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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

Efgartigimod alfa for treating generalised myasthenia gravis

NIHRIO ID	13458	**NICE ID**	10658
Developer/Company	Argenx BVBA	**UKPS ID**	661185

Licensing and market availability plans	Efgartigimod alfa is currently in phase III clinical trials for treatment of Generalised Myasthenia Gravis.

SUMMARY

Efgartigimod alfa is currently in clinical development for the treatment of adults with generalised myasthenia gravis (gMG). gMG is a long-term autoimmune disorder that leads to muscle weakness and tiredness, and which can be seriously debilitating and life-threatening. Currently there are no medicinal products recommended by NICE specifically for the treatment of gMG, and medicines that are used are mostly unlicensed, can take a long time to work and result in side-effects.

Efgartigimod alfa is a modified human antibody (a protein produced by the immune system) fragment that is administered by intravenous (IV) infusion. In patients with myasthenia gravis, the body produces antibodies against the acetylcholine receptors. This medicine works by blocking a protein called FcRn, which attaches to these antibodies and protects them from degradation. Blocking FcRn leads to the degradation of the antibodies that damage the acetylcholine receptors; this is expected to restore the normal contraction of the muscles. If licensed, efgartigimod alfa will offer a treatment option for gMG and reduce the treatment burden for these patients.

PROPOSED INDICATION

Efgartigmod is intended for treatment of adults with gMG.[1]

TECHNOLOGY

DESCRIPTION

Efgartigimod alfa (ARGX-113) works by stopping immunoglobulin G (IgG) antibodies attaching to a protein in cells called neonatal Fc receptor (FcRn). FcRn recycles IgG which extends its half-life. By blocking FcRn efgartigimod allows IgGs to be broken down, including IgGs causing damage in patients with myasthenia gravis, and removed from the body much more quickly.[2] As blocking FcRn reduces IgG antibody levels this represents a logical potential therapeutic approach for several autoimmune diseases known to be driven by disease-causing IgG antibodies, including myasthenia gravis (MG).[3]

Efgartigimod alfa is being evaluated for the treatment of patients with gMG. In the phase III trial (NCT03669588; ADAPT) participants are given intravenous (IV) infusion of efgardigimod alfa.[1,]

INNOVATION AND/OR ADVANTAGES

The National Institute for Health and Care Excellence (NICE) currently do not have specific guidance for treating gMG, efgartigimod alfa would be the first medicinal product to receive NICE recommendation for this disease.[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]

Efgartigimod alfa has been designed as the first-in-class FcRn antagonist.[7] Efgartigimod alfa met the primary endpoint.[8] The trial demonstrated positive efficacy and safety results in patients with gMG. The timing of administration of treatment cycles can be adjusted and individualised based on the patient's response. This study also shows that the drug is well tolerated in a broad population of patients with gMG including those who were not refractory to prior treatments and patients without detectable autoantibodies.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Efgartigimod alfa is in phase III clinical trials for primary immune thrombocytopenia and pemphigus vulgaris and foliaceus, and in a phase II clinical trials for chronic inflammatory demyelinating polyneuropathy and bullous pemphigoid.[7,9]

Efgartigimod alfa was designated EU orphan drug status in 2018 for MG.[2]

PATIENT GROUP

DISEASE BACKGROUND

Myasthenia gravis (MG) is a rare and chronic autoimmune disease.[3,10] Generalised MG results from an abnormal immune reaction in which the body's natural immune defences (i.e., antibodies) inappropriately attack receptors (most commonly acetylcholine receptors) in muscles that receive nerve impulses.[10] These IgG antibodies disrupt communication between

nerves and muscles, causing debilitating and potentially life-threatening muscle weakness.[3] 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.[11] In approximately 10% of patients IgG autoantibodies are not detected, however the disease is still considered to be antibody mediated.[12] Although the disorder may become apparent at any age, symptom onset typically starts in adulthood; in women under 40 and men over 60.[10,13] Peak incidence rates occur in the third decade of life in women and sixth or seventh decade in men.[14]

The hallmark of MG is weakness of skeletal muscles that worsens after periods of activity and improves after periods of rest.[15] 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.[10] Around 80% of people with MG progress to gMG within 2 years, 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.[3,14,16] 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.[10]

CLINICAL NEED AND BURDEN OF DISEASE

MG is a rare disease, affecting around 15 in every 100,000 people in the UK.[17] Using the 2020 mid-year population estimates, this equates to around 10,062 patients in the UK with MG.[18] Around 80% of people with MG will progress to gMG within 2 years equating to approximately 8050 patients.[14]
In England (2019/20) there were 4,607 finished consultant episodes 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 more 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 recommended by NICE for the treatment of gMG.[4]

Some treatments have been used unlicensed in MG these include:.[21-24]

- steroids (such as prednisolone)
- immunosuppressants (azathioprine and mycophenolate)
- Rituximab bio-similar is available through an NHSE commissioning policy

The following medicines are licensed in the UK for treatment of MG:[16,20,25,26]

- pyridostigmine

- Eculizumab is indicated for patients with refractory gMG who are AChR-antibody positive.

PLACE OF TECHNOLOGY

If licenced, efgartigimod alfa will offer a treatment option for adults with gMG.

