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Zilucoplan for treating antibody-positive generalised myasthenia gravis [ID4008]

Technology appraisal committee B [09 October 2024]

Chair: Charles Crawley

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Technical team: Luke Cowie, Yelan Guo, Emily Crowe

Company: UCB

Key issues from ACM1

Recommendation: Zilucoplan is not recommended, within its MA, as an add-on to standard treatment for generalised myasthenia gravis in adults who test positive for AChR antibodies

ACM1 conclusion/consideration		Company Updated?
Target population	Population defined in company submission similar to those who would have zilucoplan in the NHS	N/A
Comparators	• A 'basket' of standard care consistent with NICE scope and more reflective of NHS practice, so relevant comparator; • Proportions of people having each treatment could be taken from efgartigimod EAMS population as sufficiently similar to zilucoplan target population	No
Clinical effectiveness	Zilucoplan as an add-on to standard treatment more effective at improving MG-ADL score than standard treatment alone; noted substantial response in placebo group which needs to be accounted for in any indirect treatment comparisons	Yes
Relevance of evidence for refractory disease	Results from RAISE and RAISE XT can be generalised to the refractory gMG population in the NHS	N/A

Abbreviations: AChR, Anti-acetylcholine receptor; ACM, Appraisal committee meeting; gMG, Generalised Myasthenia Gravis; IVIg; MA, Marketing authorisation; MG-ADL, myasthenia gravis-activities of daily living; NMA, network meta-analysis; EAMS, Early Access to Medicines scheme

Key issues from ACM1

ACM1 conclusion/consideration		Company Updated?
Indirect treatment comparison (ITC)	Would prefer an indirect comparison that incorporates data from all available studies, includes IVIg and PLEX, and adjusts for placebo response. Uncertainty from ITC should be incorporated in model	Yes
Subsequent treatments	Subsequent treatments should be included in economic model	Yes
Response rate	Committee has not been presented with accurate estimates of treatment response for any of the treatments	Yes
Response timepoints	A response assessment timepoint of 3 weeks for all treatments reflects NHS practice	Accepted and included in model
Resource use	IVIg/PLEX costs should be applied every 4 weeks	Accepted and included in model
Uncaptured benefits	There were benefits of zilucoplan that were uncaptured in modelling, asked company to present scenario analyses that account for some of these benefits.	Yes

Abbreviations: ACM, Appraisal committee meeting; IVIg, Intravenous immunoglobulin; PLEX, plasma exchange; ITC, indirect treatment comparison

Zilucoplan (ZILBRYSQ®, UCB)

Marketing authorisation	• Zilucoplan is indicated as an **add-on to standard therapy** for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. • Date of MHRA approval: 15 January 2024
Mechanism of action	• Zilucoplan inhibits complement protein C5, thereby downregulating activity of the membrane attack complex (MAC), allowing for improved neuromuscular junction signalling

Administration	• Subcutaneous injection once daily from prefilled syringe based on weight:
	  • <56 kg: 16.6 mg dose
	  • ≥56 to <77 kg: 23 mg dose
	  • ≥77 kg: 32.4 mg dose

Price	• List price: £31.37 per mg • There is a confidential patient access scheme (PAS) for zilucoplan

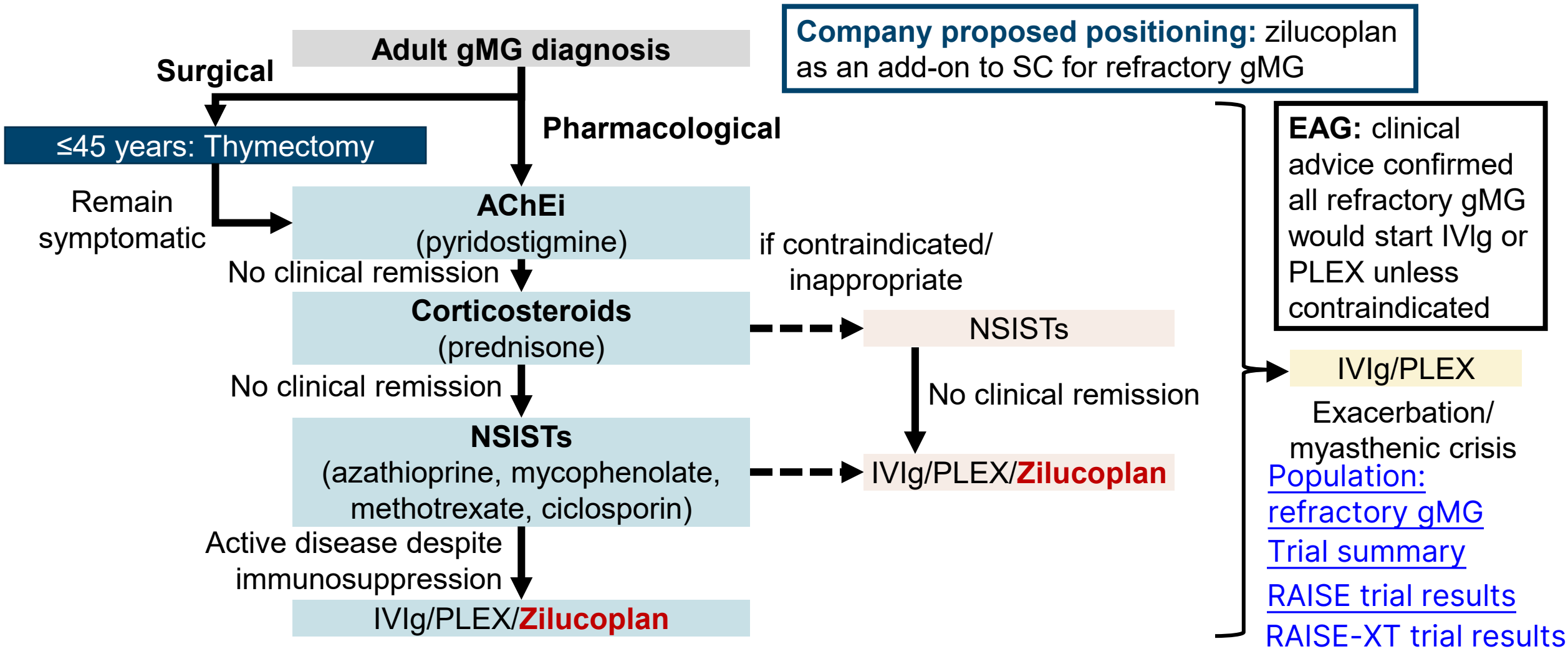
Abbreviations: AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; MHRA, Medicines & Healthcare Products Regulatory Agency

Clinical effectiveness recap

NICE National Institute for Health and Care Excellence

Treatment pathway for gMG

ACM1: Population from RAISE trial similar to population that would have zilucoplan in the NHS, a 'basket' of standard care (including IVIg/PLEX) is relevant comparator, model should include subsequent treatments



Abbreviations: AChEi, acetyl-cholinesterase inhibitor; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; SC, standard care.

Previous network meta-analysis

Company:

- Economic model is informed by MG-ADL response rate outcome
  - ↳ No IVIg studies with MG-ADL response outcome
  - ↳ No appropriate PLEX studies
- NMAs versus IVIg were possible for other outcomes but were not used in model

ACM1: Multiple issues with NMA, comparative effectiveness of zilucoplan highly uncertain:

- Several IVIg/PLEX studies excluded from NMA given no MG-ADL response outcome;
- Prefer exploring methods to obtain relative effectiveness estimates from these studies so IVIg/PLEX could be assessed, including multivariate NMA, or NMA of standardised mean difference for MG-ADL and other outcomes

Abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; NMA, network meta-analysis; PLEX, plasma exchange

Cost effectiveness recap

NICE National Institute for Health and Care Excellence

Company's model overview

ACM1: Model could be appropriate for decision making if it accounted for subsequent treatment use

Recap:

