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

For public and zoom – redacted

Technology appraisal committee B [05 February 2025]

Chair: Charles Crawley

Lead team: David McAllister, Peter Wheatley-Price, Nigel Westwood

External assessment group: Southampton Health Technology Assessments Centre

Technical team: Zain Hussain, Yelan Guo, Emily Crowe

Company: UCB

© NICE 2025. All rights reserved. Subject to Notice of rights.

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

Recommendations and key conclusions from ACM2

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

ACM2 conclusion/considerations		Company update/further information?
Target population	• Uncertainty in target population for zilucoplan in relation to company's definition of refractory MG and its preference for revised EAMs cohort to inform "basket" standard care treatments	Yes
Comparators	• A 'basket' of standard care more reflective of NHS practice • Uncertainty in appropriate proportions of people having IVIg, PLEX and NSISTs in 'basket' of standard care treatments	Yes
Relative effectiveness	• Substantial uncertainties in company's updated NMAs • Effectiveness of zilucoplan relative to IVIg and PLEX unclear	Yes
Economic model	• MSE might be clinically relevant; but sources of data for MSE and information on how MSE implemented in model not presented • EAG unable to revert company's revised base-case results to original company model submitted at ACM1	Yes

Abbreviations: AChR: Anti-acetylcholine receptor; ACM: Appraisal committee meeting; EAMS: Early Access to Medicines scheme; IVIg: Intravenous immunoglobulin; MA: Marketing authorisation; MG: Myasthenia gravis; MSE: Minimal symptom expression; NMAs: Network meta-analyses; NSISTs: Non-steroidal immunosuppressive therapies; PLEX: Plasma exchange

Key conclusions from ACM2 (continued)

ACM2 conclusion/consideration (continued)		Company update/further information?
Subsequent treatments	• Subsequent treatment should account for both costs and benefits • Further information requested	Yes
Response rate	• Uncertainty in company's revised response rates of zilucoplan and IVIg given uncertainties from bivariate NMAs	Yes
Time on treatment	• Company to provide scenario analyses that explore various time on treatment assumptions for zilucoplan and treatments in 'basket' of standard care	Yes
Utility values	• Uncertain whether EQ-5D captured all utility decrements associated with corticosteroid use, but prefer to account for this qualitatively in decision making • If appropriate to include, uncaptured benefit of zilucoplan administration should be modelled as a utility decrement for IVIg and PLEX, rather than utility increment for zilucoplan • Consider impact of zilucoplan on carers qualitatively in decision making	Yes

NICE Abbreviations: ACM: Appraisal committee meeting; EQ-5D: EuroQol-5 dimension; IVIg: Intravenous immunoglobulin; NMAs: Network meta-analyses; PLEX: Plasma exchange

Consultation responses

- **UCB (company):** comments on target population, comparators, updated NMAs and revised economic model (including several modelling parameters)
- **NHSE:** comments on subsequent treatment
- **Muscular Dystrophy UK (MDUK) and Myaware (Patient groups): joint response**
  - ❑ Comment on benefit associated with zilucoplan
- **ABN – Neuromuscular Advisory Group (Professional group)**
- **2 experts (1 patient and 1 clinical expert)**
- **3 web comments**
  - ❑ Comment on which patients zilucoplan should be offered to; benefit associated with zilucoplan

Abbreviations: ABN: Association of British Neurologists; NMAs: Network meta-analyses

Consultation responses summary (1)

Stakeholders and web comments

Muscular Dystrophy UK (MDUK) and Myaware (Patient groups), joint response:

- Draft guidance may isolate people with refractory MG, particularly who don't respond to PLEX or IVIg, leaving them with fewer treatment options and worsening their quality of life
- Draft guidance overlooks the **significant improvements in quality of life for patients who have responded positively to zilucoplan**, including achieving MSE and reducing steroid dependency and associated side effects, underscoring the unmet need for better treatment options in the MG population

ABN – Neuromuscular Advisory Group (Professional group):

- Zilucoplan should be restricted to people with severe refractory MG unresponsive or intolerant to multiple treatments, including long-term IVIg or PLEX
  - ❑ Cost effectiveness likely to favour zilucoplan by reducing the need for PLEX/IVIg and hospital admissions
- While direct comparisons to PLEX/IVIg are lacking, clinical trials show that zilucoplan significantly reduces the need for these treatments but clear criteria for discontinuation should be established

Abbreviations: ABN: Association of British Neurologists; IVIg: Intravenous immunoglobulin; MG: Myasthenia gravis; MSE: Minimal symptom expression; PLEX: Plasma exchange

Consultation responses summary (2)

Web comments

- Zilucoplan should be reserved for patients in specialist centres who don't respond to standard treatments, potentially preventing unplanned hospital admissions and ICU care, with decisions made in an MDT
- Zilucoplan can reduce hospital admissions, lower costs (e.g., IVIg), and improve patient access via self-administration, and not recommending it may disadvantage UK patients compared to Europe
- Some people with certain religious beliefs cannot have blood products such as IVIg and PLEX

Abbreviations: ICU: Intensive care unit; IVIg: Intravenous immunoglobulin; MDT: Multidisciplinary team; PLEX: Plasma exchange

Consultation responses summary (3)

UCB (company)

Key themes in company's consultation response to draft guidance 2:

- Company's target population
- Comparators
- Company's updated NMAs
- Minimal symptom expression (MSE)
- Time on treatment
- Subsequent treatments – large impact on ICER
- Utility decrement associated with IVIg and PLEX
- Corticosteroid costs
- Corticosteroid disutility

Abbreviations: ICER: Incremental cost effectiveness ratio; IVIg, Intravenous immunoglobulin; PLEX: Plasma exchange

Company's target population (1)

ACM2: committee

- Uncertainty in company's target population for zilucoplan in relation to its definition of refractory gMG and company's preference for revised EAMs cohort (n=37), which was used to inform 'basket' of standard care ("refractory standard care")

Company response to draft guidance 2 (DG2)

- Target population for zilucoplan same as stated in the company decision problem but changed wording of first criterion to be more specific and align with UK practice

Original decision problem/ACM1&2	Updated wording
• disease has not responded to other systemic treatments, including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and ciclosporin, or these options are contraindicated or not tolerated	• disease has not responded to **adequate treatment with steroids and at least 2 non-steroidal immunosuppressants** or these options are contraindicated or not tolerated

See appendix slide: 'Treatment pathway for gMG' and 'Company's target population at ACM1 & 2 versus efgartigimod EAMS cohort'

Abbreviations: ACM: Appraisal committee meeting; EAMS: Early Access to Medicines scheme; gMG: Generalised myasthenia gravis

Company's target population (2)

EAG comments

- Either wording of target population describes refractory legitimately. But change in wording may be more aligned with company's interpretation of EAMS cohort to support use of a narrower efgartigimod EAMS cohort (see appendix slide on target population) for population in model
- Company attempts to identify a specific refractory subgroup within EAMS cohort despite lack of clarity in definition of refractory

Professional group

- Zilucoplan should be restricted to people with severe refractory MG unresponsive or intolerant to multiple treatments, including long-term IVIg or PLEX

See appendix slide: 'Treatment pathway for gMG' and 'Company's target population at ACM1 & 2 versus efgartigimod EAMS cohort'

- Does the committee consider the company's revised target population (more aligned with the inclusion criteria of EAMs cohort) reflect people with refractory gMG that would have zilucoplan in practice and appropriate?
- Does the committee consider zilucoplan's treatment effect on the whole trial population generalisable to this revised target population?

