Ravulizumab for treating antibody-positive generalized myasthenia gravis

For public – redacted

Technology appraisal committee D [13 September 2023]

Chair: Megan John

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Company: Alexion

Background on generalised myasthenia gravis (gMG)

Causes

- Myasthenia Gravis (MG) is an autoimmune disorder caused by anti-acetylcholine receptor (AChR) autoantibodies targeting acetylcholine receptors and other parts of the neuromuscular junction which impairs neuromuscular transmission → When muscle groups other than the eye muscles are affected, the condition is known as generalised MG (gMG)

Epidemiology

- MG affects about 15 in every 100,000 people in the UK → Around 75% of people with MG have gMG
- About 90% of people with gMG are anti-AChR antibody-positive → approximately 6,000 people with anti-AChR antibody-positive gMG in the UK
- In women, incidence peaks between 30 and 50 and in men increases with age

Diagnosis, symptoms and prognosis of gMG

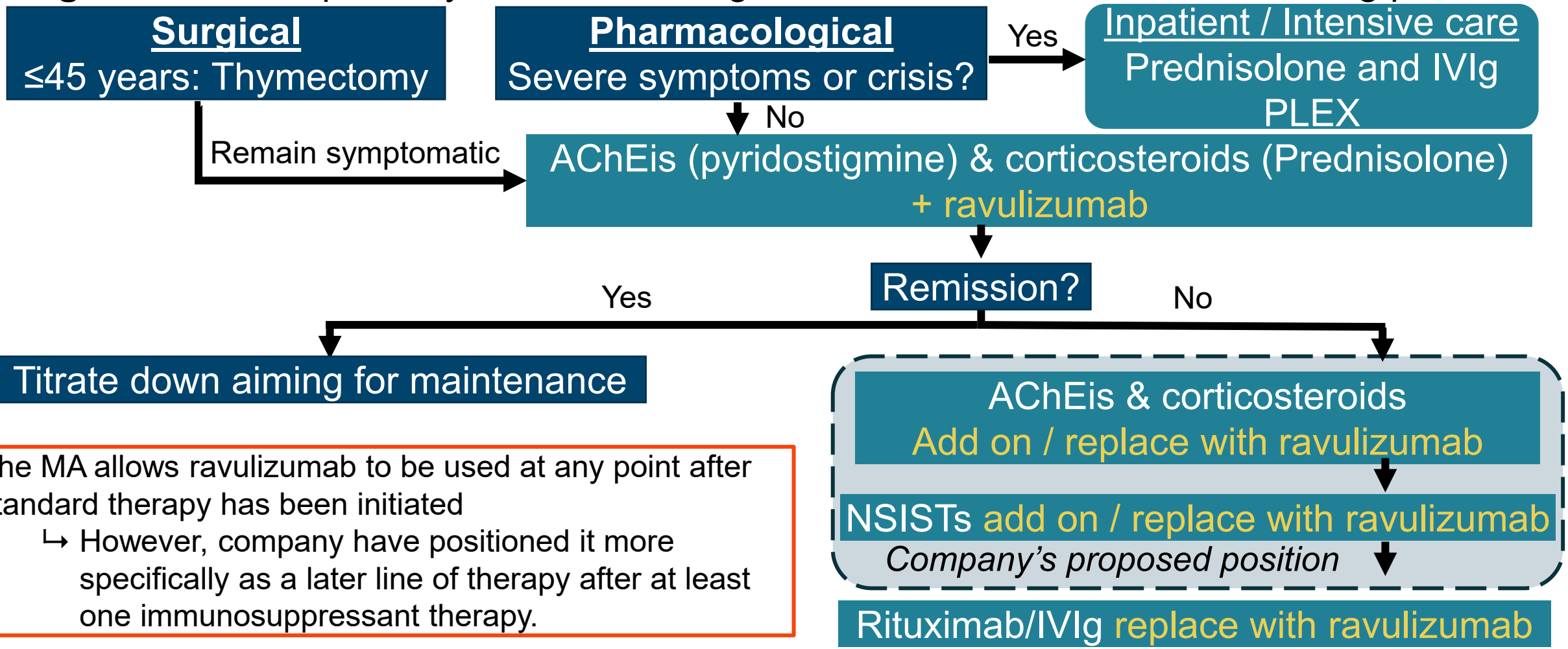
- Diagnosis via physical examination, blood tests and MRI and CT scans
- Symptoms include difficulties with swallowing, vision, speech, breathing, mobility, and fatigue
- 15% to 30% of people with gMG experience a myasthenic crisis at least once where the muscles that control breathing are affected, which requires intensive care support and is the main cause of MG-related deaths

AChR, Acetylcholine receptor; CT, Computerised tomography; gMG, Generalised Myasthenia Gravis; IgG, Immunoglobulin G; MG, Myasthenia Gravis; MRI, Magnetic resonance imaging

Treatment pathway

There is no single universally accepted treatment pathway for gMG

Figure: Potential pathway based on ABN guidelines and national commissioning policies



The MA allows ravulizumab to be used at any point after standard therapy has been initiated

↳ However, company have positioned it more specifically as a later line of therapy after at least one immunosuppressant therapy.