CLINICAL TRIAL INFORMATION

Trial	**ADAPT;** NCT03669588 ; 2018-002132-25 ; A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness **Phase III** - Completed **Location(s):** 9 EU countries, UK, USA, Canada, Japan, Russia and other countries. **Study completion date:** April 2020	**ADAPT+;** NCT03770403; 2018-002133-37; A Long-Term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Trial of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness **Phase III** - Ongoing **Location(s):** 9 EU countries, USA, Canada, Japan, Russia and other countries. **Primary completion date:** June 2023
Trial design	Randomised, parallel assignment, placebo-controlled, quadruple-blinded	Single group assignment, open label
Population	N=167; adults aged 18 years or over with a diagnosis of MG with generalized muscle weakness, and meet the clinical criteria for diagnosis of MG as defined by the Myasthenia Gravis Foundation of America (MFGA) class II, III, IVa and IVb.	N=151; adults aged 18 years or over with the ability to understand the requirements of the trial who participated in trial ARGX-113-1704 and are eligible for roll over, as specified in the protocol. Other more specific inclusion criteria are further defined in the protocol.
Intervention(s)	IV administration of efgartigimod alfa	IV administration of efgartigimod alfa
Comparator(s)	Matched placebo	N/A
Outcome(s)	Primary Outcome Measure: Efficacy of efgartigimod alfa as assessed by the percentage of "Myasthenia Gravis Activities of Daily Living (MG-ADL) responders" in the acetylcholine receptor (AChR)-antibody (Ab) seropositive population [Time Frame: Week 8] See trial record for full list of outcome measures.	Primary Outcome Measure: Safety and Tolerability as measured by the incidence of treatment emergent (serious) adverse events in the AChR-positive population. [Time Frame: Up to 3 years] See trial record for full list of outcome measures
Results (efficacy)	Between Sept 5, 2018, and Nov 26, 2019, 167 patients (84 in the efgartigimod group and 83 in the	N/A

	placebo group) were enrolled, randomly assigned, and treated. 129 (77%) were acetylcholine receptor antibody-positive. Of these patients, more of those in the efgartigimod group were MG-ADL responders (44 [68%] of 65) in cycle 1 than in the placebo group (19 [30%] of 64), with an odds ratio of 4·95 (95% CI 2·21–11·53, p<0·0001).[8]	
Results (safety)	65 (77%) of 84 patients in the efgartigimod group and 70 (84%) of 83 in the placebo group had treatment-emergent adverse events, with the most frequent being headache (efgartigimod 24 [29%] *vs* placebo 23 [28%]) and nasopharyngitis (efgartigimod ten [12%] *vs* placebo 15 [18%]). Four (5%) efgartigimod-treated patients and seven (8%) patients in the placebo group had a serious adverse event. Three patients in each treatment group (4%) discontinued treatment during the study. There were no deaths.[8]	N/A

Trial	NCT02965573; 2016-002938-73; A Randomized, Double-blind, Placebo-Controlled Phase II Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX-113 in Patients With Myasthenia Gravis Who Have Generalized Muscle Weakness **Phase II** - Completed **Location(s):** 6 EU countries, USA and Canada **Study completion date:** October 2017
Trial design	Randomised, parallel assignment, placebo-controlled, quadruple-blinded
Population	N=24; adults aged 18 years or over with a diagnosis of autoimmune MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the MGFA, clinical Classification Class II, III, or IVa, and likely not in need of a respirator for the duration of the study as judged by the Investigator.
Intervention(s)	IV administration of efgartigimod alfa
Comparator(s)	Matched placebo
Outcome(s)	Primary Outcome Measures: • Number of Patients With Treatment Emergent Adverse Events (TEAES) and Treatment Emergent Serious Adverse Events (SAEs) [Time Frame: Day 1 to Day 78]

	• Mean Change From Baseline in Vital Signs: Blood Pressure, Heart Rate, Temperature and Weight [Time Frame: Baseline and Days 8,15, 22, 29, 36, 43, 50, 64 and 78] • Number of Patients With Abnormal Clinically Relevant Findings in Electrocardiogram (ECG) Parameters [Time Frame: Day 1 to Day 78] • Number of Patients With Abnormal Clinical Laboratory Findings Reported as TEAEs [Time Frame: Day 1 to Day 78] See trial record for full list of outcome measures
Results (efficacy)	All patients treated with efgartigimod alfa showed a rapid decrease in total IgG and anti-AChR autoantibody levels, and assessment using all 4 efficacy scales consistently demonstrated that 75% showed a rapid and long-lasting disease improvement.[27]
Results (safety)	Efgartigimod alfa was well-tolerated in all patients, with no serious or severe adverse events reported, no relevant changes in vital signs or ECG findings observed, and no difference in adverse events between efgartigimod and placebo treatment.[27]

ESTIMATED COST

The cost of efgartigimod alfa is currently unknown.

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

OTHER GUIDANCE

- American Academy of Neurology. International Consensus Guidance for Management of Myasthenia Gravis. 2020.[28]
- Association of British Neurologists. Myasthenia gravis management guidelines. 2015.[29]

ADDITIONAL INFORMATION

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