Abbreviations: EAMS: Early Access to Medicines scheme; IVIg: Intravenous immunoglobulin; PLEX: Plasma exchange; MG: Myasthenia gravis

Comparator: “basket” standard care in relation to the overall and revised EAMs cohort (1)

ACM2:

Company: IVIg and PLEX the only relevant comparators for zilucoplan

- But revised efgartigimod EAMs cohort (n=48), by excluding 11 patients whom company did not consider refractory, to inform its preferred “refractory standard care basket” (used in subsequent treatment only)

Committee: ‘basket’ standard care more reflective of NHS practice

- Requested further evidence and rationale to support use of revised EAMs cohort to inform its preference

Company response to DG2: no formal or consistently used definition of refractory gMG

- Carried out expert elicitation (n=4), experts confirmed 77% (37/48) of EAMS cohort would be considered refractory
- People on no treatment (3/48) and on corticosteroids alone (10/48) would not be considered refractory
- Maintains IVIg and PLEX the only relevant comparators, but provided alternative base case comparing zilucoplan with revised “refractory standard care basket”

NICE

Abbreviations: gMG: Generalised Myasthenia gravis; ACM: Appraisal committee meeting; DG2: Second draft guidance; EAMS: Early Access to Medicines scheme; IVIg: Intravenous immunoglobulin; NSISTs: Non-steroidal immunosuppressive therapies; PLEX: Plasma exchange; SC: Standard care

Comparator: “basket” standard care in relation to the original and revised EAMs cohort (1)

Proportion of patients on ‘basket’ of standard care treatments*

	IVIg	PLEX	SoC (excluding IVIg or PLEX)
Revised EAMs (n=37)	56.7%	18.9%	24.4%
Overall EAMs (n=48)	43.8%	14.6%	41.6%

EAG comments: uncertainty in reporting of EAMs cohort

- Not all in EAMS cohort would necessarily meet criteria for being refractory, questions whether reasonable to apply specific definition of refractory which reduces an already small sample size to just 37
  - ❑ Use overall EAMS cohort (n=48) in EAG base case ➔ Approximates heterogeneous population of patients classified refractory gMG in clinical practice; more reflective of how patients would be classified as refractory gMG in clinical practice
  - ❑ Scenario analysis for more specific company-defined refractory subgroup

- Is the overall EAMS cohort (n=48) or company’s revised EAMs cohort (n=37) more reflective of patients who would have zilucoplan in clinical practice
- If so, is it appropriate to inform the proportion of patients having ‘basket’ of standard care treatments in analysis?

Abbreviations: EAMS: Early Access to Medicines scheme; gMG: Generalised myasthenia gravis; IVIg: Intravenous immunoglobulin; NSISTs: Non-steroidal immunosuppressive therapies; PLEX: Plasma exchange

Company's Updated NMAs (1)

ACM2: committee

- Requested updated NMAs addressing uncertainties including:
  - ❑ includes IVIg and PLEX in evidence network
  - ❑ accounts and adjusts for differential placebo response and baseline population heterogeneity in trials
  - ❑ explores linking networks by using IVIg as common comparator to include PLEX
  - ❑ respects randomisation

Company response to DG2

- Conducted 3 sets of NMAs supported by an updated systematic literature review (SLR) designed to identify further IVIg and PLEX evidence:
  - ❑ Bivariate (included 4 additional studies on IVIG or PLEX; informed company's base case)
  - ❑ baseline risk-adjusted (did not inform model as no study on PLEX included), and
  - ❑ two-stage analysis (comprising baseline-risk adjusted NMA followed by a bivariate NMA; informed a scenario analysis in company's model)

See appendix slide: 'Clinical evidence trial summary', 'RAISE results' and 'RAISE-XT results'

Abbreviations: ACM: Appraisal committee meeting; DG2: Second draft guidance; IVIg: Intravenous immunoglobulin; NMAs: Network meta-analyses; PLEX: Plasma exchange

Company's updated NMAs (2): results (December 2024)

EAG: for MG-ADL response, odds ratios for zilucoplan versus placebo in updated bivariate NMAs broadly similar to previously reported; bivariate NMAs the only ones showing statistically significant difference

Analysis	Zilucoplan	IVIg*	PLEX
MG-ADL response ≥3 points, odds ratio versus placebo (95% credible interval)			
Conventional NMA (RCTs)	[redacted]	[redacted]	No PLEX studies
Bivariate NMA (RCTs)*	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs + non-RCTs)*	[redacted]	[redacted]	[redacted]
Baseline risk-adjusted NMA*	Only response rate reported		No PLEX studies
Two-stage NMA (RCTs)*	[redacted]	[redacted]	[redacted]
Two-stage NMA (RCTs + non-RCTs)*	[redacted]	[redacted]	[redacted]

Source: EAG critique of company response to DGD2, Table 6

See appendix slide: 'Clinical evidence trial summary', 'RAISE results', 'RAISE-XT results' and 'Company's updated NMAs for MG-ADL change from baseline'

Abbreviations: DGD2: Second draft guidance document; IVIg: Intravenous immunoglobulin; MG-ADL: Myasthenia Gravis – Activities of Daily Living; NMAs: Network meta-analyses; PLEX: Plasma exchange; RCT: Randomised controlled trial

Company's updated NMAs (3): limitations

EAG comments:

- Two-stage analysis addresses request in DG2 since it considers 1) placebo response heterogeneity; and 2) all relevant studies for IVIg and PLEX
- EAG validated company's baseline risk adjusted NMAs, but could not validate results of bivariate NMAs within the time available for this critique ➔ 2-stage NMAs associated with very wide credible intervals

Limitations of updated NMA include:

- ❑ Risk of bias and generalisability of included studies is not reported
- ❑ NMA feasibility assessment was not conducted
- ❑ Impact of including new studies on between-study heterogeneity in updated NMAs is not reported

See appendix slide: 'Clinical evidence trial summary', 'RAISE results' and 'RAISE-XT results'

- Do the updated NMAs reduce the uncertainty committee noted at ACM2?
- Does the committee consider the updated bivariate NMA (company) or the two-stage NMA (EAG) appropriate for estimating relative treatment effect of zilucoplan and inform the base case in the model?

