscle-specific kinase (MuSK).[3] By depleting B cells, inebilizumab may lessen the production of autoantibodies and, as such, decrease disease activity and the associated symptoms.[3] If licensed, Inebilizumab will offer a new treatment option of patients with MG.

Regulatory & Development Status

Inebilizumab currently has Marketing Authorisation in the EU for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD).[2]

Inebilizumab is also in phase II and phase III clinical development for paediatric NMOSD, and adults with IgG4-related disease.[4]

Patient Group

Disease Area and Clinical Need

MG develops in adults due to a defect in the immune system.[5] Complement is a part of the immune system and normally helps to protect against certain types of infections. However, in people with MG, complement is activated by antibodies, which trigger complement to damage the area where the nerves and muscles meet, meaning that muscles are not able to contract as well as usual.[6] It most commonly affects the muscles that control the eyes and eyelids, facial expressions, chewing, swallowing and speaking, but it can affect most parts of the body.[7] AChR-Ab+ are found in approximately 80% of patients with MG, and MuSK-Ab+ are found in around 30–40% of AChR negative MG patients and are associated with

specific clinical phenotypes.[8] The most common symptoms of MG are drooping eyelids, double vision, difficulty in making facial expressions, problems with chewing and swallowing, slurred speech, weak arms, legs or neck, and shortness of breath and, occasionally, serious breathing difficulties.[7,9] Symptoms can become more severe with tiredness and can be triggered by factors such as stress, infections and certain medicines in some people.[9] Most individuals with MG have no family history of the condition.[8]

In the UK, MG affects about 15-33.7 in every 100,000 people.[5,10] Although it can affect people of any age, MG typically starts in women under 40 and men over 60.[7] In England (2022-23), there were 5,515 finished consultant episodes (FCE) for MG (ICD-10=G70.0) leading to 4,272 admissions, 2,708 day cases and 15,720 FCE bed days.[11]

Recommended Treatment Options

There is currently no treatment option recommended by NICE for MG.

The following pharmacological treatment options are currently used to treat MG.[12]

- Prednisolone is given as immunosuppressant therapy
- Azathioprine can be started at the same time as a corticosteroid
- Ciclosporin, methotrexate or mycophenolate mofetil can be used in patients who are unresponsive or intolerant to other treatments
- Anticholinesterases (neostigmine and pyridostigmine bromide) as an adjunct to immunosuppressant therapy

Clinical Trial Information

Trial	**MINT,** NCT04524273, EudraCT2020-000949-14; A Randomized, Double-blind, Multicenter, Placebo-controlled Phase 3 Study With Open-label Period to Evaluate the Efficacy and Safety of Inebilizumab in Adults With Myasthenia Gravis **Phase 3:** Active, not recruiting **Locations:** Five EU countries, USA and Canada **Primary completion date:** Primary completion May 2024
Trial Design	Randomised, parallel assignment, quadruple masked.
Population	N=238 (actual). Adults aged 18+ with a diagnosis of MG with anti-AChR or anti-MuSK antibody.
Intervention(s)	Inebilizumab (IV administered) 300mg on days 1, 15 and 183.
Comparator(s)	Matched placebo (IV administered)
Outcome(s)	**Primary outcome measure:** • Change in baseline in MG activities of daily living (MG-ADL) profile score. [Time frame: week 26 for the overall study population] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of inebilizumab is currently unknown.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Efgartigimod for treating generalised myasthenia gravis [ID4003] [GID-TA10986]. Expected publication date: TBC.
- NICE technology appraisal guidance in development. Rozanolixizumab for treating antibody-positive generalised myasthenia gravis [ID5092] [GID-TA10994]. Expected publication date: TBC.
- NICE technology appraisal guidance in development. Nipocalimab for treating generalised myasthenia gravis TS ID 11958 [GID-TA11492]. Expected publication date TBC.
- NICE technology appraisal guidance in development. Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008] [GID-TA11096]. Expected publication date: August 2024.
- NICE guideline. Suspected neurological conditions: recognition and referral [NG127]. Published May 2019. Updated October 2023.

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.
- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Rare Neuromuscular Disorders (All ages). D04/S(HSS)/a.

Other Guidance

- 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.[13]
- Sanders D. B., Wolfe G. I., Benatar M., Evoli A., Gilhus N. E., Illa I., et al. International consensus guidance for management of myasthenia gravis: Executive summary. 2016.[14]
- Sussman J, Farrugia ME, Maddison P, Hill M, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. 2015.[15]

Additional Information

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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.