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Comparative Benefits of Immunomodulatory Therapies for Generalized Myasthenia Gravis

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INTRODUCTION | METHODS

- 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 these patients 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®]), efgartigimod and hyaluronidase subcutaneous [SC] [VYVGART® HYTRULO], rozanolixizumab [RYSTIGGO®], nipocalimab [IMAAVY®]), complement inhibitors (ravulizumab [ULTOMIRIS®], zilucoplan [ZILBRYSQ®]), and the anti-CD19 B-cell depleting therapy inebilizumab [UPLIZNA®]
- With the availability of these new treatment options, it is important for health care providers, payers and other stakeholders to understand their relative benefits, risks and economic values, which have not yet been fully compared across these treatments in the literature

Objective

- To conduct a network meta-analysis (NMA) to evaluate and compare the efficacy of treatments for gMG

Data source

- Data from placebo-controlled phase III clinical trials of efgartigimod IV (ADAPT, NCT03669588)[5], ravulizumab (CHAMPION, NCT03920293)[6], rozanolixizumab (MycarinG, NCT03971422)[7], zilucoplan (RAISE, NCT04115293)[8], inebilizumab (MINT, NCT04524273)[9], and nipocalimab (Vivacity-MG3, NCT04951622)[10] were included in the NMA (**Table 1**). Efgartigimod SC was not included due to the lack of placebo-controlled clinical trials
- Efficacy outcomes assessed were the proportion of patients achieving ≥3- and ≥5-point reduction from baseline for Myasthenia Gravis-Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) at the primary timepoint of assessment of each trial
- Where available, efficacy outcomes were based on the anti-acetylcholine receptor antibody–positive (anti-AChR Ab+) population; otherwise, outcomes were drawn from the overall population

Table 1. Phase III randomized clinical trials in gMG

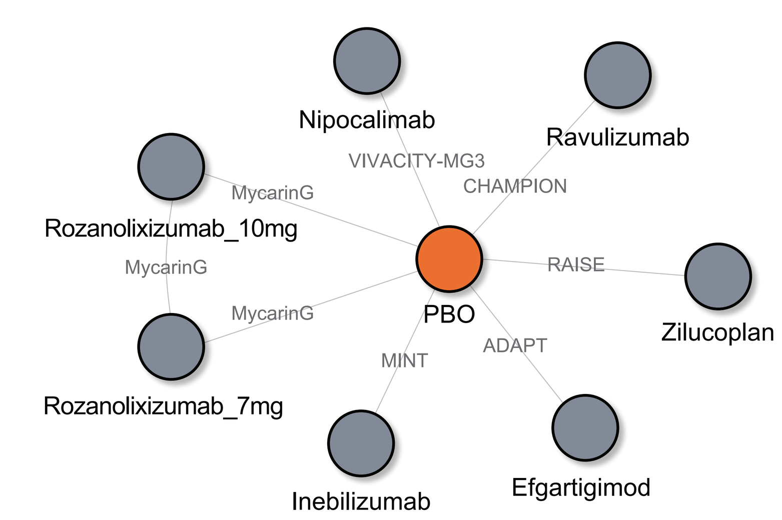
	ADAPT (NCT03669588)[5]	CHAMPION (NCT03920293)[6]	MycarinG (NCT03971422)[7]	RAISE (NCT04115293)[8]	MINT (NCT04524273)[9]	Vivacity-MG3 (NCT04951622)[10]
Study design[a]	1:1 to efgartigimod IV and placebo	1:1 to ravulizumab IV and placebo	1:1:1 to rozanolixizumab 10mg/kg SC, rozanolixizumab 7mg/kg SC and placebo	1:1 to zilucoplan SC and placebo	1:1 to inebilizumab and placebo	1:1 to nipocalimab and placebo
Population	• anti-AChR Ab+/- • Myasthenia Gravis Foundation of America (MGFA) Class II to IV • MG-ADL score ≥5 • Stable-dose gMG treatments were permitted throughout the trial	• anti-AChR Ab+ • MGFA Class II to IV • MG-ADL score ≥6 • Stable-dose gMG treatments were permitted throughout the trial	• anti-AChR Ab+ or anti-MuSK Ab+ • MGFA Class II to IVa • MG-ADL score ≥3 (non-ocular symptoms) • QMG ≥11 • Stable-dose gMG treatments were permitted throughout the trial	• anti-AChR Ab+ • MGFA Class II to IV • MG-ADL score ≥6 • QMG ≥12 • Stable-dose gMG treatments were permitted throughout the trial	• anti-AChR Ab+ or anti-MuSK Ab+ • MGFA Class II to IV • MG-ADL score 6-10 (more than 50% attributed to non-ocular items), or ≥11 • QMG ≥11 • Background therapy of cortico-steroids and/or non-steroidal immunosuppressant allowed	• anti-AChR Ab+ or anti-MuSK Ab+ or anti-LRP4 Ab+ or triple-antibody negative • MGFA class II–IV • MG-ADL score ≥6 • Stable-dose gMG treatments were permitted throughout the trial
Sample size[b]	• 167 total • 129 (77%) with anti-AChR+ were included in the analyses	• 175 anti-AChR+ were included in the analyses	• 200 total • 179 (90%) with anti-AChR+ were included for ≥3-point improvement in QMG analysis; total population were included for other outcome analyses	• 174 anti-AChR+ were included in the analyses	• 238 total • 190 (80%) anti-AChR+ were included in the analyses	• 196 total • 153 (78%) with antibody positive (AChR+, MuSK+, or LRP4+) were included in the analyses
Primary timepoint of assessment	**Week 4**	**Week 26**	**Week 6**	**Week 12**	**Week 26**	**Week 22-24**