Abbreviations: ACM: Appraisal committee meeting; DG2: Second draft guidance; IVIg: Intravenous immunoglobulin; NMAs: Network meta-analyses; PLEX: Plasma exchange

Minimal symptom expression (MSE) (1)

ACM2: Further clarification and justification on MSE requested

Company response to DG2

- Benefit of MSE (defined as MG-ADL score 0 or 1) further confirmed by expert elicitation
- Proportion of people achieving MSE on:
  - zilucoplan estimated from RAISE-XT
  - IVIg, PLEX and standard of care (excluding IVIg and PLEX) are the averages taken from Company Expert Interviews Report
- Proportions inform distribution of patients responding to their initial treatment across 'continued response' (i.e., MSE), 'loss of response' and 'stable response' health states in model
- Response rates and health state proportions differ by treatment, how company models benefit of both initial and subsequent treatment

Table: Proportion of patients in the 'continued', 'loss of' and 'stable' response categories, company revised model versus previous models at ACM1&2*

Treatment	Continued response / MSE		Loss of response		Stable response	
	Company base case (ACM2&3)	Company (ACM1)	Company base case (ACM2&3)	Company (ACM1)	Company base case (ACM2&3)	Company (ACM1)
Zilucoplan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator basket^	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Estimates in table informed by clinical experts except zilucoplan (based on RAISE-XT); Source: adapted based on EAG critique of company response to DGD2, Table 8; ^ the standard care blended comparator/comparator basket include proportion of patients on IVIg, PLEX, and corticosteroids and/or NSISTs only)

Abbreviations: ACM: Appraisal committee meeting; DG2: Second draft guidance; IVIg: Intravenous immunoglobulin; MG-ADL: Myasthenia Gravis – Activities of Daily Living; MSE: Minimal symptom expression; PLEX: Plasma exchange

Minimal symptom expression (2)

See appendix: 'MSE in comparator basket – EAG revised company base case'

EAG comments

- Proportion of patients having "basket" standard care comparator achieving MSE in company's base case:
  - ❑ Disagree with company's assumption of [redacted], because this does not account for patients on IVIg and PLEX in "basket" standard care and associated benefits
  - ❑ Consider [redacted] (also accounting for patients on IVIg and PLEX) appropriate (table 9 EAG critique)
  - ➔ EAG base case uses [redacted] based on overall EAMs data
- Uncertainty in using MSE proportions to estimate continued response because:
  - ❑ Data for zilucoplan from RAISE–XT, but no further evidence that MSE lasts over lifetime of model
  - ❑ Data for IVIg and PLEX relies on clinical expert estimates

- Is MSE appropriate basis for determining response status and subsequently inform the transition probabilities in the model?
- Is the company's approach of estimating MSE data for zilucoplan (based on RAISE-XT) and for the 'basket' of standard care (based on company's clinical interviews) appropriate?
- Is the calculation of proportion of people achieving MSE in company's base case ([redacted] or EAG's base case ([redacted]) in the 'basket' of standard care appropriate?

Abbreviations: EAMS: Early Access to Medicines scheme; IVIg: Intravenous immunoglobulin; MSE: Minimal symptom expression; PLEX: Plasma exchange

Response rates

ACM2

- Requested further analysis using revised treatment response rates informed by NMAs that explore inclusion of studies on PLEX (including Barth et al.), and with placebo response heterogeneities and baseline population heterogeneities across studies adjusted for in analysis

Company response to DG2

- Provided revised treatment response rates based on updated NMAs:

Treatment	Bivariate NMA (used in revised base case)	Two-stage NMA (used in scenario analysis)	Conventional NMA
Zilucoplan	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]	[redacted]
SoC (excluding IVIg/PLEX)	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]

* Informed by clinical expert elicitation obtained by the EAG

Source: EAG critique of company response to DGD2, Table 15

EAG comments: Two-stage baseline risk adjusted NMA aligns most closely with committee's request, so used in EAG base case and bivariate NMA results for a scenario analysis

- Substantial uncertainty associated with these results ➔ Associated with wide credible intervals, as well as being unable to validate all NMA results with in the time available for this critique

- Does the committee consider company's updated response rates for treatments appropriate? If not, does it prefer the EAG's estimates?

NICE

Abbreviations: Appraisal committee meeting; DG2: Second draft guidance; IVIg: Intravenous immunoglobulin; NMA: Network meta-analyses; PLEX: Plasma exchange; SoC: Standard of care

Time on treatment

ACM2

- Company to provide scenario analyses that explore various time on treatment assumptions for zilucoplan and treatments in 'basket' of standard care

Company response to DG2

- Provided flowcharts showing patient flow through the model for zilucoplan arm and for comparator basket arm ➔ Conducted scenarios using transition probability to 'loss of response' health state as a proxy to model zilucoplan time-on-treatment

EAG comments

- Company's proxy approach to modelling time on treatment reasonable

Treatment	Company base case		EAG base case	
	Response rate	Time on treatment (mean)	Response rate	Time on treatment (mean)
Zilucoplan	[redacted]	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]

Source: Adapted from EAG critique of company response to DGD2, Table 18

- Does the committee consider company's approach of using "loss of response" as a proxy to model zilucoplan's time on treatment appropriate?
- Is the mean time on treatment for zilucoplan, IVIg, PLEX and SoC (excluding IVIG and PLEX) in the company's base case or EAG's base case reflective of NHS clinical practice?

Abbreviations: Appraisal committee meeting; DG2: Second draft guidance; IVIg: Intravenous immunoglobulin; NMA: Network meta-analyses; PLEX: Plasma exchange; SoC: Standard of care

Subsequent treatments (1)

CONFIDENTIAL

See appendix slide: 'Company and EAG's estimates of overall subsequent treatment'

ACM2: Model should include both costs and benefits associated with subsequent treatment

Company response to DG2:

- Adapted model by applying a weighted basket of subsequent treatment, including IVIg, PLEX and SoC only (NSISTs and/or corticosteroids) to "uncontrolled off initial treatment" health state

[redacted]

Company: subsequent treatment basket assigned to zilucoplan; % on each subsequent treatment informed by expert elicitation;

EAG: % on each subsequent treatment based on overall EAMs; % of patients taking IVIg and PLEX as subsequent treatment after zilucoplan should be the same as % of patients Initially having IVIg and PLEX in comparator basket

NICE

Abbreviations: ACM: Appraisal committee meeting; DG: Draft guidance; IVIg, intravenous immunoglobulin; PLEX, Plasma exchange; NSISTs: Non-steroidal immunosuppressive therapies; SoC: Standard of care

Subsequent treatments (2)

See appendix slide: 'Company and EAG's estimates of overall subsequent treatment'

EAG: company approach reasonable; but for subsequent treatment basket assigned to comparator arm, disagree with estimates for % of patients switching from IVIG to PLEX and vice versa; model extremely sensitive to changes in these estimates

[redacted]

Company: % of first line treatment based on revised EAMs;
% on each subsequent treatment informed by expert elicitation; [redacted] switching from first line IVIG to PLEX and [redacted] vice versa (expert elicitation);

EAG: % of first line treatment based on overall EAMs; [redacted] switching from IVIG first line to PLEX and vice versa (lowest proportion estimated by experts);

- If used once, same drug won't be used as subsequent treatment again

Abbreviations: ACM: Appraisal committee meeting; DG: Draft guidance; IVIg, intravenous immunoglobulin; NSISTs: Non-steroidal immunosuppressive therapies; PLEX, Plasma exchange; SoC: Standard of care

