Eculizumab (Soliris) for refractory myasthenia gravis

LAY SUMMARY

Myasthenia gravis is a rare autoimmune condition that affects the nerves and causes certain muscles to become weak. Approximately 10-15% of patients with this condition experience muscle weakness that affects their daily activities such as speaking, swallowing, chewing and breathing. Patients with myasthenia gravis can now expect to live a near normal life due to current treatments and with supportive care. Those who survive the first 3 years of disease usually improve over time. Current treatments aim to control the symptoms, improve muscle weakness and reduce complications.

Eculizumab is a protein that works differently to current treatments. It blocks the immune system from attacking nerve cells. It is given as a drip straight into the vein once a week for the first month and then again as a drip every 2 weeks for up to 26 weeks. If licensed, eculizumab will offer an additional treatment option for patients with refractory myasthenia gravis.

NIHR HSRIC ID: 6090
TARGET GROUP

- Myasthenia gravis: refractory.

TECHNOLOGY

DESCRIPTION

Eculizumab (Soliris; AX-451; C5 cleavage inhibitor; Solaris; 5G1-1, anti-C5 monoclonal antibody 5G1-1; h5G1.1; monoclonal antibody 5G1-1) is a long acting humanised anti-C5 antibody. It is a terminal complement inhibitor that blocks the formation of the membrane attack complex and additional inflammatory responses. Eculizumab is therefore a potentially viable option for the treatment of patients with refractory myasthenia gravis. In phase III clinical trials, eculizumab was administered at 900mg via intravenous (IV) infusion once weekly for 4 weeks, followed by 1,200mg IV every 2 weeks for weeks 5-26.

Eculizumab is licensed in the EU for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome. Very common adverse effects with eculizumab when used for its current licensed indications include headache (≥10%). Common adverse effects (≥1/100 to <1/10) include: meningococcal sepsis, aspergillus infection, bacterial arthritis, upper respiratory tract infection, nasopharyngitis, bronchitis, oral herpes, urinary tract infection, viral infection, thrombocytopenia, leukopenia, haemolysis, anaphylactic reaction, decreased appetite, dizziness, dysgeusia, hypotension, dyspnoea, cough, nasal congestion, pharyngolaryngeal pain, rhinorrhea, diarrhoea, vomiting, nausea, abdominal pain, constipation, dyspepsia, rash, alopecia, pruritus, arthralgia, myalgia, muscle spasms, bone pain, back pain, neck pain, pain in extremity, oedema, chest discomfort, pyrexia, chills, fatigue, asthenia, influenza like illness, and a positive Coombs test.

Eculizumab is also in phase III clinical trials for delayed graft function and neuromyelitis optica. It is also in, phase II clinical trials for renal transplant rejection, haemolytic uraemic syndrome and membranoproliferative glomerulonephritis.

INNOVATION and/or ADVANTAGES

If licensed, eculizumab will offer an additional treatment option for patients with refractory myasthenia gravis with a new mechanism of action compared to current immunosuppressive treatments, as no complement inhibitor is currently available for the treatment of myasthenia gravis.

DEVELOPER

Alexion Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

The drug is in phase III clinical trial.

* Company comment.
PATIENT GROUP

BACKGROUND

Myasthenia gravis is an autoimmune disorder of neuromuscular transmission characterised by fatigable muscle weakness. In the most common forms of myasthenia gravis, antibodies form against nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction of the skeletal muscles, thus reducing the number of acetylcholine receptors at the postsynaptic muscle membrane. Patients become symptomatic once the number of acetylcholine receptors is reduced to approximately 30% of normal. In most cases, the first symptom is weakness of the eye muscles. In others it may be difficulty in swallowing or slurred speech. The degree of muscle weakness varies among individuals and symptoms vary in type and severity. Symptoms are usually worse at the end of the day and after exercising. The distribution of muscle weakness follows a characteristic pattern; initially 85% of patients have involvement of the eyelids and extraocular muscles, resulting in ptosis and/or diplopia. Bulbar involvement may be found with fatigable chewing, dysphagia and dysarthria. Eighty percent of patients with bulbar weakness go on to develop generalised weakness involving the limbs. Weakness in the chest muscles and diaphragm sometimes occurs, which may become severe and result in respiratory failure. Respiratory failure occurs in 1% of patients.

Approximately 10-15% of patients with myasthenia gravis are considered refractory - meaning they experience debilitating muscle weakness that severely impairs their ability to engage in simple daily activities such as speaking, swallowing, chewing and normal spontaneous breathing. Experts estimate that only 5% of patients, when properly treated, are truly refractory.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

In the UK, the prevalence of myasthenia gravis is 15 cases per 100,000 population. The incidence is bimodal, with a female: male ratio of 2:1 in younger adults, and a reversed sex ratio in older people. The incidence of myasthenia gravis ranges from 1 to 8 cases per 250,000 population per year in Europe.

Many patients with myasthenia gravis can now expect to live a near normal life due to current treatments and supportive care in an intensive care unit during periods of acute worsening of weakness. Disease specific mortality is now 3-4%; previously it was as high as 30-40%. Most patients with generalised weakness will usually reach maximal weakness within the first 3 years of the disease. This is also the period when half of the disease-related mortality also occurs. Worsening of disease is uncommon after 3 years, and those who

b Expert personal communication.
survive the first 3 years of disease usually improve over time\(^3\). The prognosis of thymectomy is variable ranging from complete remission of the disease in a number of patients to death\(^3\).