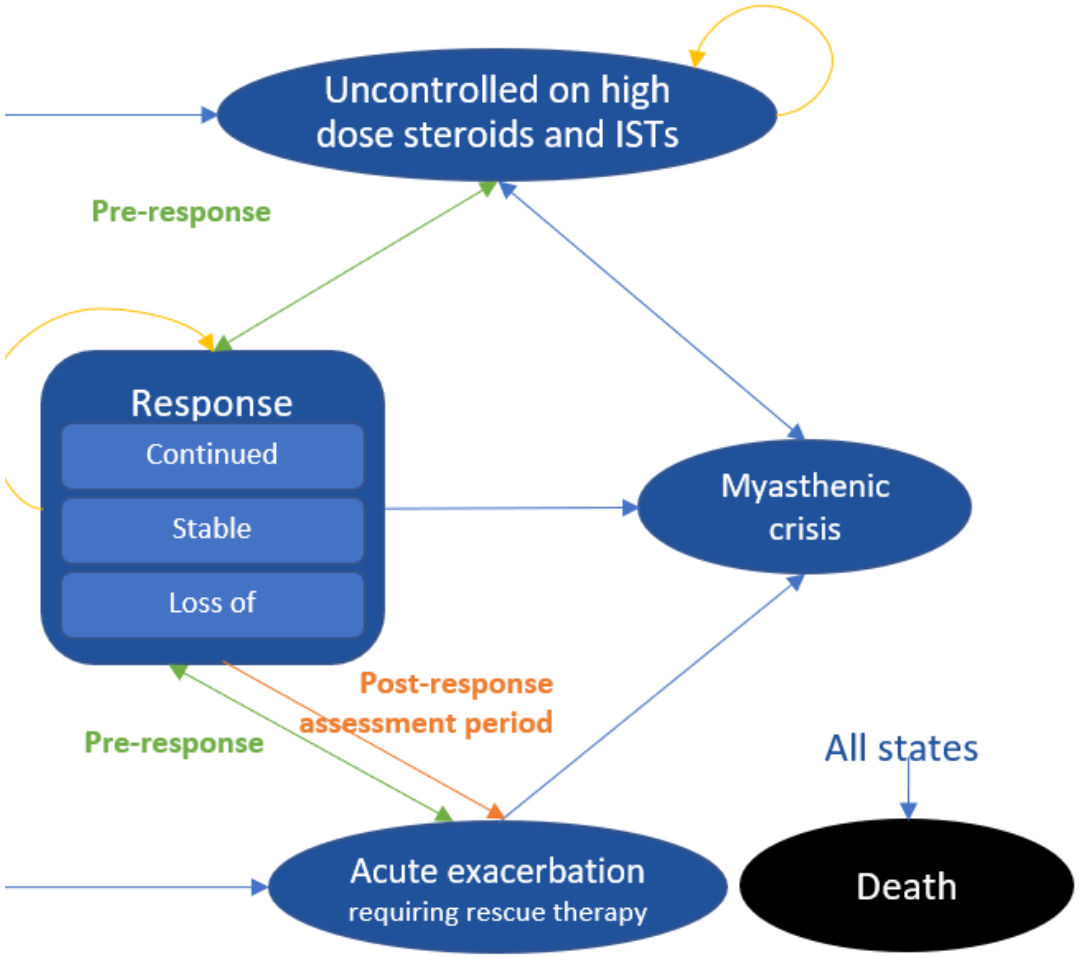
- Cohort state-transition model with 7 health states
- Responders separate into one of 3 response sub-groups (continued, loss or stable response) at response assessment timepoint, assuming
  - ↳ [redacted] to be stable
  - ↳ [redacted] to lose response
  - ↳ [redacted] to have a continued response
- Within each health state (except death), patients at risk of 'exacerbation', 'crisis' or 'death'

Company's revised model for ACM2 (see slide 32 on MSE):

- Assumed patients in *continued response health state* reached MSE, with
  - [redacted] of those on zilucoplan, 10% on IVIg or PLEX, and 0% on refractory SC

EAG comment:

- Unclear whether use of MSE clinically appropriate for model, company did not justify change in approach
- Prefers to revert to original patient distribution of ACM1 model



- Is the company's revised model using MSE appropriate?

Abbreviations: MG-ADL, Myasthenia Gravis-Activities of Daily Living; SC, standard care; MSE minimal symptom expression

Response to consultation

Consultation responses summary (1)

Stakeholders

- Muscular Dystrophy UK (MDUK) and Myaware (Patient groups): joint response
- ABN – Neuromuscular Advisory Group (Professional group)
- 2 Consultant Neurologists

UCB (company)

- **Comparator**: SC basket of treatments modelled as subsequent treatment for those who lose response
- **NMAs**: provided bivariate NMA; baseline risk-adjusted NMAs; and MAIC for IVIg (but not PLEX)
- **Response rate in model:** same approach as ACM1 but estimates updated
- **Subsequent treatment:** included in model
- **Uncaptured benefits of zilucoplan: analyses provided**

NICE technical team note:

- 3 version of revised model submitted by company for response to consultation, latest version 3 submitted on 20 September, too late for EAG to consider
- Difference between version 2 and 3: stopping rule activated in version 2
- Both EAG critique and reporting in slides based on model version 2, submitted on 15 September

Abbreviations: ABN, Association of British Neurologists; ECM, Established clinical management; IVIg, Intravenous immunoglobulin; PLEX, plasma exchange; SC, standard care; NMA, network meta-analysis; MAIC, matched-adjusted indirect comparison

Consultation responses summary (2)

Joint response – MDUK and Myaware (Patient groups)

- Emphasise benefits of zilucoplan over IVIg/PLEX: mode of administration at home (subcutaneous injection) reduces hospital stays and provides added QoL for people and their family/carers
- Transformative effect of zilucoplan in terms of speed, consistency and duration of response compared with IVIg/PLEX

ABN – Neuromuscular Advisory Group (endorsed by Royal College of Physicians)

- Barth et al. 2011 not an appropriate dataset: 70% response rate too high for rescue/maintenance use of IVIg/PLEX together with SC, where it has an additive effect in controlling refractory gMG (50% more likely)
- EAMS data on efgartigimod highly relevant, represents subgroup for whom zilucoplan will be considered in the NHS
- Many uncaptured benefits for zilucoplan, including reduced hospital visits and reduced symptom fluctuation

Abbreviations: ABN, Association of British Neurologists; PLEX, plasma exchange; IVIg, Intravenous immunoglobulin; gMG, generalised myasthenia gravis; SC, standard care; EAMS, Early Access to Medicines scheme

Consultation responses summary (3)

2 Consultant Neurologists

- Some people with refractory gMG have no access to IVIg/PLEX, so are more often admitted to hospital with MG exacerbations and experience complications of very high dose steroids
- Supporting data from large centres could be used to capture these direct and indirect costs in analysis
- Assessment timepoint of 3 weeks for all treatments appropriate and will benefit patients and the NHS
- IVIG/PLEX used as rescue therapy so comparison of Zilucoplan with IVIG/PLEX problematic
- Zilucoplan is proposed as an add on treatment to SC, so SC should be part of the comparator

Abbreviations: ABN, Association of British Neurologists; PLEX, plasma exchange; IVIg, Intravenous immunoglobulin; gMG, generalised myasthenia gravis; SC, standard care; EAMS, Early Access to Medicines scheme

Comparators (1)

Subsequent Treatments

ACM1

- A 'basket' of SC consistent with NICE scope and more reflective of NHS practice, so relevant comparator
- Proportion of people having each treatment could be taken from the efgartigimod EAMS cohort dataset

Company response to draft guidance

- Strongly disagrees with blended SC 'basket' as comparator. Only IVIg and PLEX would be displaced by zilucoplan, so the only relevant comparators
- EAG rationale for blended SC comparator is that some centres do not have access to IVIg and PLEX. But not clear if view is based on clinical expert opinion, or how many people this affects
- Disagrees with proportion of people having each comparator in published efgartigimod EAMS patient cohort because:
  - the full dataset was not reported
  - refractory defined slightly differently in efgartigimod EAMS
  - only 77% [n=37] of patients refractory, population broader than that relevant to zilucoplan
  - results do not specify standard of care therapies in refractory subgroup
- Accepts that some refractory patients who have had IVIg and/or PLEX may have periods where they do not have treatment, but this should be modelled as subsequent treatment with SC
- Also revised proportion of patients having refractory SC treatments from EAMS to inform subsequent treatment with SC:
  - 56.7% having IVIg, 18.9% having PLEX, 24.4% having only CS, NSISTs or a combination of both

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; SC, standard of care; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; EAMS, Early Access to Medicines scheme; CS, corticosteroids

Comparators (2)

EAG comments

- Company has not modelled comparators as a 'basket' of treatments (including IVIg/PLEX and SC), as per committee's preferred assumptions from ACM1
- EAG prefer to use refractory standard basket (a 'basket' of SC) as comparator in base case and scenario analyses
- Accepted company's revised proportions in EAMS cohort as appropriate (EAG's preferred comparator)

Clinical expert

- Big issue with equity of access to IVIg and PLEX across the NHS. PLEX services few and far between and not every Trust has equal access to IVIg, because:
  - managers often refuse referrals from "out of the area" without the doctor who the patient has been referred to being aware, and
  - many general neurologists without expertise on gMG only refer when significant problems or when patients insist on being referred
- Some people need more than a referral to be able to access treatment centres, also about being able to travel and cost of transport

- Would the committee change its view on standard care for refractory gMG in the NHS?
- Does committee agree with company's revised proportions for patients having standard care in EAMS cohort?