ABN, Association of British Neurologists; AChEi, Acetylcholinesterase inhibitors; gMG, Generalised Myasthenia Gravis; IVIg, Intravenous immunoglobulin; MA, Marketing authorisation; NSIST, Nonsteroidal immunosuppressive therapy; PLEX, Plasma exchange

Patient perspectives

Joint submission from Muscular Dystrophy UK and Myaware, and submissions from 2 patient experts

- People suffer from fatigue, and problems with breathing, speaking, seeing and concentrating – significantly impacting their ability to work or keep the same role
- MG and the side effects of some treatments impact individuals physically, emotionally as well as financially
- Similar impact on families and carers – 50% and 30% said that their condition has negatively impacted their family's mental health and financial situation respectively
- People with gMG struggle to balance treatments, symptom management, side effects and undertaking their day-to-day activities
- People worry about side effects of steroids and steroid sparing treatment options → ravulizumab could manage condition without the side effects of steroids
- Ravulizumab may offer better prognosis for people in whom symptoms are not well controlled with current treatment options

"It is demoralising and mentally challenging to accept help with your personal care. It has such a big impact on your general well-being"

"The side effects and additional conditions acquired because of current medications are and can often be harder to live with and manage then the MG itself"

gMG, Generalised Myasthenia Gravis; MG, Myasthenia Gravis

Clinical perspectives

Submissions Association of British Neurologists and clinical expert

- Ravulizumab is a terminal complement inhibitor and shares the same mechanism of action as eculizumab which is currently licensed but not funded for gMG
- Main aim of treatment is to reduce gMG symptoms and keep side effects to a minimum
- Several reasonably well validated rating scales for symptoms including the patient-reported rating scales of MG–ADL, MG– QoL as well as physician rating scales including QMG and composite QMG
- Well-defined pathway of care for patients with MG. Mild to moderate MG typically treated with pyridostigmine, prednisolone and, if necessary, NSIST
- Ravulizumab is fast acting so would be an option whilst waiting for more traditional oral therapies to take effect
- Ravulizumab will only be suitable for anti-AChR antibody-positive gMG resistant to standard therapies including rituximab but positioning relative to IVIG or PLEX not clear
- Significant unmet need for treatment resistant gMG → currently often treated with regular IVIG or PLEX in hospital typically as a day case admission

"Development of biological terminal complement inhibitors are an important advance in the management of patients with treatment resistant antibody positive myasthenia gravis."

"There is a need to develop new therapies for severe myasthenia given the constrained supply of immunoglobulin and difficulty ensuring provision of plasma exchange in England."

AChR, Acetylcholine receptor; gMG, Generalised Myasthenia Gravis; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL, Myasthenia Gravis quality of life; NSIST, Nonsteroidal immunosuppressive therapy; PLEX, Plasma exchange QMG, Quantitative Myasthenia Gravis

Potential equality considerations

Potential equality issues raised by patient organisation/patient expert

- The implications of treatment for people wishing to become pregnant should be considered
- There are gender-based differences in the age of onset of MG, and also some ethnicity differences

Potential equality issues raised by clinical expert

- Need for equity of access to specialist treatment centres
- Some people may not wish to receive meningococcal vaccine which is a prerequisite to starting treatment

NICE technical team considerations

- Issues related to differences in prevalence or incidence of a disease cannot normally be addressed in a technology appraisal recommendation
- Access to treatments is an implementation issue that cannot be addressed in a technology appraisal recommendation
- Any positive recommendation for ravulizumab will state that it is an option, if it is considered an appropriate treatment by patients and their clinicians

gMG, Generalised Myasthenia Gravis; MG, Myasthenia Gravis

Key issues

Key issues

Issue	Resolved?	ICER impact
Comparators	No – for discussion	Unknown
Uncertain relevance of eculizumab data for modelling long-term effects	No – for discussion	Unknown
Use of available MG-ADL data	No – for discussion	Moderate
Time on treatment extrapolations	No – for discussion	Small
Estimation of incidence of clinical events	Partially – for discussion	Small

MG-ADL, Myasthenia Gravis Activities of Daily Living

Ravulizumab (Ultomiris, Alexion)

<table>
<tr><td>Marketing authorisation</td><td>Indicated as “an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody-positive.”
GB MA September 2022</td></tr>
<tr><td>Mechanism of action</td><td>Monoclonal antibody IgG2/4K that binds to complement protein C5, preventing cleavage of C5 to C5a and C5b and subsequent generation of the terminal complement complex C5b-9</td></tr>
<tr><td>Administration</td><td>Administered by intravenous infusion. Dosage is determined by weight as detailed below. Treatment starts with an initial loading dose followed by maintenance dose every 8 weeks thereafter.
<table>
<tr><th>Body weight (kg)</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)</th></tr>
<tr><td>≥ 40 to < 60</td><td>2,400</td><td>3,000</td></tr>
<tr><td>≥ 60 to < 100</td><td>2,700</td><td>3,300</td></tr>
<tr><td>≥ 100</td><td>3,000</td><td>3,600</td></tr>
</table>
</td></tr>
<tr><td>Price</td><td>• List price: £15.11 per mg (for all vial sizes)
• £4,533 for 3 mL vial (100 mg/mL); £16,621 for 11 mL vial (100 mg/mL)
• Company has agreed confidential simple patient access scheme</td></tr>
</table>

AChR, Acetylcholine receptor; gMG, Generalised Myasthenia Gravis; IgG, Immunoglobulin G; kg, Kilogram; mg, Milligram; mL, Millilitre

Key issue: Comparators (1/2)

Background

- Indicated as add-on to standard therapy for adults with gMG who are AChR antibody-positive
- Company positions ravulizumab as a later line of therapy after people have received at least one IST
- Rituximab is used in clinical practice as a component of standard care but company have excluded rituximab as a comparator

Company

- NHS England Clinical Commissioning Policy, states rituximab is used in later lines of therapy "as a last resort for patients who have received all other treatment options"
- Rituximab can interact with COVID-19 symptoms and vaccines so is generally reserved for severe disease
- Limited robust trial data that supports rituximab in anti-AChR antibody-positive MG; most evidence is for anti-MuSK antibody-positive MG → data and clinical input that rituximab not as effective in anti-AChR antibody-positive MG
- Lack of robust studies on rituximab in refractory generalised MG → even if rituximab were considered a relevant comparator there is no appropriate data for a comparison of ravulizumab against rituximab.

