#MG57

Comparative Risk-Benefit Profiles of Immunomodulatory Therapies for Patients with Generalized Myasthenia Gravis

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INTRODUCTION

- Generalized myasthenia gravis (gMG) is a chronic autoimmune neuromuscular condition that causes muscle weakness in different parts of the body.[1,2,3] Approximately 85% of patients with gMG have anti-acetylcholine receptor antibody-positive (anti-AChR Ab+) disease[4]
- Several novel immunomodulatory therapies have been recently approved in the United States for anti-AChR Ab+ gMG, including neonatal Fc receptor inhibitors (efgartigimod intravenous [IV] [VYVGART®] and subcutaneous [PH20 SC] [VYVGART Hytrulo®], rozanolixizumab [RYSTIGGO®]) and complement inhibitors (ravulizumab [ULTOMIRIS®], zilucoplan [ZILBRYSQ®] and eculizumab [SOLIRIS®])
- With the availability of these new treatment options for gMG, it is important for health care providers, payers, and other stakeholders to understand their relative benefits, and economic value, which have not yet been fully compared in the literature

OBJECTIVE

- To evaluate the relative benefits and risks of recently approved treatmentsfor anti-AChR Ab+ gMG

METHODS

Data source

- Data from phase III clinical trials of efgartigimod IV (ADAPT, NCT03669588)[5], ravulizumab (CHAMPION, NCT03920293)[6], rozanolixizumab (MycarinG, NCT03971422)[7] and zilucoplan (RAISE, NCT04115293)[8] were used in the primary network meta-analysis (NMA) (**Table 1**). Data from the phase III trial of eculizumab (REGAIN, NCT01997229)[9] and efgartigimod PH20 SC (ADAPTsc, NCT04735432)[10] were included in the sensitivity NMA
  - The REGAIN and ADAPTsc trials were included in the sensitivity analysis because REGAIN enrolled a refractory-only population with a worse prognosis compared to other trials, and ADAPTsc was not a placebo-controlled trial, comparing efgartigimod SC to efgartigimod IV
- Efficacy outcomes included the proportions of patients achieving a ≥3- and ≥5-point reductions from baseline in MG-ADL and QMG score at the primary assessment timepoints in the respective clinical trials
  - **MG-ADL** is an 8-item patient-recorded outcome measure assessing MG symptoms and their impact on daily living.11 The total score ranges from 0 to 24, with a higher score indicating more disability. MG-ADL is typically used as the primary endpoint in MG trials due to strong regulatory consensus on its utility to guide trials focusing on disability improvement[12]
  - **QMG** is a quantitative examiner assessment of patient function across 13 domains, based on strength and endurance of specific muscle groups.13 The total score ranges from 0 to 39, with a higher score indicating more severe disease. QMG is a common secondary endpoint in MG trials
- Safety outcomes commonly reported across trials were assessed, including serious adverse events (AEs), treatment-emergent AEs, and specific AEs of headache, nasopharyngitis ,nausea, diarrhea, upper respiratory tract infection, and urinary track infection

Table 1. Phase III randomized clinical trials in gMG (primary analysis)

	ADAPT (NCT03669588)[5]	CHAMPION (NCT03920293)[6]	MycarinG (NCT03971422)[7]	RAISE (NCT04115293)[8]
Study Design and Randomization[a]	1:1 to efgartigimod IV and placebo	1:1 to ravulizumab IV and placebo	1:1:1 to rozanolixizumab 10 mg/kg SC, rozanolixizumab 7 mg/kg SC and placebo	1:1 to zilucoplan SC and placebo
Population (Patients with gMG)[b]	N=167 • Myasthenia Gravis Foundation of America (MGFA)Class II to IV • anti-AChR Ab+/- • MG-ADL score ≥5 • On a stable dose of at least one gMG treatment throughout the trial	N=175 • MGFA Class II to IV • anti-AChR Ab+ • MG-ADL score ≥6 • Stable-dose gMG treatments were permitted throughout the trial	N=200 • MGFA Class II to IV • anti-AChR Ab+ or anti-MuSK Ab+ • MG-ADL score ≥3 (non-ocular symptoms) • QMG score ≥11 • Stable-dose gMG treatments were permitted throughout the trial	N=174 • MGFA Class II to IV • anti-AChR Ab+ • MG-ADL score ≥6 • QMG score ≥12 • Stable-dose gMG treatments were permitted throughout the trial
Primary timepoint of assessment	Week 4	Week 26	Week 6	Week 12

Notes:
[a] In all trials, conventional therapy (CT) was used as background treatment in both the active treatment and placebo arms.
[b] In ADAPT, the AChR Ab+ population was used for efficacy analyses and the overall trial population was used for the safety analysis. In MycarinG, the AChR Ab+ population was used to evaluate the outcomes of ≥3 point improvement in QMG and ≥2 point improvement in MGADL, and the overall trial population was used to assess other efficacy and safety outcomes. CHAMPION and RAISE used the overall trial population for all analyses.