SoC excluded as comparator

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Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; SC, standard care; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; gMG, generalised myasthenia gravis; EAMS, Early Access to Medicines scheme

Uncertainty in NMA results (1)

ACM1: requested an improved indirect treatment comparison that:

- uses data from all available studies, including any additional evidence for IVIg and PLEX
- considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness
- accounts and adjusts for differential placebo response observed in trials
- respects randomisation, and that
- uncertainty from indirect treatment comparisons should be incorporated in model

Company response:

Provided 3 sets of NMAs:

- **Conventional NMA**
- **Bivariate NMA:**
  - Only this NMA informs model, using both MG-ADL and QMG outcomes to enable estimation of MG-ADL where this outcome was missing; 1 additional study of IVIg versus placebo included;
  - But does not adjust for placebo response heterogeneity between trials;
- **Baseline risk-adjusted NMAs:** account for placebo response heterogeneity

- **Also provided 2 unanchored MAICs** comparing zilucoplan and Ivlg on the outcomes of:
  - % of patients with worsening QMG score (≥4 points) from baseline;
  - QMG score and QMG response rates at 2 and 4 weeks (1 additional study included in this MAIC)

Abbreviations: ACM, Appraisal Committee Meeting; gMG, generalised myasthenia gravis; CFB, change from baseline; MAIC, matched-adjusted indirect comparison; NMA, network meta-analysis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis scale; MG-ADL, Myasthenia Gravis-Activities of Daily Living; OR, odds ratio

Updated NMA results: MG-ADL response (≥3-point improvement)

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Analysis	Treatment	OR vs placebo (95% CrI)
Conventional NMA (random effects), non-informative prior	**Zilucoplan**	[redacted]
	IVIg	Stated "NA" (no IVIg study included in the network)
	PLEX	No studies in network
Bivariate NMA (random effects) - ***Results informed model***	**Zilucoplan**	[redacted]
	IVIg	[redacted] (0.19 to 17.95) (NS, 1 extra study included)
	PLEX	No studies in network *(odds ratio from Barth et al. 2011 used instead for model)*
Baseline risk-adjusted NMA (random effects), 0,1 uniform prior for SD	**Zilucoplan**	[redacted]**(NS)**
	IVIg	Stated in NMA Report section 3.4 that data for IVIg was not available, without explanation (an IVIg versus placebo study had been included in the conventional NMA)
	PLEX	No studies in network
Baseline risk-adjusted NMA (random effects), 0,2 uniform prior for SD	**Zilucoplan**	[redacted] [redacted]**(NS)**
	IVIg	No studies in network
	PLEX	No studies in network
Baseline risk-adjusted NMA (random effects), half-normal prior distribution for SD with median 0.3	**Zilucoplan**	[redacted] [redacted]**) (NS)**
	IVIg	No studies in network
	PLEX	No studies in network

EAG: randomisation kept in NMAs as odd ratios for relative treatment comparisons provided, but model informed by response rate, which was derived via referent placebo response rate;

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Abbreviations: NMA, network meta-analysis; OR, odds ratio; NA, not applicable; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; NS, not statistically significant; SD, standard deviation

Uncertainty in NMA results (2)

EAG comments:

- Company has not included PLEX in any updated indirect treatment comparisons
- Search and identification of relevant RWE:
  - Company did not extend its original search or screening eligibility criteria or ITC feasibility assessment transparently; so uncertain whether further evidence, particularly for PLEX, could be available

- Statistical approaches for NMAs and MAICs appear to be broadly appropriate, but
  - Statistical code for NMA/MAIC analyses not provided, so EAG unable to verify if implemented correctly
  - Only bivariate NMA informs economic analysis, with 1 additional study of IVIg against placebo included, but lack of MG-ADL outcomes for comparisons involving PLEX not resolved
  - Baseline-risk adjusted NMAs adjust for heterogeneity of placebo responses between studies, but do not inform economic analysis (company's original approach of using a referent placebo response rate adjustment retained)
  - MAICs do not reduce any uncertainty in analysis; not used in model, as they provide ORs vs IVIg rather than vs placebo

- Do the new indirect treatment comparisons reduce the uncertainty committee noted at ACM1?
- Does the committee consider new bivariate NMA appropriate for estimating relative treatment effect of zilucoplan?

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Abbreviations: EAG, External assessment group; MAIC, matched-adjusted indirect comparison; NMA, network meta-analysis; IVIg, intravenous immunoglobulin; ORs: odds ratios; PLEX, plasma exchange; MG-ADL, Myasthenia Gravis-Activities of Daily Living; RWE, real-world evidence

Placebo response heterogeneity and incorporating uncertainties from ITCs in model

ACM1: Company's original NMAs did not account or adjust for heterogeneity of placebo responses observed in trials. Uncertainty from ITCs should be incorporated in model

Company response

- A baseline risk-adjusted NMA conducted. This showed that the placebo response not significantly different between studies, and that results for CFB in MG-ADL score similar to those from conventional network meta-analysis

EAG comments:

- Company's modelling approach not changed to capture uncertainty from NMAs, credible intervals of NMAs or confidence intervals of primary studies not used in model
- Differential placebo responses still not adjusted for odds ratio used in model, company retained its original placebo referent response rate adjustment
- Baseline-risk-adjusted NMA adjusts for placebo response heterogeneity but does not inform model.
- Bivarate NMA (which informs model) does not account for heterogeneity in placebo response rates

- Does the heterogeneity in the placebo response need to be resolved?
- Which NMA should or can be used to estimate the relative treatment effect in the model?

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Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; MG-ADL, myasthenia gravis-activities of daily living; CFB, change from baseline; NMA, network meta-analysis; ITC, indirect treatment comparison

Response rates (1)

ACM1

- Committee had not been presented with accurate estimates of treatment response for any of the treatments. It asked the company to provide more analyses to clarify this

Company response:

- **Response rates in revised model informed by:**
  - Odds ratio of [redacted] for PLEX informed by the 57% responder rate for PLEX from Barth et al **(same approach as for ACM1)**
  - Odds ratios for response of [redacted] for IVIg and [redacted] for zilucoplan are from the bivariate NMA **(same approach as for ACM1)**
- **New referent response rate:**
  - calculated as the overall mean of log odds based on individual log odds for each study reporting MG-ADL response for placebo (previously calculated as the average response rate for the placebo arms across studies identified in NMA)
  - Outcomes from both calculations are similar, with the mean of log odds giving 31.5% response, compared with a [redacted] simple average of included studies reporting MG-ADL response (bivariate NMA)

Abbreviations: ACM, Appraisal committee meeting; MG-ADL, myasthenia gravis-activities of daily living; CFB, change from baseline; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; NMA, network meta-analysis

Response rates (2)

Treatment response rates used in the model

Treatment	Response rate used in the revised (ACM2) model	Response rate used in the ACM1 model
Referent	31.5%	[redacted]
Zilucoplan	[redacted]	[redacted]
IVIg/SCIg	[redacted]	[redacted]
Refractory standard of care	[redacted]	[redacted]
PLEX	57.00%	57.00%

EAG comments

- Notes that response rate for refractory SC (company used for its subsequent treatment basket) is the same as the referent rate (i.e. average placebo response)
- People having refractory SC include people having IVIg and PLEX, so considers response rate for refractory SC to be [redacted]%, based on following calculation:
  - 56.7% of patients take IVIg, 18.9% PLEX, the remaining 24.4% corticosteroids and/or NSISTs: (56.7% x [redacted]%) + (18.9% x 57.00%) + (24.4% x 31.50%) = [redacted]%

- Does committee consider company's updated response rates for treatments appropriate?
- Which is the preferred response rate for revised refractory SC?

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Abbreviations: EAG, External assessment group; MG-ADL, myasthenia gravis-activities of daily living; CFB, change from baseline; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; NSISTs, non-steroidal immunosuppressive therapies; SC, standard care

Subsequent treatments (1)

ACM1

- Subsequent treatments should be included in the economic model

Company response

- Uncertainty around number lines of subsequent treatments needed, what treatments will be considered after IVIg/PLEX, and whether lack of response to index treatment is a treatment effect modifier
- Provided an adapted model where subsequent treatments assumed to be in steady state but reflecting movement of people between treatment with IVIg/PLEX and SC

EAG comments

- Subsequent treatment costs applied for people who do not respond, or lose response, to 1L treatment
- Company revised EAMS population used in refractory SC arm (see slide 14) which EAG considers appropriate
- Substantial increase in total costs for all treatments (annual uncontrolled state resource use increased, £14,896 for ACM1 to £94,417 in revised model)
- Not appropriate to apply costs of IVIg and PLEX to subsequent treatment of people who had IVIg, PLEX or refractory SC first-line (because would not be offered again)

Abbreviations: ACM, Appraisal committee meeting; SC, standard care; 1L, first line; NSISTs, non-steroidal immunosuppressive therapies; EAMS, Early Access to Medicines Scheme; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

Subsequent treatments (2)

EAG preferred subsequent treatment costs

Subsequent treatment pathway, zilucoplan

Subsequent treatment pathway, comparator

Example breakdown of total costs for zilucoplan

Cost	ACM1 model (£)	Revised model (£)
Treatment cost	[redacted]	[redacted]
Admin costs	-	[redacted]
Admins	-	[redacted]
Uncontrolled	[redacted]	[redacted]
Continued response	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]
Stable response	[redacted]	[redacted]
Exacerbation	[redacted]	[redacted]
Crisis	[redacted]	[redacted]
Terminal costs	[redacted]	[redacted]

Increase in total costs for all treatments in the company's revised model

Treatment	ACM1 model (£)	Revised model (£)
Zilucoplan	[redacted]	[redacted]
IVIg/SCIg	535,341	1,968,712
(Refractory) standard of care	614,382	1,943,092
Plasma exchange	696,316	1,928,092

EAG comments

- Company did not model any treatment benefit from subsequent IVIg and PLEX, only the costs

- Is company's approach to modelling subsequent treatments appropriate?
- What proportion of people would be expected to switch from IVIg to PLEX, and vice versa?
- Is it appropriate to model costs of subsequent treatments without modelling treatment benefit?