Subsequent treatments (3)

See appendix slide: 'Company and EAG's estimates of overall subsequent treatment'

Proportion of patients on each subsequent treatment after receiving zilucoplan

Subsequent treatment	Company base case*	Overall EAMS cohort (EAG base case)	Modified EAMS cohort (EAG scenario)
IVIg	[redacted]	43.8%	56.7%
PLEX		14.6%	18.9%
SoC (excluding IVIg/PLEX)		41.6%	24.4%

* Company estimates informed by expert elicitation; Source: EAG critique of company response to DGD2, Table 14

Patient treatment proportions in the comparator basket (company vs. EAG)

1st line treament	Approach	First-line treatment	Proportion on subsequent treatment	*Overall* subsequent treatment
IVIg	**Company***	**56.7%**	[redacted] receive PLEX	[redacted] receive PLEX
	*EAG^*	*43.8%*	receive PLEX	receive PLEX
PLEX	**Company***	**18.9%**	receive IVIg	receive IVIg
	*EAG^*	*14.6%*	receive IVIg	receive IVIg
SoC (excluding IVIg/PLEX)	**Company***	**24.4%**	-	receive SoC
	*EAG^*	*41.6%*	-	[redacted] receive SoC

*Company's first line % based on revised EAMs cohort; same drug could be used again as subsequent treatment; ^ EAG's first line % based on overall EAMs cohort; same drug won't be used again as subsequent treatment; Source: EAG critique of company response to DGD2, Table 13

Does the committee also agree that company's modelling of subsequent treatments reasonable? If not:

- Is the EAG's approach of using treatment proportions from the overall EAMS cohort to inform zilucoplan subsequent treatment appropriate?
- Is the EAG's estimates of the proportions of patients switching from IVIg to PLEX [redacted] and vice versa [redacted] in subsequent treatment in the comparator arm appropriate:
- Is the EAG's approach (the same drug won't be used again in subsequent treatment) of estimating overall proportions for subsequent treatment appropriate?

NICE

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

Utility decrement associated with IVIg and PLEX

ACM2

- If appropriate to include, uncaptured benefit of zilucoplan administration should be modelled as a utility decrement for IVIg and PLEX, rather than utility increment for zilucoplan

Company response to draft guidance 2

- Administration utility benefit for zilucoplan removed
- A per-model cycle disutility of IVIg ([redacted] per cycle) and PLEX ([redacted] per cycle) administrations is calculated by weighting the number of IVIg/PLEX infusions per model cycle
- Values derived from a study assessing utility impact of intravenous infusion in haemophilia A because lack of available data in gMG; ➔ in absence of data, the same disutility applied to PLEX

EAG comments

- Evidence showing haemophilia A an appropriate proxy for gMG not provided
  - Unclear how disutilities in revised model were calculated from Johnston et al. 2021➔ Utility data derived from vignette-based time trade-off exercise by Canadian adults, small sample size (n=82) and not from people with haemophilia
- Exclude utility decrement associated with IVIg and PLEX in EAG base case

- Is it appropriate to exclude the utility decrement associated with IVIg and PLEX in the model?

Abbreviations: ACM: Appraisal committee meeting; DG2: Second draft guidance; gMG: Generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, Plasma exchange

Corticosteroid costs (1)

ACM2

- Requested analysis that explores corticosteroid costs from Lee et al. (2018) study

Company response to draft guidance 2

- Maintains that Stirnadel-Farrant et al (2023) is most appropriate source to inform corticosteroid costs
- Provided scenario analysis using costs of corticosteroids from Lee et al.
- Considers Lee et al. study has several limitations:
  - absence of data on AEs for patients not receiving corticosteroids ➔ Makes it challenging to distinguish between AEs caused by corticosteroids and those associated with gMG
  - the severity of AEs not specified, and many may not meet threshold for severe AEs (grade ≥3), which are typically considered for costing in NICE appraisals
  - Costs according to dose were not included unlike Stirnadel-Farrant et al (2023) study

EAG comments

- NICE committee assessing efgartigimod submission accepted using data for intolerable side effects caused by corticosteroid use from Lee et al. (2018) as the source of the costs of managing corticosteroids
- Lee at al. data are from people with gMG, whereas Stirnadel-Farrant et al. report costs for people with systemic lupus erythematosus
- Use costs for corticosteroids from Lee et al. in its base case for consistency with previous NICE appraisals ➔ Add costs for corticosteroid management for patients achieving MSE in the zilucoplan arm

Abbreviations: ACM: Appraisal committee meeting; AE: Adverse events; IVIg, intravenous immunoglobulin; MSE: Minimal symptom expression; gMG: Generalised myasthenia gravis

Corticosteroid costs (2)

Cost of corticosteroid management, company's revised model

Health state	Source of costs	All Tx except IVIg and PLEX (£)	IVIg and PLEX (£)
Uncontrolled	Stirnadel-Farrant et al.	10,087	10,087
	Lee at al.	2,448	2,448
Stable response	Stirnadel-Farrant et al.	4,671	4,671
	Lee et al.	343	343
Continued response / MSE	Stirnadel-Farrant et al.	0	4,671
	Lee et al	0	343

- Is Stirnadel-Farrant et al (2023) or Lee et al (2018) more appropriate to inform the costs of costicosteroids in the economic model?

NICE

Abbreviations: IVIg: Intravenous immunoglobulin; MSE: Minimal symptom expression; PLEX: Plasma exchange

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 and PLEX
	• Basket comparator using proportion of patients on each treatment in revised EAMS cohort (n=37) in an alternative base case
	  ○ 56.7% IVIg + steroids + NSISTs,
	  ○ 18.9% PLEX + steroids + NSISTs,
	  ○ 24.4% steroids + NSISTs only
		Basket comparator using proportion of patients on each treatment in overall EAMS cohort (n=48):
		• 43.8% IVIg + steroids + NSISTs,
		• 14.6% PLEX + steroids + NSISTs,
		• 41.6% steroids + NSISTs only

Relative effectiveness	Informed by Bivariate NMA*	Informed by Two-stage NMA*
Minimal symptom expression	[redacted] achieve MSE in the basket standard care (excluding IVIg and PLEX)	[redacted] achieve MSE in the comparator arm (incorporate proportion of people having IVIg and PLEX into the MSE achieved in the basket standard care)

*Bivariate NMA not validated by EAG given time constraints, hence also the two-stage NMA is not validated

Abbreviations: EAMS: Early Access to Medicines scheme; IVIg: Intravenous immunoglobulin; MSE: Minimal symptom expression; NMA: Network meta-analysis; NSISTs: Non-steroidal immunosuppressive therapies; PLEX: Plasma exchange