AChR, Acetylcholine receptor; MG, Myasthenia Gravis; gMG, Generalised Myasthenia Gravis; IST, immunosuppressive therapy; MuSK, Muscle-specific kinase

Key issue: Comparators (2/2)

EAG comments

- Advice from 2 clinical experts is they use rituximab for AChR antibody-positive gMG and consider it a part of SoC. Neither concerned about limitations placed on rituximab by COVID-19
- Even if rituximab used in later lines of therapy, the refractory population is within the licensed indication and company do not state whether they believe ravulizumab would be used before, instead of, or after, rituximab
- Company do not present any assessment of evidence for potential comparison of rituximab against ravulizumab → but seems unlikely that there is adequately robust clinical efficacy evidence to enable ITC
- Conducted scenario analyses to assess impact of a proportion of patients (5-15%) treated with rituximab as part of SoC, and after discontinuation of ravulizumab
    - however scenarios do not account for clinical effects of rituximab, so may not provide realistic estimate of impact of rituximab use as part of standard care

Other considerations

- Professional organisation: agrees with EAG that rituximab should be included in the analysis to reflect UK clinical practice
- Clinical expert: rituximab takes longer to take effect than ravulizumab and has limited use and efficacy in AChR antibody-positive MG → not a direct comparator for ravulizumab

Is rituximab a relevant comparator for ravulizumab? Does the EAG scenario address the uncertainty?

AChR, Acetylcholine receptor; EAG, Evidence Assessment Group; ITC, Indirect treatment comparison; MG, Myasthenia Gravis; gMG, Generalised Myasthenia Gravis; SoC, Standard of care

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial: CHAMPION-MG and OLE

Clinical data for ravulizumab from CHAMPION-MG trial and open-label extension

	CHAMPION-MG (n=175)	CHAMPION-MG OLE (n=161)
Design	Phase 3, randomised, double-blind, placebo-controlled	Phase 3, extension of CHAMPION-MG, single-arm, open-label
Population	Adults with anti-AChR antibody-positive generalised MG, MG-ADL score of ≥ 6 and no prior complement inhibitor treatment	Patients who completed the randomised-controlled period of CHAMPION-MG
Intervention	Ravulizumab	Ravulizumab
Duration	26 weeks	2 years (currently 60 weeks data from time of randomisation available)
Primary outcome	Change from baseline in MG-ADL total score at 26 weeks	-
Secondary outcomes	Change from baseline in QMG total, MG-QoL15r and Neuro-QoL Fatigue at Week 26; Improvement ≥3 points and ≥5 points from baseline in MG-ADL and QMG total scores, respectively at week 26	-
Locations	85 sites in 13 countries (no UK sites)	-

AChR, Acetylcholine receptor; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL, Myasthenia Gravis quality of life; QMG, Quantitative Myasthenia Gravis; OLE, Open-label extension

Trial results: CHAMPION-MG and OLE (1/2)

Treatment with ravulizumab associated with a statistically significant reduction MG-ADL total score at Week 26 versus placebo

MG-ADL is a patient-reported scale developed to assess MG symptoms and their effects on daily activities

- It has an eight-item scale where each item is given a value from 0 (normal) to 3 (severe) → total score can range from 0 to 24 (higher = more severe)

MG-ADL is used to define model health states that capture disease activity levels

Mean change from baseline in MG-ADL total score at 26 weeks in CHAMPION-MG study

	Ravulizumab	Placebo	Difference (95% CI)
Least squares mean change	-3.1	-1.4	-1.6 (-2.6 to -0.7); p<0.001

Mean change from baseline in MG-ADL total score at 60 weeks in CHAMPION-MG OLE study*

	Ravulizumab to Ravulizumab	Placebo to Ravulizumab
Least squares mean change (95% CI)	[redacted]	[redacted]

*EAG: Week 26 is the OLE baseline for the Ravulizumab/Ravulizumab group. The baseline for the placebo/Ravulizumab group is unclear due to ambiguous reporting in the CS and CSR

AChR, Acetylcholine receptor; CI, Confidence interval; CS, Company submission; CSR, Clinical study report; EAG, Evidence Assessment Group; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OLE, Open-label extension

Trial results: CHAMPION-MG and OLE (2/2)

Treatment with ravulizumab associated with a statistically significant reduction MG-ADL total score at Week 26 versus placebo

In the model, a response was defined as a reduction in MG-ADL score of at least 3 points.

Proportion with ≥3 point reduction from baseline in MG-ADL at week 26 in CHAMPION-MG

	Ravulizumab	Placebo	Difference (95% CI)
Proportion with ≥3 point improvement in MG-ADL (95% CI)	Unadjusted: 60.3% (CI not reported) Adjusted*: 56.7% (44.3 to 68.3)	Unadjusted 36.6% (CI not reported) Adjusted*: 34.1% (23.8 to 46.1)	Unadjusted 23.7% (p-value not reported) Adjusted*: 22.6% (p-value not reported)

*Adjusted based on a generalized linear mixed model that included treatment arm stratification factor, region, and outcome score at baseline, at trial visit and at trial visit multiplied by treatment arm interaction.