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Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

Uncaptured benefits - steroid sparing (1)

ACM1

- Considered there were several uncaptured benefits associated with zilucoplan and asked company to provide further evidence

Company response

- CS use associated with severe side effects such as diabetes, osteoporosis, depression and infection
- Model updated to include costs and disutilities of corticosteroids and corticosteroids-sparing effect of zilucoplan
- CS costs from a proxy condition, lupus erythematosus, because no data available for costs associated with CS use in gMG (Stirnadel-Farrant, 2023)

EAG comments

- Considers costs of managing adverse clinical outcomes from CS use already incorporated into ACM1 model
- NICE committee assessing ID4003 (efgartigimod) previously accepted weighted average of NHS reference costs for intolerable adverse events reported in Lee et al. (2018) for estimating CS complication costs associated with gMG

- Does committee agree with company's approach to costs associated with CS use in the model?
- Is it appropriate to include utility decrement associated with corticosteroid use?

Abbreviations: ACM, Appraisal committee meeting; MG-ADL, myasthenia gravis-activities of daily living; CFB, change from baseline; MSE, minimal symptom expression; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; CS, corticosteroids

Uncaptured benefits - MSE

ACM1

- Considered there were several uncaptured benefits associated with zilucoplan and asked company to provide further evidence

Company response

- Proportion of people with gMG who achieve complete stable remission is low with current treatments
- MSE defined as MG-ADL score of 0 or 1, representing people who are free or virtually free of symptoms
- Of responders in RAISE (defined as 3-point CFB in MG-ADL at Week 12), [redacted]% had MSE (so no CS use)
- Revised company model assumes people in continued response health state have reached MSE
- Model assumes [redacted]% of people having zilucoplan achieve MSE
- Clinical expert opinion used to estimate MSE for other treatments: 10% for IVIG and PLEX, 0% for SC

EAG comments

- MSE not used in ACM1 model and no sufficient clinical justification why it is being used in revised model
- Uncertain if a clinically appropriate way to adjust transition probabilities within the controlled health state in model. Not an uncaptured benefit, more a different way of modelling benefits using MG-ADL
- Prefer to revert to ACM1 distribution of [redacted]% with loss of response, [redacted]% with continued response, and [redacted]% with stable response in EAG base case

Does committee agree with company's use of new MSE data in the model?
What is the link between MSE in continued response health state and steroid-sparing costs?

Abbreviations: ACM, Appraisal committee meeting; MG-ADL, myasthenia gravis-activities of daily living; CFB, change from baseline; MSE, minimal symptom expression; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; gMG, generalised myasthenia gravis; SC, standard care; CS, corticosteroids

Uncaptured benefits: self-administration

Company response

- Benefits to patients (improved QoL) and the NHS (reduced resource utilisation) associated with at-home self-administration of zilucoplan, compared with in-hospital IV administration of IVIg/PLEX
- Calculate time saved for patients and NHS staff from self-administration:
  - [redacted] hours of NHS staff time and [redacted] hours of patient time for zilucoplan compared with IVIg
  - [redacted] staff hours and [redacted] patient hours saved for zilucoplan compared with PLEX
- Apply a 0.05 per-administration utility to account for health-related benefit of self-administering zilucoplan and explore removing this utility in scenario analysis

EAG comments

- None of company's references regarding utility gain relate to gMG, but are for: Gaucher disease, bone metastases, pulmonary arterial hypertension, transfusion-dependent β-thalassemia and haemophilia A.
- These studies refer to different modes of administration (e.g. oral, infusions)
- EAG prefers to remove this utility benefit because it is already captured in a patient's global EQ-5D score

Is it appropriate for company's updated model to include utility increment associated with self-administration?
Why is this this 0.05 utility benefit not already captured in EQ-5D data?
Is the time saved for patients and NHS staff already captured within IVIg and PLEX costs?

Abbreviations: ACM, Appraisal committee meeting; MG-ADL, myasthenia gravis-activities of daily living; CFB, change from baseline; IV, intravenous; QoL, quality of life; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; gMG, generalised myasthenia gravis

Uncaptured benefits: carers

Company's revised utility assumptions

Company response

- gMG associated with a significant carer burden
- Societal costs for patients (work time lost) and caregiver burden (time spent caring for a person with gMG) by MG-ADL range now included as an option in updated model
- Scenarios have been provided with these options included

EAG comments

- Note that caregiver utility decrements from a study in multiple sclerosis by Acaster et al. (2013)
- This data also presented at ACM1 for efgartigimod for treating gMG [ID4003]
- Agree with company that caregiver disutilities should not be included in base case, because there is no evidence that multiple sclerosis is a suitable proxy for gMG
- In ID4003, committee preferred to exclude caregiver disutilities and consider effect of gMG on caregivers qualitatively

Does committee agree that carer disutilities should be excluded from the base case?

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; MG-ADL, myasthenia gravis-activities of daily living; gMG, generalised myasthenia gravis

Other analysis provided by company: 2-year treatment stopping rule

Company response

- Treatment stopping rule included to simulate patient intolerance to treatment or a physician choice to limit long-term use of some treatments (assuming improved symptoms mean people may taper treatment)
- Revised base case assumes that people who have had 2 years of treatment will maintain health improvements for the rest of their lifetime, with no ongoing treatment costs

EAG comments

- Company's revised base case assumes a maximum treatment duration (treatment-stopping rule) of 2 years (104 weeks) for all patients on all treatments; note this stopping rule not included in company's ACM1 model
- Prefers to remove stopping rule in EAG base case, as gMG is a chronic disease requiring lifelong treatment, and treatments are not curative
- Further clinical advice on the appropriateness of 2-year stopping rule would be helpful

- Is it appropriate to include a 2-year stopping rule for all treatments?
- Is it reasonable to assume that after stopping treatments, treatment effect in responders continues indefinitely?

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Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; gMG, generalised myasthenia gravis

Company and EAG revised base cases – key inputs/assumptions

Model inputs	Company revised base case	EAG base case
Population	Baseline characteristics of refractory patients in RAISE	Same as company
Comparator	• IVIg/SCIg • PLEX	Blended SC comparator, agree with company's refined % from efgartigmod EAMS: • 56.7% IVIg + steroids + NSISTs, • 18.9% PLEX + steroids + NSISTs, • 24.4% steroids + NSISTs only
Treatment response rates	• Zilucoplan: [redacted]%, bivariate NMA for zilucoplan vs placebo • IVIg: [redacted]%, bivariate NMA for IVIg vs placebo • PLEX: 57%, Barth 2011	• Zilucoplan, IVIg, and PLEX the same as company, plus refractory standard care response rate of [redacted]% which differs from company
Referent response rate	• 31.5%	• 31.5% (also the same as company, but note company's referent response rate same as that of its refractory standard care)

Abbreviations: EAMS, early access to medicines scheme; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin; NMA, network meta-analysis; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; SC, standard care

Company and EAG revised base cases – key inputs/assumptions

Model inputs	Company revised base case	EAG base case
Dosing frequency of IVIg/SCIg	In line with ACM1 committee conclusions (every 4 weeks) but 100% of patients on Ivlg (closer to practice)	ACM1 committee conclusion but 50% of patients have IVIg and 50% SCIg
Costs for subsequent treatment	Costs for IVIg/PLEX applied in subsequent treatment of patients who have had IVIg/PLEX or standard refractory first-line treatment	IVIg/PLEX won't be offered again if patients did not respond the first time
Extra costs from corticosteroid use/complications	Patients on IVIg or PLEX and exhibiting a continued response accrue annual healthcare resource use (HCRU) costs of £4,671 for corticosteroid use	Use HCRU corticosteroid costs from ACM1 model (£2,950); extra HCRU costs for managing corticosteroid complications removed

Abbreviations: ACM, appraisal committee meeting; HCRU, healthcare resource use; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

Company and EAG revised base cases – key inputs/assumptions

Model inputs	Company revised base case	EAG base case
Uncaptured benefits		
minimum symptom expression (MSE)	[redacted]% of patients in continued response health state reached MSE	• MSE data not used; prefer ACM1 distribution: [redacted]% with loss of response, [redacted]% with continued response, and [redacted]% with stable response
• **Utility benefit associated with zilucoplan self-administration**	• 0.05 per-administration utility	• Remove
• **Annual disutility of corticosteroid use**	• Additional utility decrement associated with corticosteroid use included	• No additional utility decrement associated with corticosteroid use
• **Caregiver disutility**	• Caregiver disutility not included in base case but included in scenario analysis	• Agree excluding caregiver disutilities in model
Treatment stopping rule	• 2-year stopping rule for all treatments	• No stopping rule (stopping rule not included in company's ACM1 model either)

Abbreviations: MSE, minimal symptom expression; ACM, appraisal committee meeting

Key questions (1)

Comparator:
- Would the committee change its view on standard care for refractory gMG in the NHS?
- Does committee agree with company's revised proportions for patients having standard care in EAMS cohort?

Comparative effectiveness of zilucoplan:
- Do the new indirect treatment comparisons reduce the uncertainty committee noted at ACM1?
- Does the committee consider bivariate NMA appropriate for estimating relative treatment effect of zilucoplan?