Company and EAG revised base cases – key inputs/assumptions

Model inputs	Company revised base case	EAG base case
Subsequent treatments	Weighted basket of subsequent treatment • **Zilucoplan arm**: proportion of people on subsequent treatments informed by clinical experts • **Comparator basket**: proportion of subsequent treatments also informed by clinical opinion; with [redacted] switching from IVIg to PLEX, and [redacted] from PLEX to IVIg • If used once, the same treatment could be used again as subsequent treatment	Weighted basket of subsequent treatment • **Zilucoplan arm**: used overall EAMs cohort to inform proportion of people on subsequent treatments • **Comparator basket**: % of patients taking IVIg and PLEX as subsequent treatment following zilucoplan should be the same as % of patients initially having IVIg and PLEX in comparator basket (prefer informed by EAMs), with [redacted] switching from IVIg to PLEX, and [redacted] vice versa • If used once, the same treatment won't be used again as subsequent treatment
Treatment response rates	Informed by **bivariate NMA** • Zilucoplan: [redacted] • IVIg: [redacted] • PLEX: [redacted] • SoC: [redacted]	Informed by **two-stage NMA** • Zilucoplan: [redacted] • IVIg: [redacted] • PLEX: [redacted] • SoC: [redacted]

Abbreviations: EAMS: Early Access to Medicines scheme; IVIg: Intravenous immunoglobulin; NMA: Network meta-analysis; PLEX: Plasma exchange; SoC: Standard of care

Company and EAG revised base cases – key inputs/assumptions

Model inputs	Company revised base case	EAG base case
Mean time on treatment (month)	Estimated from model; • Zilucoplan: [redacted] • IVIg: [redacted] • PLEX: [redacted] • SoC comparator basket : [redacted] Conducted scenario analyses using ”loss of response” as proxy to model zilucoplan time-on-treatment	Estimated from model; • Zilucoplan: [redacted] • IVIg: [redacted] • PLEX: [redacted] • SoC comparator basket: [redacted]
Utility decrement (IVIg and PLEX)	IVIg = ([redacted] per model cycle PLEX = ([redacted] per model cycle	Remove the disutilities for IVIg and PLEX use
Costicosteroid costs	• Costs for corticosteroid management from Stirnadel-Farrant et al (2023) • Costs not applied to zilucoplan arm for patients achieving MSE	• Costs for corticosteroid management from Lee et al. (2018). • Costs applied to zilucoplan arm when MSE achieved

Abbreviations: IVIg: Intravenous immunoglobulin; MSE: Minimal symptom expression; PLEX: Plasma exchange; SoC: Standard of care

Cost-effectiveness results

- All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- Both company's and EAG's base case ICER for zilucoplan versus 'basket' of standard care are above the £30k threshold

ICER: Incremental cost effectiveness ratio; PAS: Patient access scheme

Other considerations

Potential for managed access

- Managed access not proposed by the company

Severity modifier

- Both the company and the EAG consider severity modifier is not applicable

Equality considerations

- Patients with certain religious beliefs may not be able to access IVIg /PLEX due to contraindication to blood products but they would be able to access complement inhibitor treatment
- Concern that patients living away from centres with MG experts will not have access to zilucoplan. This will be even more concerning in patients of lower social or economic classes. Therefore, education of patients and doctors will be crucial to ensure we avoid unlawful discrimination against patients that are geographically away from large centres

Abbreviations: IVIg: Intravenous immunoglobulin; MG: Myasthenia gravis; PLEX: Plasma exchange; SoC: Standard of care

Key questions (1)

Company's target population

- Does the committee consider the company's revised target population (more aligned with the inclusion criteria of EAMs cohort) reflect people with refractory gMG that would have zilucoplan in practice and appropriate?
- Does the committee consider zilucoplan's treatment effect on the whole trial population generalisable to this revised target population?

Comparators

- Is the overall EAMS cohort (n=48) or company's revised EAMs cohort (n=37) more reflective of patients who would have zilucoplan in clinical practice
- If so, is it appropriate to inform the proportion of patients having 'basket' of standard care treatments in analysis?

Company's updated NMAs

- Do the updated NMAs reduce the uncertainty committee noted at ACM2?
- Does the committee consider the updated bivariate NMA (company) or the two-stage NMA (EAG) appropriate for estimating relative treatment effect of zilucoplan and inform the base case in the model?

Abbreviations: ACM: Appraisal committee meeting; EAMS, Early Access to Medicines scheme; gMG: Generalised Myasthenia Gravis; NMA: Network meta-analysis

Key questions (2)

Minimal symptom expression

- Is MSE appropriate basis for determining response status and subsequently inform the transition probabilities in the model?
- Is the company's approach of estimating MSE data for zilucoplan (based on RAISE-XT) and for the 'basket' of standard care (based on company's clinical interviews) appropriate?
- Is the calculation of proportion of people achieving MSE in company's base case ([redacted] or EAG's base case ([redacted]) in the 'basket' of standard care appropriate?

Response rates:

- Does the committee consider company's updated response rates for treatments appropriate? If not, does it prefer the EAG's estimates?

Time on treatment:

- Does the committee consider company's approach of using "loss of response" as a proxy to model zilucoplan's time on treatment appropriate?
- Is the mean time on treatment for zilucoplan, IVIg, PLEX and SoC comparator basket in the company's base case or EAG's base case reflective of NHS clinical practice?

Abbreviations: IVIg: Intravenous immunoglobulin; MSE: Minimal symptom expression; NMA: Network meta-analysis; PLEX: Plasma exchange; SoC: Standard of care

Key questions (3)

Subsequent treatments:

Does the committee also agree that company's modelling of subsequent treatments reasonable? If not:

- Is the EAG's approach of using treatment proportions from the overall EAMS cohort to inform zilucoplan subsequent treatment appropriate?
- Is the EAG's estimates of the proportions of patients switching from IVIg to PLEX ([redacted] and vice versa ([redacted] in subsequent treatment in the comparator arm appropriate?
- Is the EAG's approach (the same drug won't be used again in subsequent treatment) of estimating overall proportions for subsequent treatment appropriate?

Utility decrement associated with IVIg and PLEX:

- Is it appropriate to exclude the utility decrement associated with IVIg and PLEX in the model?

Corticosteroid costs:

- Is Stirnadel-Farrant et al (2023) or Lee et al (2018) more appropriate to inform the costs of corticosteroids in the economic model?

Corticosteroid disutility:

- Does the committee agree to include corticosteroid disutility quantitatively in the model?
- What are the committee's preferred assumptions?
- What is the committee's preferred ICER threshold?
- What is the committee's preferred ICER?