CHAMPION-MG OLE study

Proportion of patients with ≥3 reduction from baseline in MG-ADL at week 60: **67.9%**

CI, Confidence interval; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OLE, Open-label extension

Inclusion of REGAIN trial of eculizumab

- Company use eculizumab outcomes from REGAIN (and OLE) to inform long-term predictions for ravulizumab.
- To explore similarity, company conducted an ITC comparing CHAMPION-MG (ravulizumab versus placebo) and REGAIN (eculizumab versus placebo), using placebo arm as the common comparator.

	REGAIN (n=125)	REGAIN OLE (n=117)
Design	Phase 3, randomised, double-blind, placebo-controlled	Phase 3, extension of REGAIN, single-arm, open-label
Population	Adults with anti-AChR antibody-positive generalised MG, MG-ADL score of ≥ 6 and prior treatment with **at least 2 ISTs or at least one IST and required chronic PLEX or IVIg**	Patients who completed the randomised-controlled period of REGAIN
Intervention	Eculizumab	Eculizumab
Duration	26 weeks	208 weeks (~4 years)
Primary outcome	Change from baseline in MG-ADL total score at 26 weeks	-

AChR, Acetylcholine receptor; IST, Immunosuppressive therapy; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL, Myasthenia Gravis quality of life; PLEX, Plasma exchange; QMG, Quantitative Myasthenia Gravis; OLE, Open-label extension

ITC results

Company conducted three types of ITCs of ravulizumab against eculizumab. Overall, the ITC results lacked statistical significance

- Only 1 outcome (change in EQ-5D VAS) from an adjusted ITC (MAIC or IPW) showed a statistically significant effect.
- Heterogeneity evident among the ITC results, with magnitude of change from baseline in MG-ADL and in QMG varying with the outcome assessment method and between the ITC adjustment methods
- Company interpret overall lack of statistical significance as indicating similar efficacy between ravulizumab and eculizumab. MG-ADL outcome results presented below:

Summary of MG-ADL outcome ITC results

	Unadjusted	MAIC	IPW
Outcome	Ravulizumab - eculizumab Mean (95% CI)	Ravulizumab - eculizumab Mean (95% CI)	Ravulizumab - eculizumab Mean (95% CI)
Change from baseline at week 26	[redacted]	[redacted]	[redacted]
AUC (baseline to week 26)	[redacted]	[redacted]	[redacted]
≥2 point improvement, OR	[redacted]	[redacted]	[redacted]
≥3 point improvement, OR	[redacted]	[redacted]	[redacted]

*Point estimate favours ravulizumab

AUC, area under curve; CI, Confidence interval; EQ-5D VAS, EuroQoL-5 dimension visual analogue scale; IPW, Inverse probability weighting; ITC, Indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL, OR, Odds ratio; QMG, Quantitative Myasthenia Gravis

Key issue: Uncertain relevance of eculizumab (1/2)

Background

- Company use eculizumab outcomes in submission since longer follow up available than for ravulizumab
- To explore similarity between ravulizumab and eculizumab, company performed ITC.

Company

- Previous NICE appraisals in other indications considered eculizumab to have similar effectiveness as ravulizumab (TA698 and TA710)
- Lack of statistically significant differences between ravulizumab and eculizumab in efficacy or HRQoL outcomes in ITC demonstrates similarity
- Eculizumab outcomes have been used as a proxy to represent long-term outcomes with ravulizumab in order to reduce uncertainty of long-term outcomes with ravulizumab
- Eculizumab and ravulizumab have the same mechanism of action and over 99% homology so it is expected that ravulizumab would have at least similar long-term effects
- Ravulizumab engineered from eculizumab to have a longer half-life and has benefits in dosing schedule providing greater complement inhibition → long-term outcomes with ravulizumab would be expected to be improved and use of long-term eculizumab considered conservative approach

HRQoL, Health-related quality of life; ITC, Indirect treatment comparison

Key issue: Uncertain relevance of eculizumab (2/2)

EAG comments

- Company do not provide data to support claim that ravulizumab has greater complement inhibition than eculizumab
- EAG's clinical experts considered TA698 and TA710 to have uncertain relevance to gMG and that company's assumption of similar efficacy of eculizumab and ravulizumab seems plausible but speculative
- ITC limited to short-term comparison and results highly uncertain due to methodological limitations
- Company also assume that comparable short term clinical effectiveness of these therapies can predict long-term clinical effectiveness of ravulizumab, which cannot be tested in ITC
- Preferred to use CHAMPION-MG trial data only (and not REGAIN) for certain modelling aspects

Other considerations

- Professional organisation: agrees with EAG's rationale of why it is not suitable to use eculizumab outcomes as a proxy for ravulizumab outcomes
- Clinical expert: supportive of long-term eculizumab clinical efficacy outcomes being used as a proxy for long-term ravulizumab → not aware of any reasons why ravulizumab should be less effective than eculizumab for gMG

Is it appropriate to use eculizumab outcomes as a proxy to represent long-term outcomes with ravulizumab?