Model
- Is the company's revised model using MSE appropriate?

Placebo response heterogeneity:
- Does the heterogeneity in the placebo response need to be resolved?
- Which NMA should or can be used to estimate the relative treatment effect in the model?

Response rates:
- Does committee consider company's updated response rates for treatments appropriate?
- Which is the preferred response rate for revised refractory SC?

Subsequent treatments:
- Is company's approach to modelling subsequent treatments appropriate?
- What proportion of people would be expected to switch from IVIg to PLEX, and vice versa?
- Is it appropriate to model costs of subsequent treatments without modelling treatment benefit?

Abbreviations: ACM, appraisal committee meeting; SC, standard care; gMG, generalised myasthenia gravis; NMA, network meta-analysis; EAMS, Early Access to Medicines Scheme; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

Key questions (2)

Uncaptured benefits:

- Does committee agree with company's approach to costs associated with CS use in the model?
- Is it appropriate to include utility decrement associated with corticosteroid use?
- Does committee agree with company's use of new MSE data in the model?
- What is the link between MSE in continued response health state and steroid-sparing costs?
- Is it appropriate for company's updated model to include utility increment associated with self-administration?
- Why is this this 0.05 utility benefit not already captured in EQ-5D data?
- Is the time saved for patients and NHS staff already captured within IVIg and PLEX costs?
- Does committee agree that carer disutilities should be excluded from the base case?

Stopping rule:

- Is it appropriate to include a 2-year stopping rule for all treatments?
- Is it reasonable to assume that after stopping treatments, treatment effect in responders continues indefinitely?

- What are the committee's referred assumptions?

- What is the committee's preferred ICER threshold?

- What is the committee's preferred ICER?

Abbreviations: CS, corticosteroids; MSE, minimum symptom expression; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

Cost-effectiveness results

Company base case results (based on model version 2)

Deterministic pairwise base case results

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.65			
IVIg/SCIg	1,968,712.49	9.44	[redacted]	0.21	[redacted]
PLEX	1,928,092.55	9.47	[redacted]	0.18	[redacted]

Probabilistic sensitivity analysis results

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.26			
IVIg/SCIg	4,512,564.45	9.08	[redacted]	0.18	[redacted]
Plasma exchange	4,506,160.32	9.07	[redacted]	0.19	[redacted]

- Deterministic sensitivity analysis shows that assumptions on resource use associated with IVIg and PLEX in uncontrolled health state for subsequent treatments was consistently influential on ICERs for both comparisons

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year.

Impact of subsequent treatment costs (based on model version 2)

EAG preferred subsequent treatment costs, company revised base case

Scenario		Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER
1	Revised company base case	Zilucoplan	[redacted]	9.65	-	-	-
		IVIg/SCIg	1,968,712	9.44	[redacted]	0.205	[redacted]
		Refractory std care	1,943,093	9.39	[redacted]	0.261	[redacted]
		PLEX	1,928,093	9.47	[redacted]	0.176	[redacted]
2	EAG preferred approach to subsequent treatment	Zilucoplan	[redacted]	9.65	-	-	-
		IVIg/SCIg	717,707	9.44	[redacted]	0.205	[redacted]
		Refractory std care	632,155	9.39	[redacted]	0.261	[redacted]
		PLEX	771,388	9.47	[redacted]	0.176	[redacted]

Abbreviations: EAG, External assessment group; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year

Cumulative effect of the EAG's preferred assumptions, zilucoplan versus refractory standard of care (based on model version 2)

Assumption	Incr. costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Use refractory SoC as the comparator, **company revised base case**	[redacted]	0.261	[redacted]
+ Remove the added HCRU costs for managing the complications associated with CS use	[redacted]	0.261	[redacted]
+ Use the previous patient distribution ([redacted]%/[redacted]%/[redacted]%) and MG-ADL CFB data for the refractory population from the NMA (Tech report Table 8)	[redacted]	0.157	[redacted]
+ Use refractory SoC response rate of [redacted]%	[redacted]	0.117	[redacted]
+ Use the EAG's approximation of subsequent treatment	[redacted]	0.117	[redacted]
+ Remove the utility benefit of self admin of zilucoplan	[redacted]	0.041	[redacted]
+ Remove the disutility associated with CS use	[redacted]	0.038	[redacted]
+ 50% of patients receive IVIg; 50% receive SCIg	[redacted]	0.038	[redacted]
+ Remove the treatment stopping rule	[redacted]	0.038	[redacted]
EAG base case	[redacted]	**0.038**	[redacted]

Abbreviations: EAG, External assessment group; SoC, standard of care; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year; CS, corticosteroids; NMA, network meta-analysis; HCRU, healthcare resource use; CFB, change from baseline; MG-ADL, MG-ADL, myasthenia gravis-activities of daily living;

Scenario results for zilucoplan versus refractory standard of care, EAG base case (based on model version 2)

No.	Scenario description	Incr. Costs	Incr. QALYs	ICER (£/QALY)
EAG base case		[redacted]	0.038	[redacted]
1	Include the added HCRU costs for managing the complications associated with CS use and the disutilities associated with CS use	[redacted]	0.041	[redacted]
2	Include the utility benefit of SC admin of zilucoplan	[redacted]	0.115	[redacted]
3	Use the Minimum Symptom Expression data	[redacted]	0.148	[redacted]
4	Use the company's approximation of subsequent treatment	[redacted]	0.038	[redacted]
5	Include the treatment stopping rule	[redacted]	0.038	[redacted]
6	Use response rates for the refractory gMG population from the bivariate NMA ('ZLP refractory data in NMA')	[redacted]	0.083	[redacted]

Abbreviations: EAG, External assessment group; CS, corticosteroids; SC, subcutaneous; gMG, generalised myasthenia gravis; NMA, network meta-analysis; HCRU, healthcare resource use; ZLP, zilucoplan; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

NICE National Institute for Health and Care Excellence

Thank you.

Supplementary slides

NICE National Institute for Health and Care Excellence

Population: refractory gMG

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Company has positioned zilucoplan for refractory gMG, narrower than market authorisation, defined based on criteria from RAISE trial:

- the disease is uncontrolled, as defined by a MG-ADL ≥ 6 or a QMG ≥ 12, **and**
- **an additional therapy such as IVIg or PLEX is being considered, or patients are being treated chronically with IVIg/PLEX and/or**
- as an alternative option to efgartigimod (subject to NICE approval – appraisal ongoing as of now)

Previous treatments to include the following

↳ prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other immunosuppressants

Either

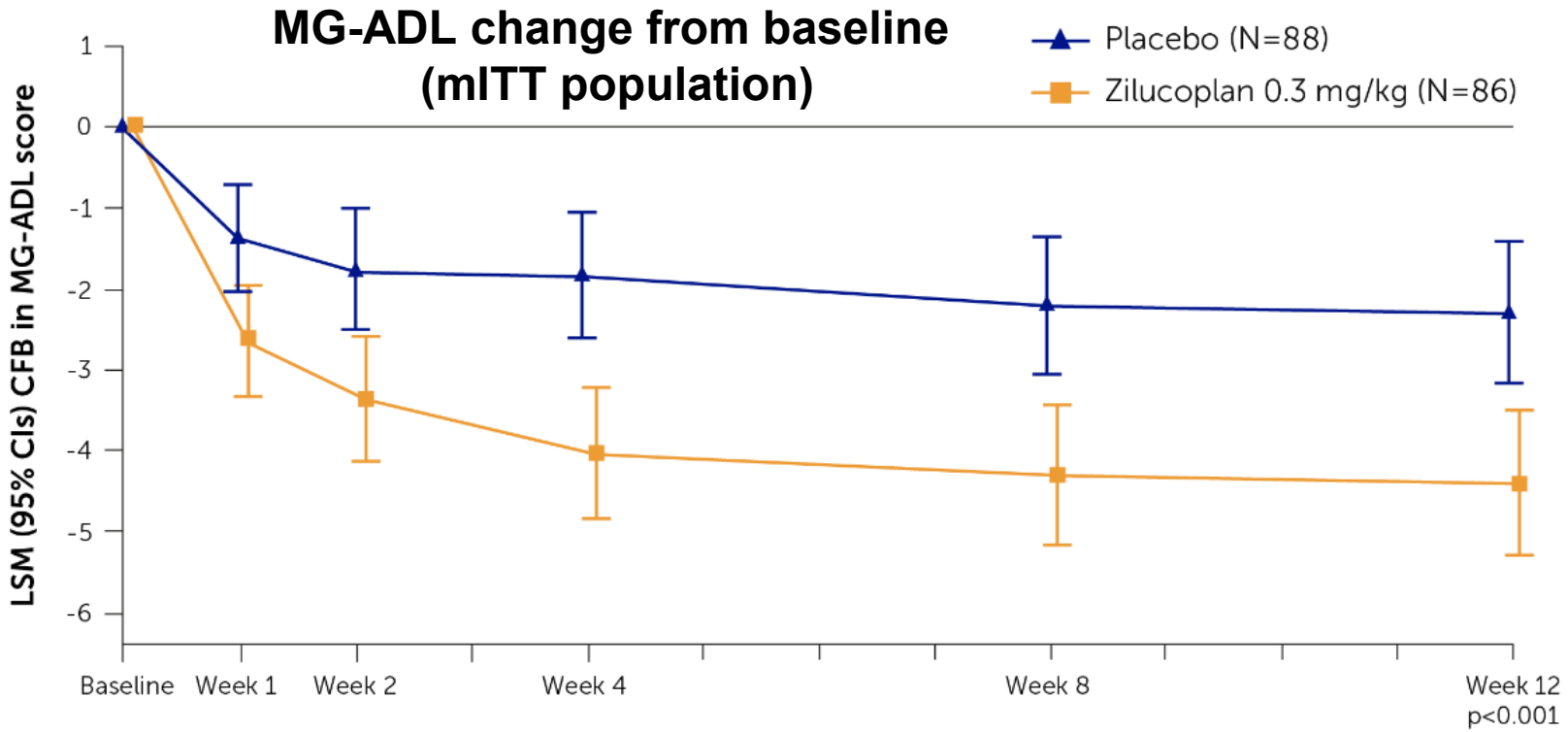
- Patients are on treatment with 2 or more of the above treatments

Or

- Patients have a history of treatment with at least 1 of the above treatments and required chronic PLEX/IVIg, at least every 3 months for 12 months

Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis.