Abbreviations: EAMS: Early Access to Medicines scheme; ICER: Incremental cost effectiveness ratio; IVIg: Intravenous immunoglobulin; PLEX: Plasma exchange

Zilucoplan for treating antibody-positive generalised myasthenia gravis

Supplementary appendix

NICE National Institute for Health and Care Excellence

Company's updated NMAs (4): results (December 2024)

Analysis	Zilucoplan	IVIg	PLEX
MG-ADL change from baseline, difference versus placebo (95% credible intervall)			
Conventional NMA (RCTs)	[redacted]	[redacted]	No PLEX studies
Conventional NMA (RCTs + non-RCTs)	[redacted]	[redacted]	No PLEX studies
Bivariate NMA (RCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs + non-RCTs)	[redacted]	[redacted]	[redacted]
Baseline risk-adjusted NMA	Not reported	Not reported	Not reported
Two-stage NMA (RCTs)	[redacted]	[redacted]	[redacted]
Two-stage NMA (RCTs + non-RCTs)	[redacted]	[redacted]	[redacted]

Source: EAG critique of company response to DGD2, Table 7

Back to main deck

Abbreviations: IVIg: Intravenous immunoglobulin; MG-ADL: Myasthenia Gravis – Activities of Daily Living; NMAs: Network meta-analyses; PLEX: Plasma exchange; RCT: Randomised controlled trial

Proportion of patients achieving minimal symptom expression in the comparator basket arm, company revised base case

Treatment	Proportion achieving MSE	Proportion in the comparator basket	Proportion achieving MSE in the comparator basket
IVIg	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]
Total			[redacted]

Source: EAG critique of company response to DGD2, Table 9

Back to main deck

Abbreviations: IVIg: Intravenous immunoglobulin; MSE: Minimal symptom expression; PLEX: Plasma exchange

Estimates of overall subsequent treatment in comparator basket: company vs. EAG

Treatment	Company base case	EAG base case
Subsequent PLEX switching from IVIg	(56.7% x [redacted] + (18.9% x [redacted] = [redacted]	43.8% x [redacted] = [redacted]
Subsequent IVIG/ switching from PLEX:	(56.7% x [redacted]) + (18.9% x [redacted]) = [redacted]	14.6% x [redacted]= [redacted]
Subsequent SoC only:	(56.7% x [redacted]) + (18.9% x [redacted]) + 24.4% = [redacted]	100% - [redacted] - [redacted]= [redacted]

Back to main deck

Abbreviations: IVIg: Intravenous immunoglobulin; PLEX: Plasma exchange; SoC: Standard of care

Corticosteroid disutility

ACM2

- Uncertain whether EQ-5D captured all utility decrements associated with corticosteroid use, but prefer to account for this qualitatively in decision making

Company response to draft guidance 2

- As per the NICE appraisal of efgartigimod (ID4003), UCB believes that the disutility should be included quantitatively
  - unlikely that utility decrement associated with corticosteroid use is captured in EQ-5D scores
  - Given rarity of gMG and the paucity of data in this therapy area, data from Sullivan et al. and Brexelius et al from systemic lupus in the UK have been used as a proxy to quantitatively estimate utility impact of steroid use
- The utilities from the regression analysis come from RAISE trial, before the full steroid-sparing effect of zilucoplan has been captured. Applying these utilities will not be reflecting the benefit of reducing the dose/discontinuing at any timepoint so the disutility bridges this gap

- Does the committee agree to include corticosteroid disutility quantitatively in the model?

Back to main deck

NICE

Abbreviations: ACM: Appraisal committee meeting; EQ-5D: EuroQol-5 dimension; gMG: Generalised myasthenia gravis

Further analysis requested from ACM2 (1)

RECAP

Back to main deck

ACM2 conclusion/consideration
1. Clarification on the target population for zilucoplan
2. An indirect treatment comparison that: • uses data from more of the identified studies • includes IVIg and PLEX • considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness • accounts and adjusts for the differential placebo response and baseline population heterogeneity observed in the trials • explores linking the networks by using IVIg as the common comparator to include PLEX • respects randomisation
3. Statistical codes for any NMAs conducted (these must be submitted for verification)
4. Information and justification to support its use of a revised EAMS cohort to inform its preferred refractory 'basket' standard care treatments
5. Additional modelling and information on subsequent treatments, including: • Model includes both the costs and benefits associated with subsequent treatment • information on the routine practice for subsequent treatment in the NHS • analysis on the proportions of people with refractory gMG who have IVIg and PLEX after IVIg, IVIg and PLEX after PLEX, and corticosteroids and or NSISTs only after IVIg or PLEX

Abbreviations: ACM: Appraisal committee meeting; EAMS: Early Access to Medicines scheme; gMG: Generalised myasthenia gravis; IVIg: Intravenous immunoglobulin; MG-ADL: Myasthenia Gravis-Activities of Daily Living; NMAs: Network meta-analyses; NSISTs: Non-steroidal immunosuppressive therapies; PLEX: Plasma exchange

Further analysis requested from ACM2 (1)

Further analysis requested by committee at ACM2
6. Information and justification for MSE including • sources of data for MSE and information on how MSE was implemented in the model, particularly its effect on transition probabilities • additional evidence on the estimation of proportion of people on zilucoplan reaching MSE • further details and justifications for the proportion of people on IVIg and or PLEX, and proportion of people on refractory standard care treatment reaching MSE in the model • evidence on the proportion of people in the RAISE placebo arm reaching MSE • further details and justification for MSE enduring through the lifetime of the model
7. Revised treatment response rates informed by NMAs that explore the inclusion of studies on PLEX (including Barth et al.), and with placebo response heterogeneities and baseline population heterogeneities across studies adjusted for in the analysis
8. Scenario analyses that explore a range of time on treatment assumptions
9. Analysis that explores corticosteroid costs from the Lee et al. study
10. Analysis for utility decrement associated with IVIg and PLEX