EAG, Evidence Assessment Group; ITC, indirect treatment comparison; gMG, Generalised Myasthenia Gravis;

Cost effectiveness

NICE National Institute for Health and Care Excellence

How company incorporated evidence into model (1/2)

Input	Source
Baseline characteristics	Pooled CHAMPION-MG and REGAIN trials
Mean change in MG-ADL score by sub-state⁺	CHAMPION-MG trial (in SoC arm there is evidence of a substantial placebo effect in the trial. Base case assumes that placebo effect is for the first year, but then patients return to baseline MG-ADL‡).
Discontinuation due to non-response⁺	CHAMPION-MG trial
Time on treatment extrapolations	Pooled CHAMPION-MG (and OLE) and REGAIN trial (and OLE)
Incidence of clinical events (exacerbation and crises)	Pooled CHAMPION-MG (and OLE) and REGAIN trial*
Proportion of exacerbations	Pooled CHAMPION-MG and REGAIN trials
Mortality	UK Life Tables; fatality rate from Alsgekhlee et al. 2009 for MG crisis
Adverse event rates	CHAMPION-MG trial

⁺half-cycle correction added at TE to adjust estimates of change in MG-ADL score and treatment discontinuation mid-way within three-month model cycles

‡EAG conducted scenarios testing faster (than 12 months), or no loss of placebo effect

*number of participants and events in trial period reported in company's model does not match the numbers reported in CS

CS, Company submission; MG; Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OLE, Open-label extension; SoC, standard of care; TE, Technical engagement

How company incorporated evidence into model (2/2)

Input	Source
Health state utilities/ clinical event disutility	EQ-5D-5L data from CHAMPION-MG and REGAIN mapped to EQ-5D-3L equivalent values, using Hernández Alava et al. methodology.
Clinical event caregiver disutility (not included in base case)	Published literature: Thomas et al. (1997); Neumann et al. (2020)
Adverse event disutility	Published literature: Chirikov et al. (2019); Jit et al. (2010)
Health state resource use	Advised by UK clinical experts
Standard of care therapy distribution	CHAMPION-MG and UK clinical experts
Costs	**Categories**: drug acquisition, drug administration, vaccination costs, routine care costs, clinical event management costs and AE costs **Sources**: NHS Reference Costs, PSSRU Unit Costs of Health and Social Care, MIMS, and eMIT

EQ-5D-3L, EuroQoL-5 dimension 3 Level; EQ-5D-3L, EuroQoL-5 dimension 5 Level ; AE, adverse event; eMIT, Electronic Market Information Tool; MG, Myasthenia Gravis; MIMS, Monthly Index of Medical Specialities; PSSRU, Personal Social Services Research Unit

Key issue: Use of available MG-ADL data

Background

- In CHAMPION-MG, response was assessed at 18 weeks and 26 weeks
- Company models a 16-week response assessment for ravulizumab (patients stop ravulizumab if reduction in MG-ADL score <3 points), using 18-week data ([redacted] were responders)
- Company models SoC arm using 26-week data to assign patients to MG-ADL sub-states for first year of model
- EAG noted that model does not make use of MG-ADL data between 18 and 26 weeks in ravulizumab arm

Company

- 18-week data best reflects data if response assessment is at 16 weeks in clinical practice
- Model updated to include option to retain the 16-week assessment (based on 18-week data), combined with 26-week data to assign patients continuing ravulizumab to the 6-month (long-term) MG-ADL sub-states

EAG comments

- Agree with use of 18-week data to estimate response at 16 weeks
- Preferred analysis retaining 16-week assessment (based on 18-week data), combined with 26-week data to assign patients continuing ravulizumab to the 6-month (long-term) MG-ADL sub-states but believed there was an error in calculation in proportion of patients assigned to each sub-state→ provided updated scenario analysis

Is a < 3-point reduction from baseline in MG-ADL an appropriate definition of non-response?

What is the most appropriate method to model long-term change in MG-ADL in the ravulizumab arm:

- A 16-week stopping rule (using 18-week data), with 18-week data used to extrapolate long-term outcomes?
- A 16-week stopping rule (using 18-week data), with 26-week data used to extrapolate long-term outcomes?

EAG, Evidence Assessment Group; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; SoC, Standard of care

Key issue: Time on treatment extrapolations (1/2)

Background

- Company modelled ToT by pooling KM data from the CHAMPION-MG and REGAIN RCT and OLE studies with parametric curves fitted to the KM data to extrapolate beyond available data
- While all the parametric models had good fit to the pooled data up to 2 years, none of them fitted plateau and subsequent spike in treatment discontinuation between year 3 and 4

Company

- Pooled data used because the dataset is larger (compared to CHAMPION-MG only); and discontinuation of ravulizumab and eculizumab showed a similar trend up to the maximum follow up point in CHAMPION-MG
- Based on AIC/BIC statistics and long-term outcomes, exponential distribution used in base case
- Provided scenario analysis using CHAMPION-MG data only for ToT extrapolations (also used exponential distribution based on AIC/BIC) → resulted in ICER reduction compared to base case

EAG comments

- Disagrees with use of pooled data for ToT and prefers use of CHAMPION-MG data only
- Plateau and drop off in treatment rates after year 3 in the REGAIN OLE study may be caused by people exiting the study when eculizumab became commercially available in country of residence → if so, then not reflective of discontinuation in UK if ravulizumab became available on NHS
- Fit of all extrapolations to long-term KM pooled data is poor (but agree exponential distribution provides best fit)
- Conducted scenarios with a log-logistic distribution, as this has a similar fit to the KM data and a declining hazard over time, which clinical experts advising the EAG thought might be more realistic.

AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, Evidence Assessment Group; KM, Kaplan-meier; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; SoC, Standard of care; OLE, Open-label extension; RCT, Randomised-controlled trial; ToT, Time on treatment

Key issue: Time on treatment extrapolations (2/2)

Parametric models fitted to pooled CHAMPION-MG and REGAIN ToT data

Parametric models fitted to CHAMPION-MG ToT data only

Exponential = [redacted] on treatment at 10 years compared to [redacted] for log-logistic

Exponential = [redacted] on treatment at 10 years compared to [redacted] for log-logistic

Is it more appropriate to use pooled data or data from CHAMPION-MG only for ToT extrapolations? Is the exponential or log-logistic distribution most appropriate?

KM, Kaplan-meier; ToT, Time on treatment

Key issue: Estimation of incidence of clinical events

Background

- Company fitted Poisson regression to pooled data from CHAMPION-MG and REGAIN to estimate the incidence of acute clinical events, including myasthenic exacerbations and crises, for the ravulizumab and SoC arms
- Company base case regression includes covariates 'treatment' and 'prior clinical event' (added at TE) fitted to pooled data
- EAG noted concerns with the lack of clarity over the methods used to fit and test the model specification, but company provided further information at TE, which EAG considered appropriate

Company

- Updated base case retained use of pooled data from CHAMPION-MG and REGAIN for estimation of incidence of clinical events → larger dataset compared to using CHAMPION-MG only
- Provided scenario analysis using only CHAMPION-MG data for estimation of incidence of clinical events

EAG comments

- Serious concerns over use of pooled data → it has not been demonstrated that these therapies have similar effects on clinical event rates
- Preferred to use CHAMPION-MG data only for estimation of incidence of clinical events

Is it more appropriate to use pooled data or data from CHAMPION-MG only to calculate incidence of clinical events?

EAG, Evidence Assessment Group; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OLE, open-label extension; SoC, Standard of care; TE, technical engagement

Other issues

Utility regression model

- Company's base case utility regression* included MG-ADL scores and baseline EQ-5D as independent variables
- Model also includes scenarios for regressions including additional covariates: baseline disease duration and exacerbation or crisis within 3 months
- EAG: company do not justify the choice of regression model or provide statistics to show whether adding or removing alternative covariates improves fit of regression model
- EAG conducted scenario including disease duration and prior clinical events (within 3 months) as additional covariates (along with MG-ADL score and baseline EQ-5D) → EAG preferred analysis

Estimation of hospital cost for acute clinical events (exacerbations and crises)

- EAG noted uncertainty related to the methods used to calculate hospital costs for acute clinical events:
  - company assume that in addition to ICU admission for intubation for myasthenic crisis, [redacted]% of patients will also have extended ICU stay → scenario conducted to assess impact of removing additional ICU stay costs
  - intubation cost of £4,219 (weighted average for the non-elective long stay HRG categories) may be an overestimate → scenario conducted using the cost for a non-elective short stay (£870 instead of £4,219)
  - company multiply HRG cost for each type of hospital care by length of stay. EAG note that HRG costs already cover an average length of stay per FCE→ scenario conducted removing length of stay multipliers.

*company submission states that pooled CHAMPION-MG and REGAIN HRQoL trial data were used to inform the regression; although the company model only reports coefficients using CHAMPION-MG 26-week trial data

EAG, Evidence Assessment Group; EQ-5D, EuroQoL-5 dimension; FCE, Finished Consultant Episode; HRG, Healthcare Resource Group; ICU, Intensive Care Unit; MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Baseline characteristics	Pooled CHAMPION-MG and REGAIN trials	Champion-MG trial only
Time on treatment	Pooled CHAMPION-MG and REGAIN trials (exponential distribution)	CHAMPION-MG trial only (exponential distribution)
Utility regression model	Adjustment for MG-ADL score and baseline EQ-5D	Include coefficients for clinical event within 3 months and disease duration

Other considerations

- For estimation of long-term treatment effect (MG-ADL): EAG prefer analysis retaining the 16-week assessment for response to ravulizumab (based on 18-week trial data), combined with 26-week data for patients continuing ravulizumab.
- For estimation of incidence of clinical events (regression): EAG prefer CHAMPION-MG only data to be used for calculation of incidence of clinical events.

These analyses were provided after close of TE so have not been incorporated into the EAG base case but have been presented as scenario analyses.

EAG, Evidence Assessment Group; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; TE, Technical engagement

Uncaptured benefits

Company

- At UK advisory board, clinical experts noted that key benefit of ravulizumab was its speed of onset
- Clinicians believe they could assess whether condition was responding, or likely to respond to treatment, after approximately two treatment cycles (16 weeks) allowing change of therapy if no response
- With current SoC, patients often spend over a year receiving treatment before response can be accurately assessed
- Early understanding of response to treatment provides patients (and their carers) with peace of mind that they can avoid the need to continue treatment if no benefit

Other considerations

Any other uncaptured benefits within cost-effectiveness modelling?