RAISE: results



MG-ADL: higher scores indicate more severe symptoms; MCID of ≥2 points

EAG: improvement also observed in placebo arm

ACM1: Zilucoplan as an add-on to standard treatment more effective at improving MG-ADL score than standard treatment alone

MG-ADL CfB and response (≥3 point improvement) by refractory status at week 12

	Placebo, n=88		Zilucoplan, n=86	
	n	Mean CfB [95%CI] (SD)	n	Mean CfB [95%CI] (SD)
mITT	88	-2.30 [-3.17, -1.43]	86	-4.39 [-5.28, -3.50]
Refractory	[redacted]	[redacted]	[redacted]	[redacted]
	n	**Response (n/N)**	n	**Response (n/N)**
mITT	88	46.1% (NR)	86	73.1% (NR)
Refractory	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; CI, confidence interval; MCID, minimum clinically important difference; MG-ADL, Myasthenia Gravis-Activities of Daily Living; mITT, modified intent-to-treat; SD, standard deviation.

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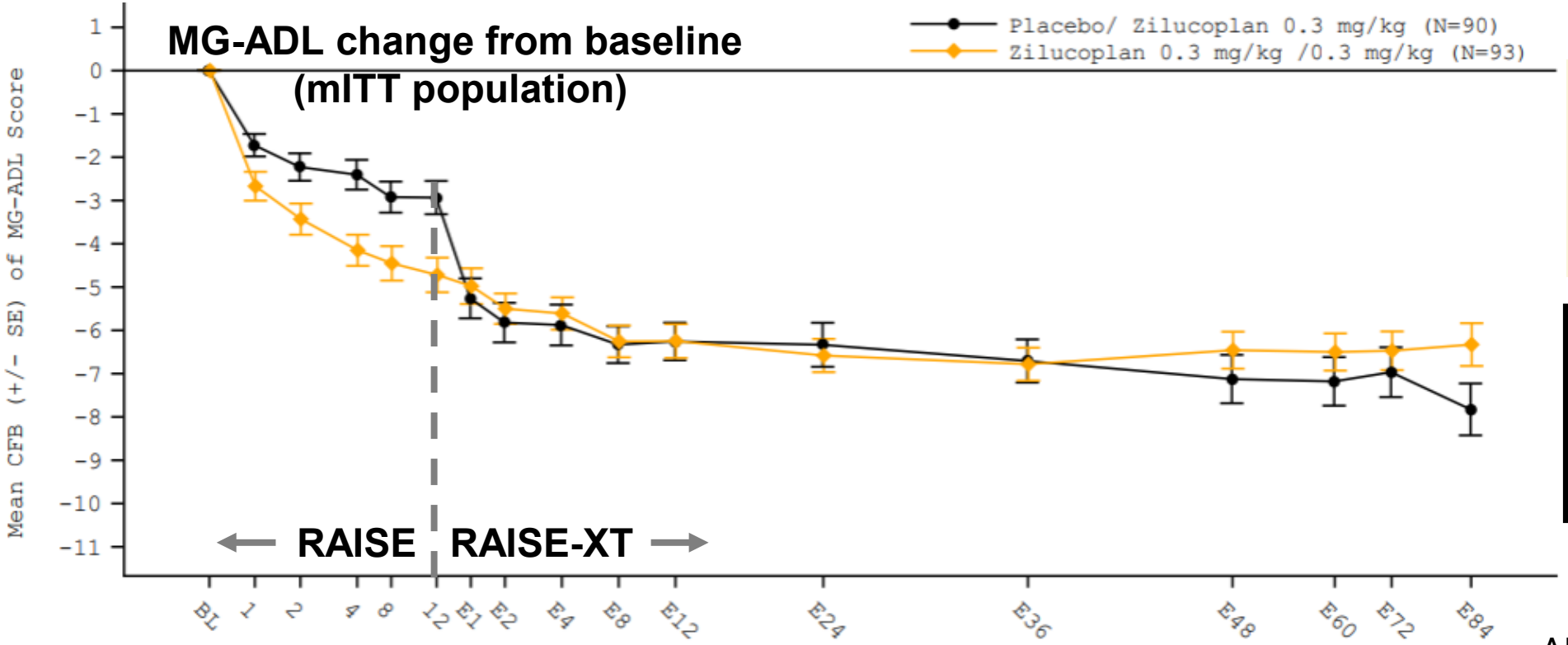
RAISE-XT: results



Number of Participants (n):

	BL	1	2	4	8	12	E1	E2	E4	E8	E12	E24	E36	E48	E60	E72	E84
Placebo/Zilucoplan 0.3 mg/kg:	90	90	88	89	90	90	88	89	89	88	86	84	75	72	67	59	46
Zilucoplan 0.3 mg/kg/ 0.3 mg/kg:	93	91	93	93	93	93	91	92	90	90	89	86	87	83	82	70	55

MG-ADL: higher scores indicate more severe symptoms; MCID of ≥2 points

EAG: higher drop out from placebo/ zilucoplan group (treatment switchers)

MG-ADL CfB by refractory status at extension week 12

	Placebo, n=90		Zilucoplan, n=92	
	n	Mean CfB (SD)	n	Mean CfB (SD)
Refractory	[redacted]	[redacted]	[redacted]	[redacted]
Not refractory	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; CI, confidence interval; MCID, minimum clinically important difference; MG-ADL, Myasthenia Gravis-Activities of Daily Living; mITT, modified intent-to-treat; SD, standard deviation.

Clinical evidence – trial summary

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	RAISE (completed)	**RAISE-XT** (ongoing)
Design	Randomised, double-blind, placebo-controlled study	Open label extension (OLE) study
Intervention(s)	• Zilucoplan 0.3 mg/kg/day, SC injection + SoC (n=86)	Zilucoplan 0.3 mg/kg/day, SC injection + SoC (n=200)
Population	Inclusion criteria: • gMG (MGFA Class II–IV) • Positive serology for anti-AChR autoantibodies • MG-ADL score ≥6 • QMG score ≥12 • No change in NSISTs for ≥30 days prior to treatment or anticipated to occur during study • No requirement to have failed multiple prior therapies	Completion of the RAISE Phase III or Phase II study
Comparator	• Placebo + SoC (n=88)	N/A
Pre-planned subgroups	Patients who are treatment refractory, as defined in RAISE	Patients who are treatment refractory, as defined in RAISE
Outcomes	Change from baseline up to week 12 in MG-ADL	Safety and tolerability at extension week 12 Long-term data up to extension week 84
Locations	North America, Europe (including UK), and Japan	North America, Europe (including UK), and Japan

Abbreviations: AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC subcutaneous; SoC, standard of care.