Thymoma is reportedly found in 10-30\% of patients with myasthenia gravis\(^7\). Thymectomy is associated with clinical improvement in 85\% of cases, and 35\% of patients appear to have complete remission\(^5\). Expert opinion states that thymectomy is used in non-thymomatous myasthenia to improve symptoms and in the hope of reducing subsequent drug burden. This was confirmed in the recent MGTX trial (reported in Jan 2016 but full paper not yet published)\(^c\). Thymectomy in patients with thymoma has an unpredictable effect on the symptoms and progression of myasthenia\(^d\).

In 2014-2015, there were 3,188 admissions due to Myasthenia gravis and other myoneural disorders (ICD G70) in England, resulting in 15,881 bed days and 3,874 finished consultant episodes\(^8\). In 2014, 104 deaths were reported from myasthenia gravis in England and Wales\(^9\).

### PATIENT PATHWAY

#### RELEVANT GUIDANCE

**NICE Guidance**

- No relevant guidance identified.

**Other Guidance**

- European Federation of Neurological Societies (EFNS). Guidelines for treatment of autoimmune neuromuscular transmission disorders. 2010\(^{10}\).

### CURRENT TREATMENT OPTIONS

Current treatments aim to control the symptoms, improve muscle weakness and reduce the effects of disease complications.

Current treatment options include\(^{11}\):

- Acetylcholinesterase inhibitors such as pyridostigmine, neostigmine, and edrophonium, which help improve neuromuscular transmission and increase muscle strength. However, experts note that edrophonium is very short-acting and only used for diagnosis\(^d\).
- Long term immunosuppressive therapy is needed when muscular weakness is not adequately controlled by anticholinesterase drugs. This includes:
  - Corticosteroids, such as prednisolone.
  - Other immunosuppressive medications, used to treat difficult cases and as corticosteroid-sparing agents, include azathioprine, mycophenolate mofetil, ciclosporin, cyclophosphamide, and rituximab.
- Thymectomy.
- Plasmapheresis removes causative or pathogenic antibodies from the circulation.
- Intravenous immunoglobulin (IVIG).

\(^c\) Expert personal communication.
None of the immunosuppressants currently used in the treatment of myasthenia gravis are approved for the treatment of refractory generalised myasthenia gravis in the UK\(^d\).

## EFFICACY and SAFETY

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<tr>
<td>Sponsor</td>
<td>Alexion pharmaceuticals.</td>
<td>Alexion pharmaceuticals.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry(^12).</td>
<td>Trial registry(^13).</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<td>Participants</td>
<td>n=92 (planned); aged ≥18 years; myasthenia gravis; Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV at screening; myasthenia gravis–specific activities of daily living scale (MG-ADL) total score ≥6 at screening and randomisation; failed treatment with ≥2 immunosuppressive agents or failed treatment with ≥1 immunosuppressive agent and require chronic plasma exchange or IVIG; no history of thymoma or other neoplasms of the thymus; no thymectomy 12 months prior to screening; no MGFA class I or V (MG crisis) at screening; no rituximab 6 months prior to screening; no IVIG or plasma exchange 4 weeks prior to randomisation.</td>
<td>n=92 (planned); aged ≥18 years; subjects completed NCT01997229 trial.</td>
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<td>Schedule</td>
<td>Randomised to eculizumab 900mg IV once weekly for 4 weeks, followed by 1,200mg IV every 2 weeks for weeks 5-26; or placebo IV once weekly for 4 weeks, then once every 2 weeks for weeks 6-26.</td>
<td>Eculizumab administered IV at 1,200 mg every 2 weeks.</td>
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<td>Follow-up</td>
<td>Active treatment and follow up to week 26.</td>
<td>Follow up to week 208.</td>
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<td>Primary efficacy endpoint</td>
<td>Total MG-ADL score at week 26.</td>
<td>MG-ADL total score.</td>
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<td>Secondary efficacy endpoint/s</td>
<td>Quantitative myasthenia gravis (QMG) total score at week 26; percentage of patients with ≥3 point reduction in the MG-ADL total score with no rescue therapy; percentage of patients with ≥5 point reduction in the QMG total score and with no rescue therapy; MG composite at week 26; MG-QoL15(^e).</td>
<td>QMG total score; proportion of subjects with ≥3-point reduction in the MG-ADL total score with no rescue therapy; proportion of subjects with ≥5-point reduction in the QMG total score with no rescue therapy; MGC scale total score; MG-QoL-15(^e).</td>
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\(^d\) Company comment.

\(^e\) Patient reported quality of life rating scale related to myasthenia gravis.
## ESTIMATED COST and IMPACT

### COST

Eculizumab is already marketed in the UK for paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome; a 30mL vial (10mg/mL) costs £3,150.\(^\text{x14}\).

### IMPACT - SPECULATIVE

#### Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability: *the vast majority of myasthenia patients achieve very good or good symptom control for the majority of their disease course. Those in whom relapses or crises occur can be restabilised with IVIG or plasma exchange. Only a small minority do not, and the number eligible for eculizumab would be small, but for those patients for whom no other treatments work, it would be very useful to have this further option*.\(^\text{x1}\)
- Other: *may improve patient’s ability to perform their activities of daily living, and reduce fatigue.*
- No impact identified

#### Impact on Health and Social Care Services
- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other: *may decrease requirement for assistive devices.*
- None identified

#### Impact on Costs and Other Resource Use
- Increased drug treatment costs: *its cost is likely to be the main barrier to adoption by the NHS.*
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other
- None identified

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\(^{x1}\) Expert personal communication.
Other Issues

- Clinical uncertainty or other research question identified: Experts consider there is a place for eculizumab if the phase III trial shows efficacy, tolerability and long-term safety. However, access should be restricted to patients who have truly refractory disease and who are under the care of specialists in myasthenia, otherwise there is a risk that it would be overused. This is a concern due to safety issues but the very high cost of the drug cannot be ignored.

- None identified

REFERENCES


9 Expert personal communication.