SoC, standard of care

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator CMU prices

Note: only deterministic ICERs presented in part 2. Probabilistic ICERs very close to deterministic, however EAG are concerned that the probabilistic results do not accurately reflect uncertainty because the probabilistic sensitivity analysis omits some key parameters

Scenarios presented in part 2

Applied to	Scenario(s)	ICER impact
Company base case	Baseline patient characteristics: Champion-MG trial only	Small
	Time on treatment: CHAMPION-MG RCT and OLE only (exponential)	Small
	Utility regression: including covariates for clinical event within 3 months and disease duration	Small
	Ravulizumab treatment effect: Using 26-week MG-ADL data for 18-week responders	Moderate
	Incidence of clinical events regression: Using CHAMPION-MG trial data only	Small
EAG base case	Choice of parametric distribution for time on treatment extrapolation for ravulizumab	Small
	Incidence of clinical events regression: Using CHAMPION-MG trial data only	Small
	Ravulizumab treatment effect: Using 26-week MG-ADL data for 18-week responders	Moderate
	Placebo effect: return to baseline at 6 months, at 9 months; no loss of placebo effect	Small – large*
	Use of rituximab as part of standard care: 5%, 10% and 15% of patients in SoC arm and after discontinuation of ravulizumab	Small-moderate
	Methods for costing clinical events: removal of additional ICU costs; lower cost for intubation (£870); removal of length of stay multiplier applied to FCE	Small - moderate

*small impact for return to baseline at 6 or 9 months; large impact for no loss of placebo effect

DSA, Deterministic scenario analyses; EAG, External assessment group; FCE, Finished Consultant Episode; RCT, Randomised controlled trial; OLE, Open-label extension

Key issues and other considerations

Key issues

Issue	Resolved?	ICER impact
Comparators	No – for discussion	Unknown
Uncertain relevance of eculizumab data for modelling long term effects	No – for discussion	Unknown
Use of available MG-ADL data	No – for discussion	Moderate
Time on treatment extrapolations	No – for discussion	Small
Estimation of incidence of clinical events	Partially – for discussion	Small

Other considerations

- Any other issues for committee consideration?

MG-ADL, Myasthenia Gravis Activities of Daily Living

Back up slides

NICE National Institute for Health and Care Excellence

Decision problem (1/2)

	Final scope	Company	EAG comments
Population	Adults with generalised MG	Adult patients with anti-AChR antibody-positive generalised MG → aligned with the licensed population and clinical evidence available for ravulizumab	Appropriate and matches the licensed population
Intervention	Ravulizumab	As per scope	In practice in the CS, intervention evaluated is ravulizumab plus standard of care which reflects the licensed indication and is appropriate
Comparators	ECM without ravulizumab including corticosteroids and immunosuppressive therapies, with or without intravenous immunoglobulin or plasma exchange	As per scope	As per scope but did not include rituximab as comparator. Expert advice to the EAG is that rituximab is used as ECM in practice

AChR, Acetylcholine receptor; CS, Company submission; EAG, Evidence Assessment Group; ECM, Established clinical management; MG, Myasthenia Gravis; gMG, Generalised Myasthenia Gravis

Decision problem (2/2)

	Final scope	Company	EAG comments

Outcomes	• Improvement in MG
	• hospitalisations
	• mortality
	• adverse effects of treatment
	• health-related quality of life
		As per final scope:
		• Improvement in MG
		  • Change in MG-ADL score
		  • Change in QMG score
		• Number of hospitalizations
		• Mortality
		• Adverse effects of treatment
		• Health-related quality of life
		
		Plus:
		• MG exacerbations and crises
		MG exacerbations and crises also relevant for consideration due to impact on HRQoL, mortality and resource use
			All outcomes specified in final scope included in addition to MG exacerbations and crises which are relevant outcomes in the context of generalised MG treatment

HRQoL, Health-related quality of life; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis

ITC methodology (1/2)

Rationale for ITC

- Company assume that if the short-term effectiveness of ravulizumab and eculizumab can be demonstrated to be similar in gMG, then REGAIN could be a useful source of evidence for predicting long-term outcomes with ravulizumab
- To explore similarity, company conducted an ITC comparing the CHAMPION-MG (ravulizumab versus placebo) and REGAIN (eculizumab versus placebo) trials, using the placebo arm as the common comparator.

CHAMPION-MG and REGAIN heterogeneity assessment

Patients in CHAMPION-MG tended to be older and have lower QMG and MG-ADL scores and were more likely to be male. Statistically significant differences were also observed in group 2 nonsteroidal IST use (Group 2: azathioprine, methotrexate, mycophenolate mofetil) between CHAMPION-MG and REGAIN.

Outcomes assessed:

- Primary objective: changes from baseline in MG-ADL and QMG
- Secondary objective: changes from baseline in MG-ADL sub-domains, Neuro-QoL Fatigue, EQ-5D, and EQ-5D VAS scores
- Other: Responder analysis- with responders defined as those participants who had a change, without rescue therapy, from a baseline score of 2 to 9 for MG-ADL and a change from baseline score of 3 to 10 for QMG

EQ-5D, EuroQoL-5 dimension; EQ-5D VAS, EuroQoL-5 dimension visual analogue scale; ITC, Indirect treatment comparison; IST, Immunosuppressive therapy; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL, Myasthenia Gravis quality of life; Neuro-QoL, Quality of life in neurological disorders; QMG, Quantitative Myasthenia Gravis; OLE, Open-label extension

ITC methodology (2/2)