Comparator: company excluded SoC as a comparator for patients with refractory generalised myasthenia gravis

Company

- Excluded steroids and NSISTs from zilucoplan and SoC arms
- Modelled pairwise comparisons with IVIg, PLEX, efgartigimod

EAG

- Zilucoplan, IVIg, and PLEX used as an add-on to steroids and NSISTs
- Efgartigimod EAMS (n=48), patients starting efgartigimod:
  - ↳ 43.8% chronic IVIg
  - ↳ 14.6% chronic PLEX
  - ↳ 41.6% steroids and NSISTs only
- EAG considers EAMS cohort (see box) comparable with likely cohort who would have zilucoplan in the NHS
- EAG prefers to model a blended comparator of SC treatments based on distribution received in EAMS
- ID4003 (efgartigimod) appraisal similarly used a blended comparator

Efgartigimod EAMS cohort

- AChR ab-positive gMG
- Average age 49.2 years
- 66.7% disease duration >10 years
- Average MG-ADL at baseline 11.2
- ≥1 past non-steroidal immunosuppressant (average 2.6)
- Restricted efgartigimod to patients who were:
  - ↳ Refractory (≥2 NSISTs), or
  - ↳ Intolerant/ineligible to NSISTs, or
  - ↳ Dependent on IVIg/PLEX

EAG preferred subsequent treatment costs

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controlled condition	uncontrolled condition	Cost per model cycle
EAG preferred approach for people having zilucoplan first-line:		
[redacted]%* accrue costs for SoC basket (including IVIg and PLEX) plus HCRU costs	[redacted]% accrue HCRU costs (without IVIg and PLEX costs), plus costs for the refractory standard basket without IVIg or PLEX costs	([redacted]% x (£[redacted] + £[redacted])) + ([redacted]% x £[redacted] + £[redacted]) = **£[redacted]**
EAG preferred approach for people having IVIg first-line:		
10.77%* accrue costs for SoC basket (excluding IVIg costs) plus HCRU costs	89.23% accrue HCRU costs (without IVIg and PLEX costs), plus costs for the refractory standard basket without IVIg or PLEX costs	(10.77% x (£[redacted] + £[redacted]) + (89.23% x £[redacted] + £[redacted]) = [redacted]
EAG preferred approach for people having PLEX first line:		
[redacted]%** accrue costs for SoC basket (excluding PLEX costs) plus HCRU costs	[redacted]%, accrue HCRU costs (without IVIg and PLEX costs), plus costs for the refractory standard basket without IVIg or PLEX costs	([redacted]% x (£[redacted] + £[redacted]) + ([redacted]% x £[redacted] + £[redacted]) = **£[redacted]**
EAG preferred approach for people having SoC first-line:		
Receive HCRU costs (without IVIg or PLEX costs) plus costs for SoC basket without IVIg or PLEX costs		(£[redacted] / [redacted]) + £[redacted] = **£[redacted]**

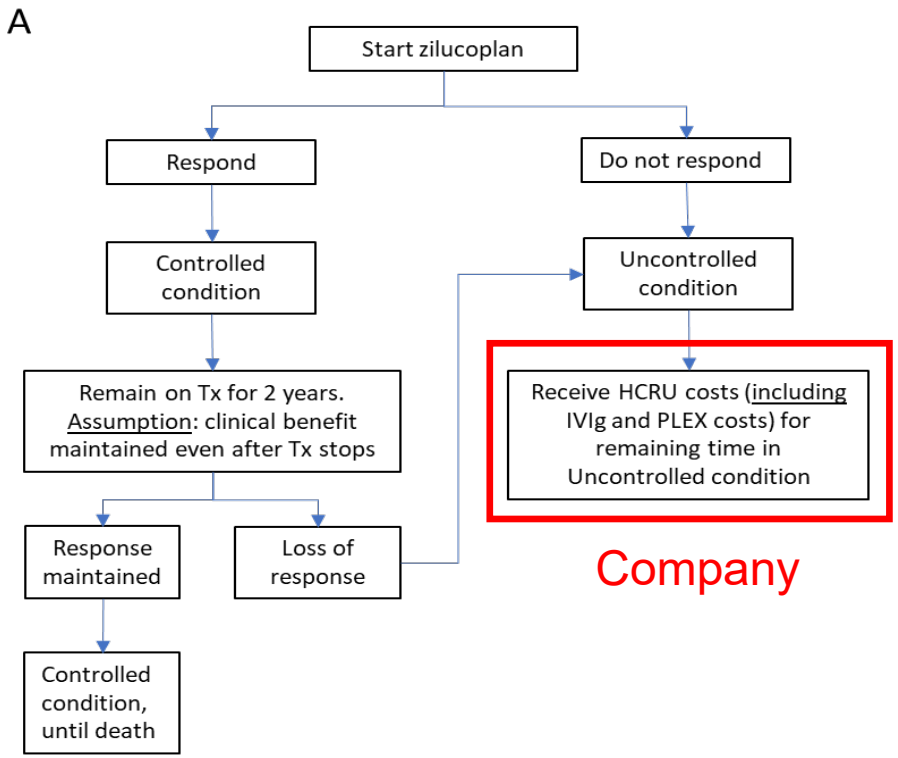
* 18.9% in EAMS who have PLEX in SoC basket, multiplied by the 57% who respond

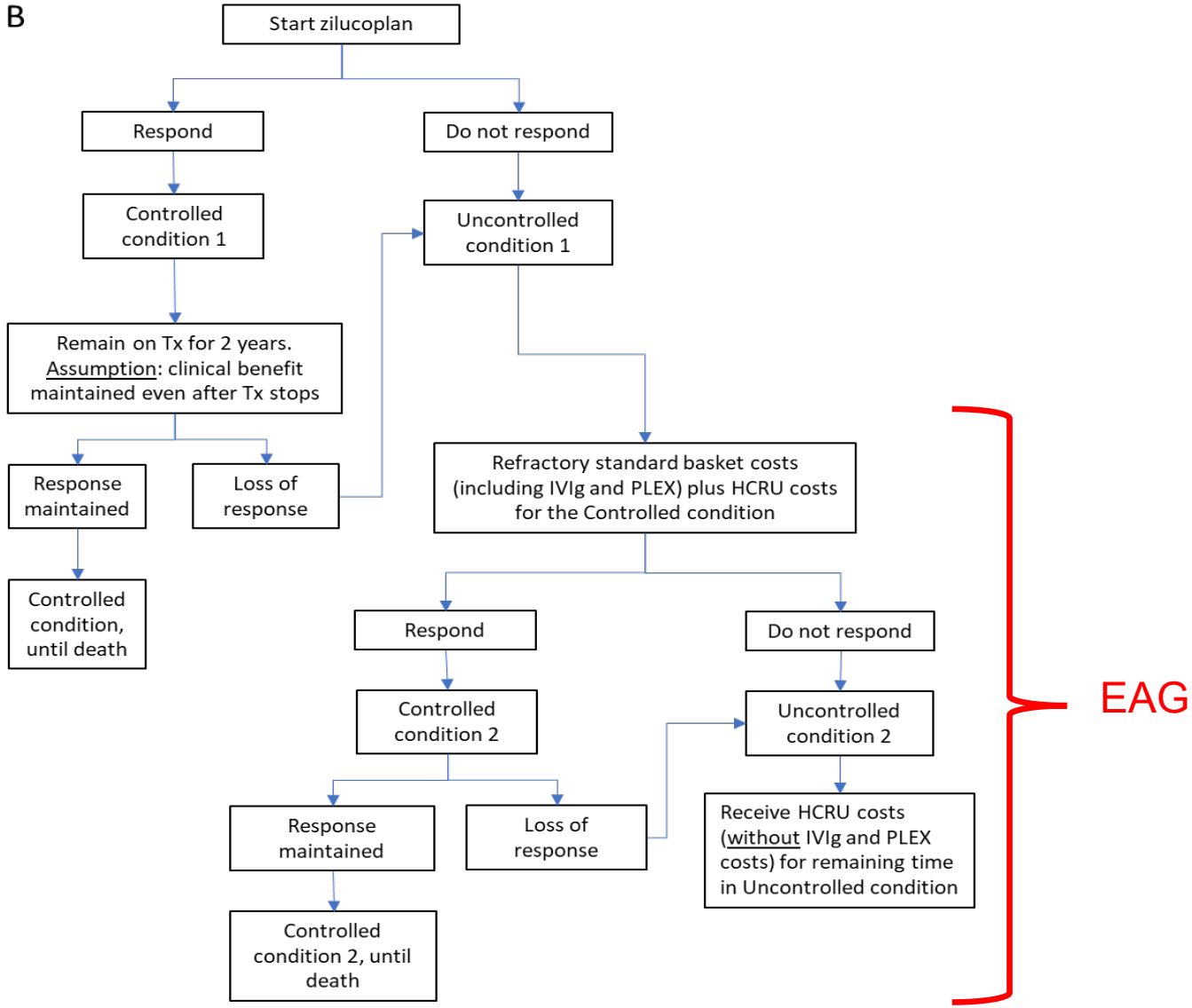
** 57.6% in EAMS who have IVIg in the refractory standard basket, multiplied by the [redacted]% who respond

Abbreviations: EAG, External assessment group; SoC, standard of care; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; HCRU, healthcare resource utilisation; EAMS, early access to medicines scheme; SoC, standard of care

EAG and company preferred subsequent treatment flowcharts (1)

A = Company model for zilucoplan arm ; B = EAG preferred approach for zilucoplan arm