Statistical analyses

- A Bayesian **NMA** was used to compare both efficacy and safety outcomes (**Figure 1a, 1b**). Based on the NMA results,the number needed to treat (NNT) and number needed to harm (NNH) were estimated for each treatment

Figure 1a. Primary NMA evidence network

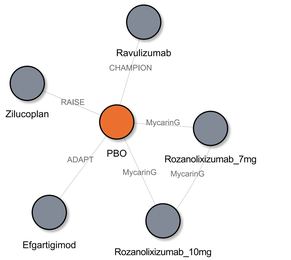
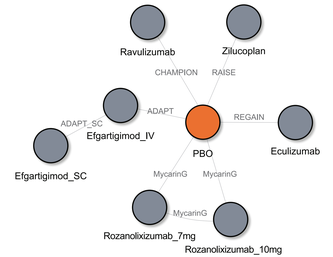


Figure 1b. Sensitivity NMA evidence network



- **NNT** represents the number of patients needed to treat to achieve one additional improved outcome relative to placebo. A lower NNT represents a more favorable efficacy[16]

$$\text{NNT} = \frac{1}{\text{Clinical response rate of active treatment} - \text{Clinical response rate of placebo}}$$

- **NNH** represents the number of patients needed to treat for one additional patient to experience an undesired outcome (e.g., an AE) relative to placebo.[16] Negative NNH values indicate fewer AEs with treatment compared to placebo

$$\text{NNH} = \frac{1}{\text{AE rate of active treatment} - \text{AE rate of placebo}}$$

RESULTS

Results of the NMA - efficacy outcomes comparing active treatments to placebo

- In both the primary and sensitivity NMAs, efgartigimod IV or efgartigimod PH20 SC had the highest probability of being the best treatment for a ≥3- and ≥5-point improvement in QMG score and ≥5-point improvement in MG-ADL score, whereas rozanolixizumab 10 mg/kg had an equal or higher probability achieving a ≥3-point improvement in MG-ADL score
- **Table 2** shows the NMA ranking probabilities to be the best treatment for each efficacy outcome

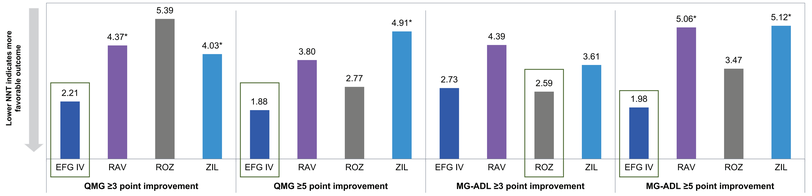
Table 2. Probabilities to be the best treatment from the NMA efficacy analysis

Treatment	≥3-point improvement in QMG score	≥5-point improvement in QMG score	≥3-point improvement in MG-ADL score	≥5-point improvement in MG-ADL score
Primary analysis				
Efgartigimod IV	**90%**	**83%**	30%	**86%**
Ravulizumab	1%	2%	1%	1%
Rozanolixizumab 10 mg/kg	8%	9%	**39%**	8%
Rozanolixizumab 7 mg/kg	0%	6%	26%	5%
Zilucoplan	1%	0%	4%	0%
Placebo	0%	0%	0%	0%
Sensitivity analysis				
Efgartigimod IV	27%	**62%**	15%	11%
Ravulizumab	0%	2%	1%	0%
Rozanolixizumab 10 mg/kg	4%	8%	**30%**	3%
Rozanolixizumab 7 mg/kg	0%	5%	20%	1%
Zilucoplan	1%	0%	3%	0%
Eculizumab	-	2%	1%	0%
Efgartigimod PH20 SC	**68%**	21%	**30%**	**85%**
Placebo	0%	0%	0%	0%

Results of NNT

- In the primary analysis, efgartigimod IV was associated with a significantly lower (better) NNT compared to ravulizumab and zilucoplan for a ≥3-point improvement in QMG score and ≥5-point improvement in MG-ADL score, as well as significantly lower NNT compared to zilucoplan for a ≥5-point improvement in QMG. There were no significant differences across treatments in the NNT to achieve a ≥3-point improvement in MG-ADL score (**Figure 2a**)