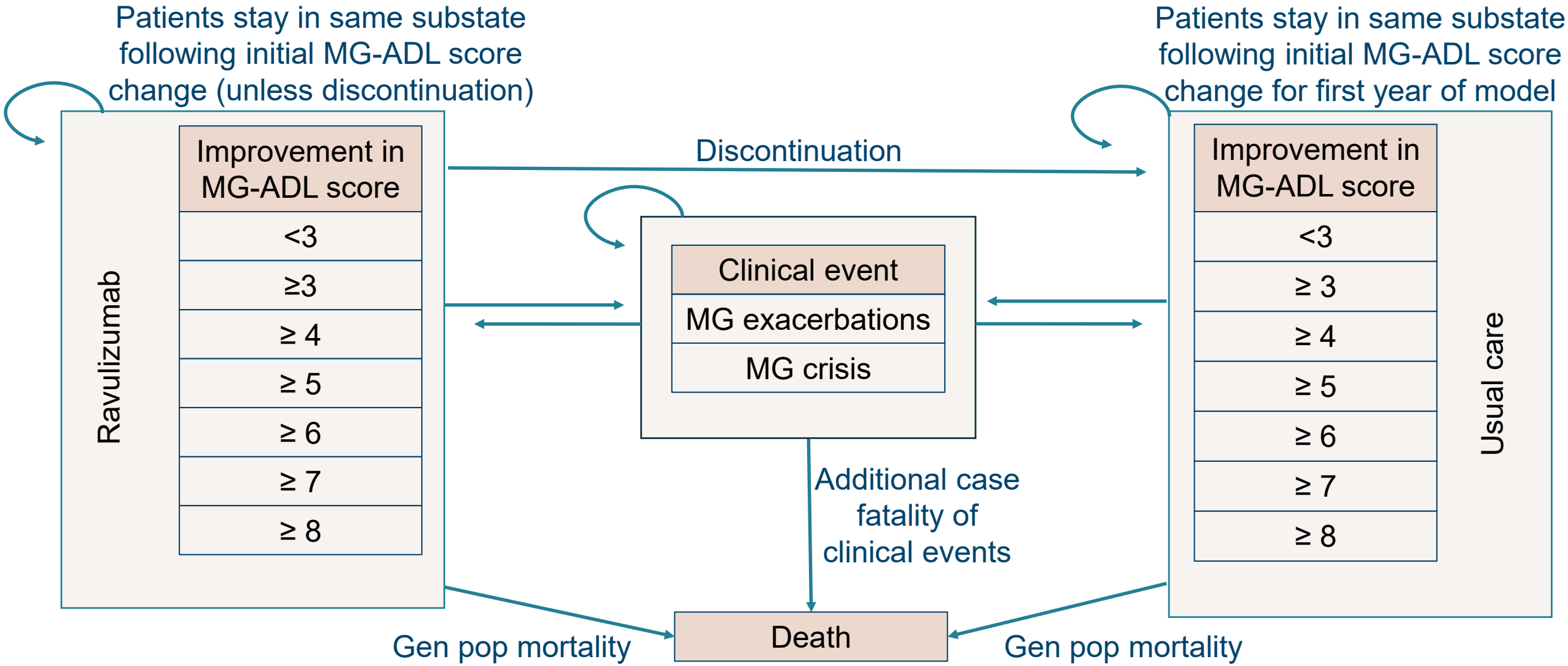
Company conducted three types of ITCs of ravulizumab against eculizumab

ITC method	EAG comments
Unadjusted analysis using Bucher method, anchored on the placebo arms	• Unadjusted is weakest analysis because does not take into account heterogeneity between studies
MAIC analysis using IPD from CHAMPION-MG and aggregate data from REGAIN. Intervention and placebo arms matched separately to account for within-trial differences between arms.	• Baseline characteristics included in MAIC well-matched but at the expense of a low effective sample size (19.7 and 36.2 for the ravulizumab and placebo arms of CHAMPION-MG respectively • Results potentially biased by a number of patients with high weights (>5.0) for ravulizumab arm of CHAMPION-MG
IPW analysis using IPD from both trials. Intervention and placebo arms of the RCTs were matched separately to account for within-trial differences between arms, with separate regression models conducted on the paired active and placebo arms	• Adjusted baseline characteristics more homogenous than in unadjusted analysis but less homogenous compared with MAIC analysis • Higher effective sample sizes achieved compared with MAIC analysis and relatively low frequency of high weights → less prone to bias • IPW is strongest analysis due to best use of available data but confidence in results undermined by missing prognostic factors and lack of sensitivity analyses

EAG, Evidence Assessment Group; IPD, Individual patient data; IPW, Inverse probability weighting; ITC, Indirect treatment comparison; IST, Immunosuppressive therapy; MAIC, Matching-adjusted indirect treatment comparison; MG, Myasthenia Gravis; RCT, Randomised controlled trial

Company's model overview (1/2)

State transition model with a lifetime time horizon and 3-month cycle length



MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; Gen pop, General population

Company's model overview (2/2)

Inputs and assumptions affecting costs and QALYs

Technology affects costs by:

- Increased costs for drug acquisition and administration
- Reduced costs due to reduced incidence of clinical events
- Costs related to the treatment of adverse events

Technology affects QALYs by:

- Improving symptoms (MG-ADL status), associated with improved quality of life
- Reducing incidence of acute clinical events (exacerbations and crises), which are associated with disutility and a risk of mortality
- Disutility associated with adverse effects

Assumptions with the greatest ICER effect:

- Source of data and extrapolation for time on treatment
- Timing of response assessment and discontinuation due to loss of response
- Population baseline characteristics
- Mortality relative to general population

ICER, Incremental cost-effectiveness ratio; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QALY, Quality-adjusted life year

Time on treatment extrapolations: parametric predictions

Percentage of patients on treatment: pooled CHAMPION-MG and REGAIN

Distribution	1-year	3-year	5-year	10-year	20-year
Pooled CHAMPION-MG and REGAIN RCT and OLE data					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHAMPION-MG RCT and OLE data only					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RCT, Randomised controlled trial ; ToT, Time on treatment; OLE, Open-label extension