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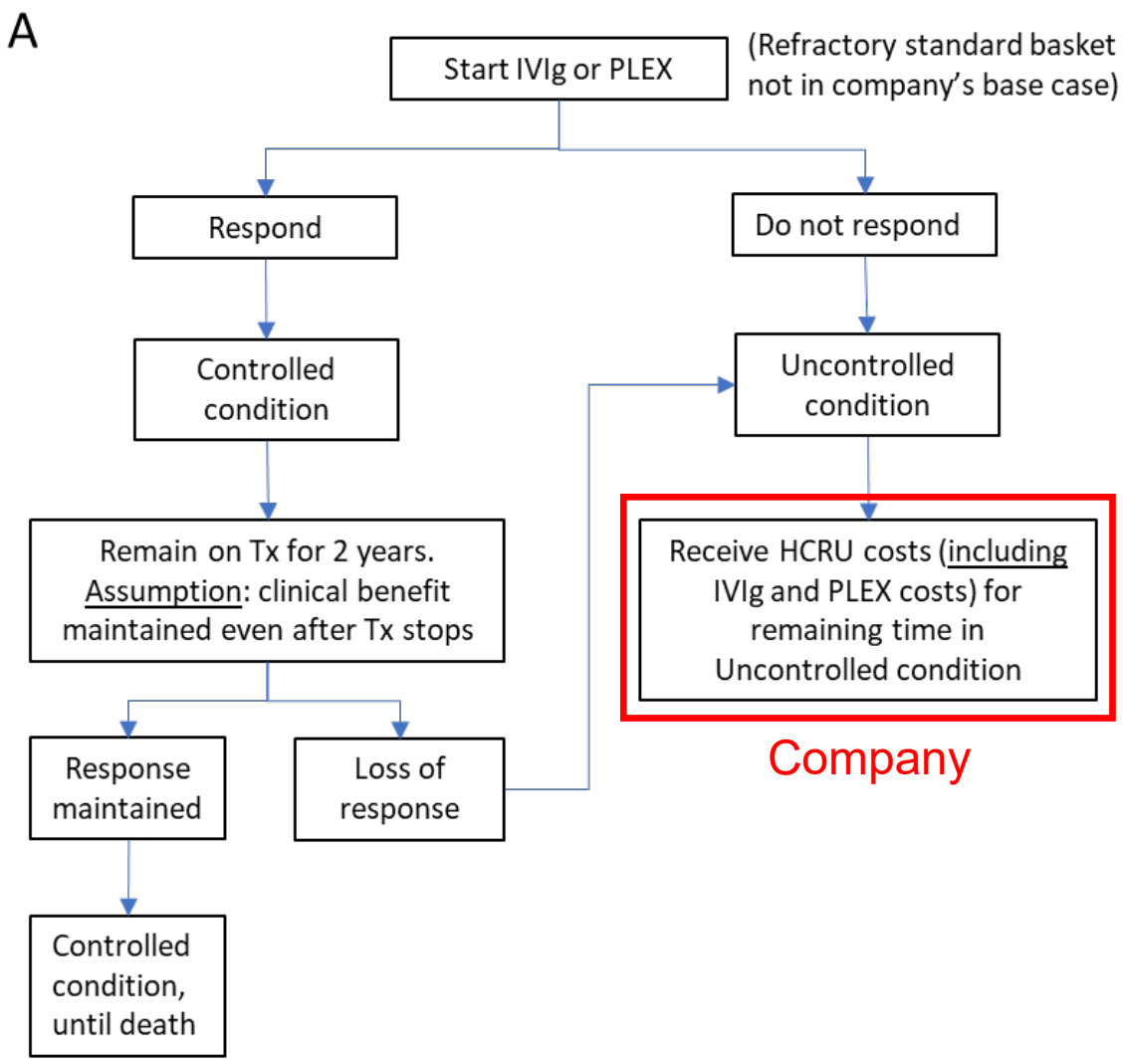
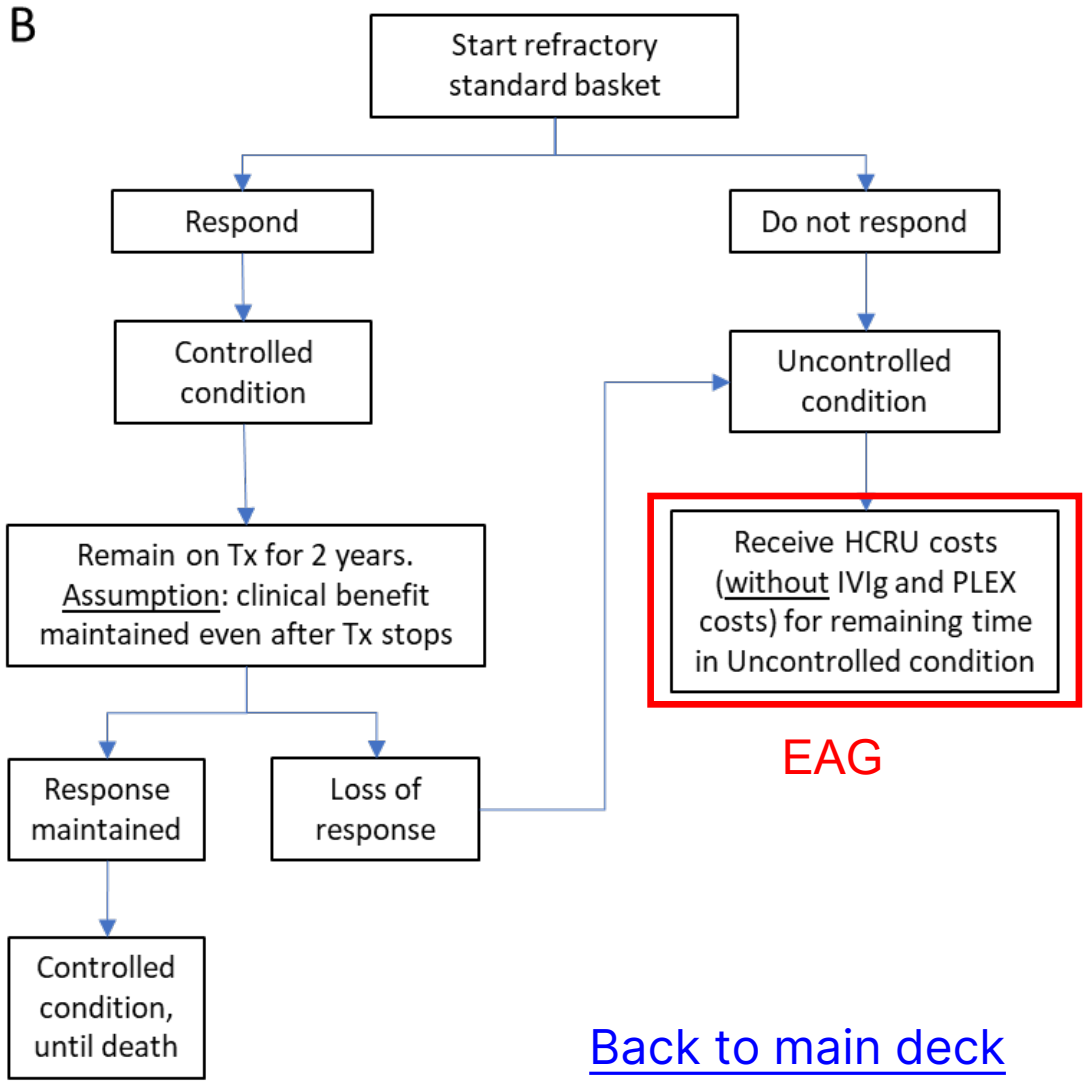
Abbreviations: EAG, External assessment group; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; HCRU, healthcare resource utilisation

EAG and company preferred subsequent treatment flowcharts (2)

A = Company model for comparator arm; B = EAG preferred approach for comparator arm





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Abbreviations: EAG, External assessment group; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; HCRU, healthcare resource utilisation

Company's revised utility assumptions

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Company's caregiver disutility assumptions

MG-ADL score range		Proportion of patients requiring a caregiver	Utility decrement	Average utility decrement per model cycle
0	1	6%	-0.002	0.000
2	3	10%	-0.002	0.000
4	5	29%	-0.002	-0.001
6	7	40%	-0.045	-0.018
8	9	50%	-0.142	-0.071
10	11	57%	-0.160	-0.091
12	13	74%	-0.160	-0.119
14	24	85%	-0.160	-0.135
Crisis/exacerbation		85%	-0.180	-0.152

Annual disutility of steroid use

	Disutity	Duration (days)
Uncontrolled - High-dose (> 10 mg/day)	0.18	365.25
Stable response - Low-dose (< 10 mg/day)	0.07	365.25
Continued response - no steroid use	0.00	365.25

Utility decrements with steroid use

Steroid use	Health state	Utility decrement
High (≥10 mg/day)	Uncontrolled	0.18
Low (<10 mg/day)	Stable response	0.07

- Company's updated model incorporates caregiver disutilities, considering the proportion of patients requiring caregiver support and utility decrements reported in previous submissions to NICE
- No data available on the costs or utility values associated with CS use in gMG; therefore, proxy conditions had to be used to incorporate the CS cost and disutility in the model

Per-administration utility of self-administration

Utility	Duration (days)
0.05	1.00

Abbreviations: MG-ADL, Myasthenia Gravis-Activities of Daily Living; CS, corticosteroids

How NMA results were transformed for the model

Treatment response rates were calculated based on the odds ratio output from the NMA, applied to a referent response rate

1. Odds ratios converted to relative risks due to difficulties associated with the interpretation of odds ratios

$$RR[t] = \frac{OR_t}{(1 - ReferentResponse) + (ReferentResponse \times OR_t)}$$

Where *t* is the comparator treatment with known odds ratio versus the referent treatment

2. Then, the relative risk was applied to the referent response rate in order to determine each treatment's response rate:

$$Response\ rate[t] = ReferentResponse \times RR_t$$

Referent response calculated as the simple average response across the NMA studies ([redacted])