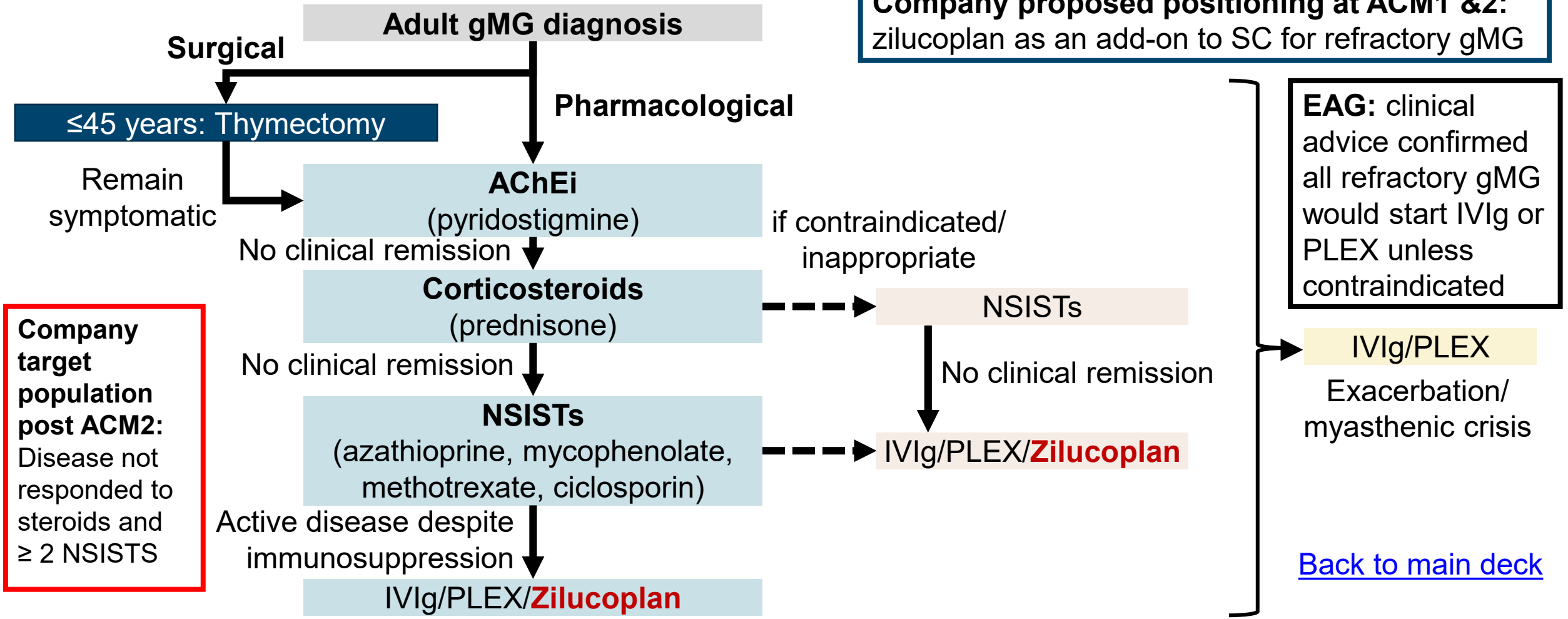
Back to main deck

NICE Abbreviations: ACM: Appraisal committee meeting; IVIg: Intravenous immunoglobulin; MSE: Minimal symptom expression; Network meta-analyses; PLEX: Plasma exchange

Treatment pathway for gMG

ACM2: 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

Company proposed positioning at ACM1 &2: zilucoplan as an add-on to SC for refractory gMG



Back to main deck

Abbreviations: AChEi: Acetyl-cholinesterase inhibitor; gMG: Generalised myasthenia gravis; IVIg: Intravenous immunoglobulin; NSIST: Non-steroidal immunosuppressive therapy; PLEX: Plasma exchange; SC, Standard care.

Company's target population at ACM1&2 versus efgartigimod EAMS cohort

Back to main deck

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

- Not responded to systemic treatments, including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and ciclosporin, or these options are contraindicated or not tolerated, and
- Uncontrolled, defined by a MG-ADL score of 6 or more or a QMG score of 12 or more, and:
- − an additional treatment such as IVIg or PLEX is being considered, or
- − people are having long-term treatment with IVIg or PLEX, or − efgartigimod would be an alternative option (subject to NICE evaluation).

Inclusion criteria for efgartigimod EAMS cohort's target population

- Restricted efgartigimod to patients who were:
  - Refractory (≥2 NSISTs), or
  - Intolerant/ineligible to NSISTs, or
  - Dependent on IVIg/PLEX

ID4008 ACM2:

- Company's target population similar to those that would have zilucoplan in the NHS, but definition of refractory uncertain;
- Noted no definite inclusion criteria for efgartigimod EAMS, variation in how refractory defined in RAISE and EAMs

Abbreviations: ACM: Appraisal committee meeting; EAMS: Early Access to Medicines Scheme; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; NSISTs: Non-steroidal immunosuppressive therapies; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis

Company's model overview

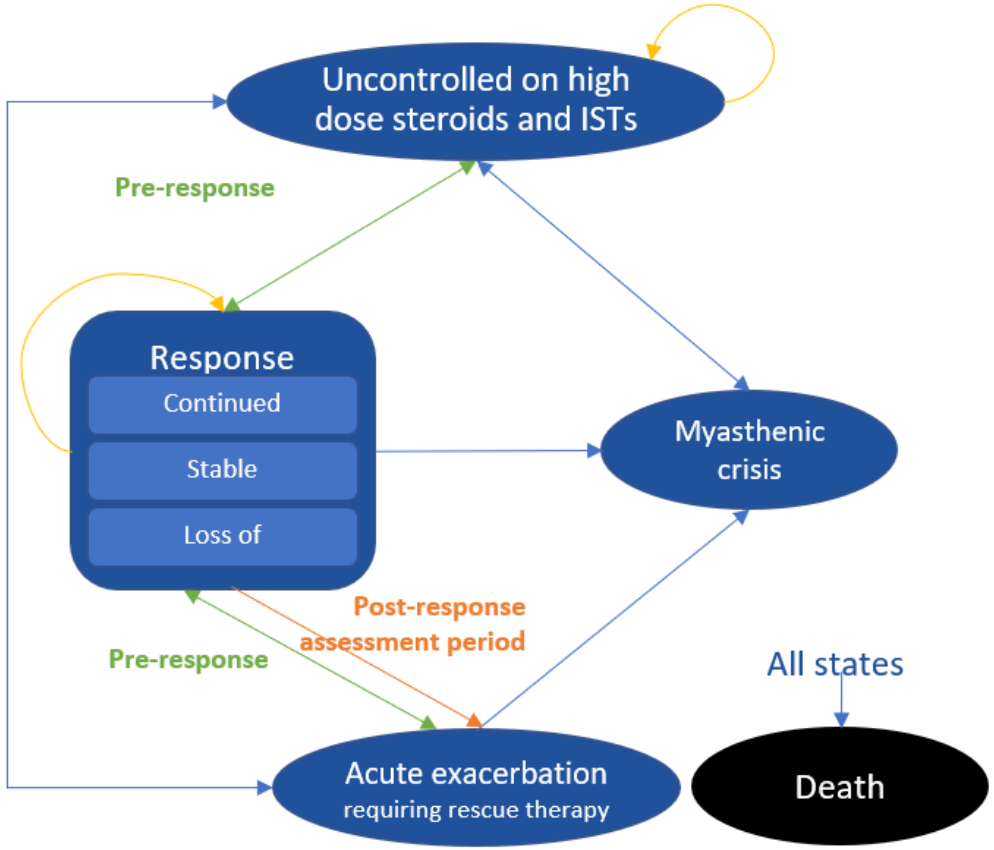
ACM2: MSE might be clinically relevant, but sources of data for MSE and further information needed

Recap:

- Cohort state-transition model with 7 health states*
- Responders separate into one of 3 response sub-states (stable, continued, or loss response) at response assessment timepoint, assuming
  - [redacted] stable
  - [redacted] lose response
  - [redacted] have a continued response

At ACM2: assumed a proportion of patients in *continued response health state* reached MSE and remains for lifetime horizon of model, with

- [redacted] of those on zilucoplan, 10% on IVIg or PLEX, and 0% on refractory SC (corticosteroids and NSISTs);



EAG:

- Unable to revert company's revised base-case results to original company model at ACM1, preferred to remove MSE from model

*Within each health state (except death), patients at risk of 'exacerbation', 'crisis' or 'death'

Abbreviations: ACM: Appraisal committee meeting; IVIg: Intravenous immunoglobulin; MG-ADL: Myasthenia Gravis-Activities of Daily Living; PLEX: Plasma exchange; SC: Standard care; MSE: Minimal symptom expression