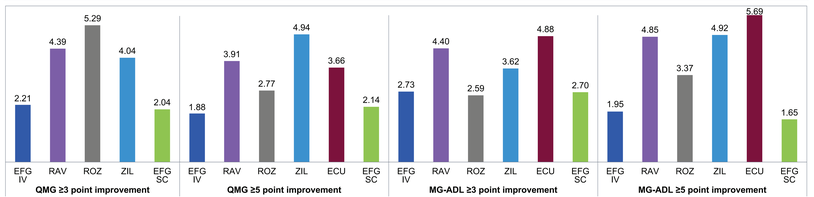
Figure 2a. NNT estimates by treatment versus placebo and incremental NNT (primary analysis)



* indicates statistical significance compared to the treatment with the lowest NNT within each outcome, which is marked with a box.

- The sensitivity analysis results were generally consistent with the primary analysis. Efgartigimod PH20 SC and efgartigimod IV performed comparably, and eculizumab had similar performance compared to the other complement inhibitors (**Figure 2b**)

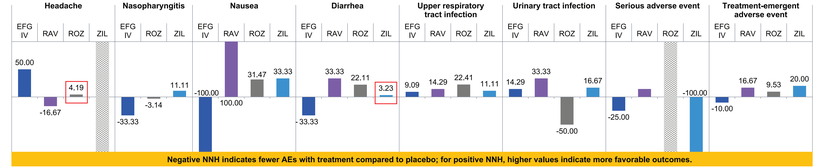
Figure 2b. NNT estimates by treatment versus placebo and incremental NNT (sensitivity analysis)



Results of NNH

- In the primary analysis, all treatments had a generally similar NNH with regards to individual AEs. The only notable safety differences identified in comparison with placebo were a significantly higher headache rate for rozanolixizumab and a significantly higher diarrhea rate for zilucoplan (**Figure 3a**)

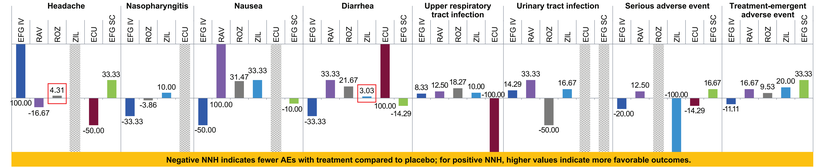
Figure 3a. NNH estimates by treatment versus placebo and incremental NNT (primary analysis)



NNH is not measurable as the rates of AE are the same or very similar between treatment and placebo arms.
Significantly higher AE rates than placebo

- The sensitivity analysis results were similar to those of the primary analysis, and the only significant differences identified in comparison with placebo remained the higher headache rate for rozanolixizumab and the higher diarrhea rate for zilucoplan (**Figure 3b**)

Figure 3b. NNH estimates by treatment versus placebo and incremental NNT (sensitivity analysis)



NNH is not measurable as the rates of AE are the same or very similar between treatment and placebo arms.
Significantly higher AE rates than placebo

Limitations

- Cross-trial differences were harmonized to the extent possible. The AChR Ab+ patient populations of trials were used for assessment of efficacy outcomes to maximize similarity with patients of ADAPT. However, residual differences may remain.
- The varying dosing schedules led to inherent differences in assessment timepoints between the trials, which the current methodology cannot fully address

DISCUSSION AND CONCLUSIONS

This risk-benefit analysis provides important and timely insights on the comparative efficacy and safety profiles of currently available gMG treatments in the US. The findings indicate that each therapy evaluated was both safe and effective compared to placebo.

Notably, efgartigimod exhibited a greater treatment effect on most efficacy measures compared to eculizumab, ravulizumab, rozanolixizumab, and zilucoplan. All active treatments were generally safe, and the only notable safety differences identified in comparison with placebo were a significantly higher headache rate for rozanolixizumab and a higher diarrhea rate for zilucoplan

In the absence of head-to-head comparisons, this assessment may be used to inform treatment decision-making for patients with gMG

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ABBREVIATIONS: adverse events (AEs); anti-acetylcholine receptor antibody-positive (anti-AChR Ab+); conventional therapy (CT); Generalized myasthenia gravis (gMG); intravenous (IV); Myasthenia Gravis Foundation of America (MGFA); Myasthenia Gravis-Activities of Daily Living (MG-ADL); network meta-analysis (NMA); number needed to harm (NNH); number needed to treat (NNT); Quantitative Myasthenia Gravis (QMG); subcutaneous (SC)

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