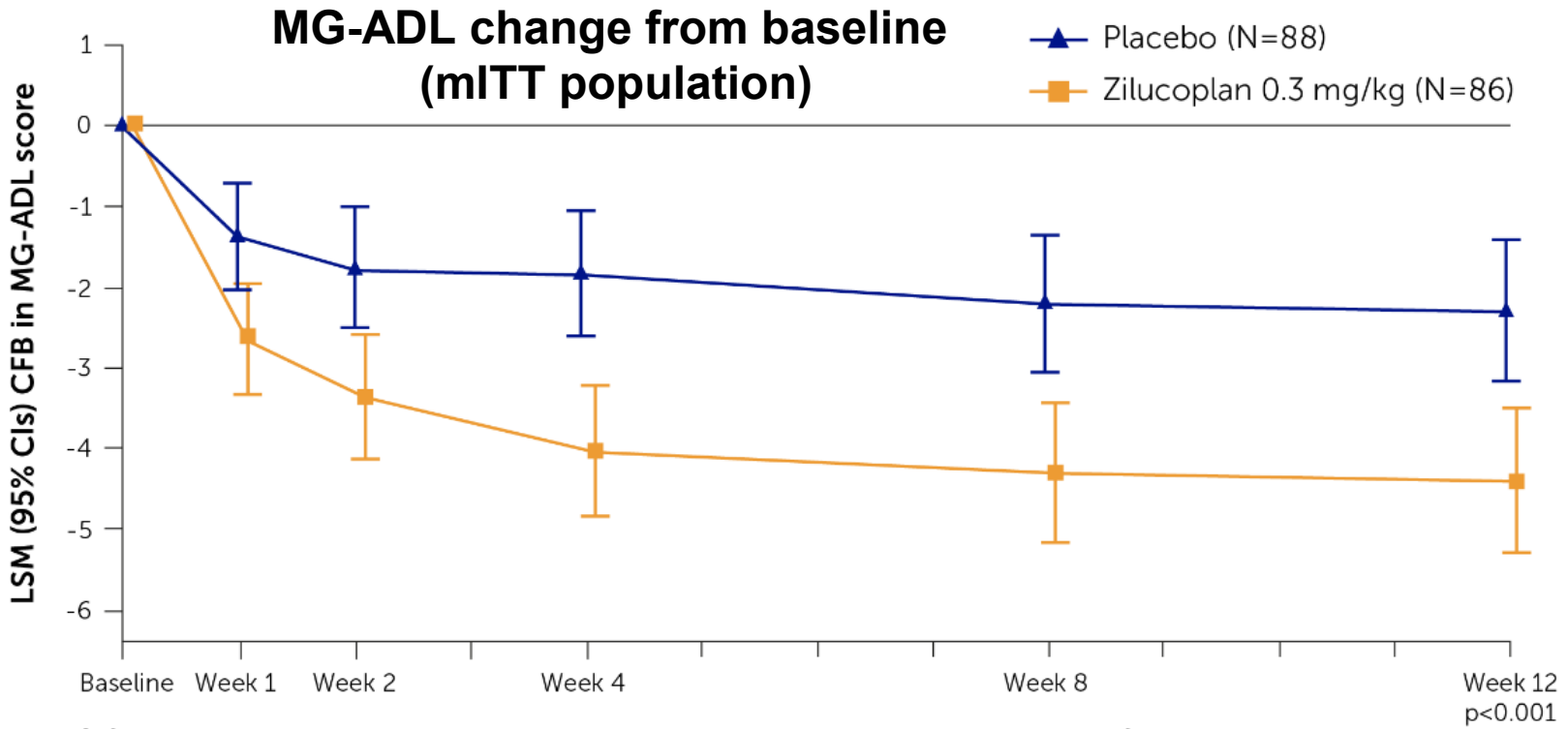
Clinical evidence – trial summary

Back to main deck

	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

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

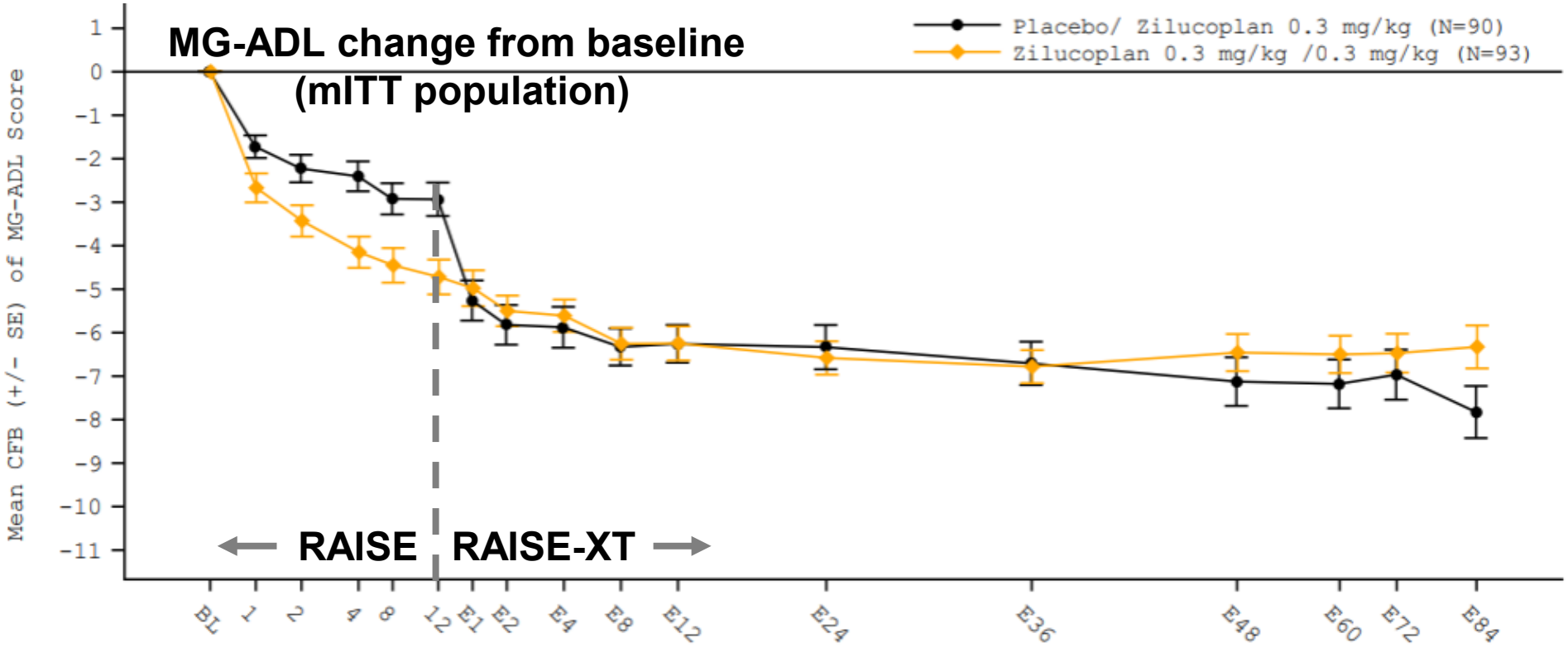
MG-ADL CfB and response (≥3 point improvement) by refractory status at week 12

	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: ACM: Appraisal committee meeting; 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

Back to main deck

RAISE-XT: results



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

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

Back to main deck

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