Note:
[a] In all trials, conventional therapy (CT) was used as background treatment in both the active treatment and placebo arms.
[b] For analyses not conducted in the total trial population, analyses were performed in the relevant subpopulation with available efficacy outcomes.

Statistical analyses

- A **Bayesian NMA** was conducted to compare efficacy outcomes (**Figure 1**). Based on NMA results, **number needed to treat (NNT)** was estimated. **NNT** represents the number of patients needed to treat to achieve one additional improved outcome relative to placebo.[11]

FIGURE 1. NMA evidence network



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

RESULTS

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

- **Table 2** presents the relative differences versus placebo (median and 95% credible interval [CrI]) for each efficacy outcome
- **Table 3** shows the NMA ranking probabilities to be the best treatment for each efficacy outcome
- Efgartigimod IV had the highest probability of being the best treatment for ≥3- and ≥5-point improvement in QMG score and ≥5-point improvement in MG-ADL score, whereas rozanolixizumab 10 mg/kg had higher probability achieving ≥3-point improvement in MG-ADL score

TABLE 2. Relative differences with placebo (median and 95% CrI)

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
Efgartigimod IV	0.46 (0.32, 0.55)	0.53 (0.34, 0.67)	0.36 (0.20, 0.48)	0.51 (0.31, 0.67)
Ravulizumab	0.23 (0.06, 0.38)	0.26 (0.07, 0.48)	0.23 (0.07, 0.36)	0.21 (0.05, 0.41)
Rozanolixizumab 10 mg/kg	0.31 (0.13, 0.46)	0.38 (0.18, 0.57)	0.39 (0.24, 0.50)	0.32 (0.11, 0.55)
Rozanolixizumab 7 mg/kg	0.11 (-0.07, 0.29)	0.36 (0.15, 0.55)	0.38 (0.22, 0.49)	0.29 (0.08, 0.53)
Zilucoplan	0.25 (0.09, 0.39)	0.21 (0.07, 0.36)	0.28 (0.12, 0.41)	0.21 (0.07, 0.37)
Inebilizumab	0.21 (0.06, 0.36)	0.12 (-0.00, 0.28)	0.20 (0.05, 0.34)	0.09 (-0.02, 0.24)
Nipocalimab	0.19 (0.03, 0.35)	0.31 (0.13, 0.50)	0.23 (0.07, 0.38)	0.28 (0.10, 0.46)

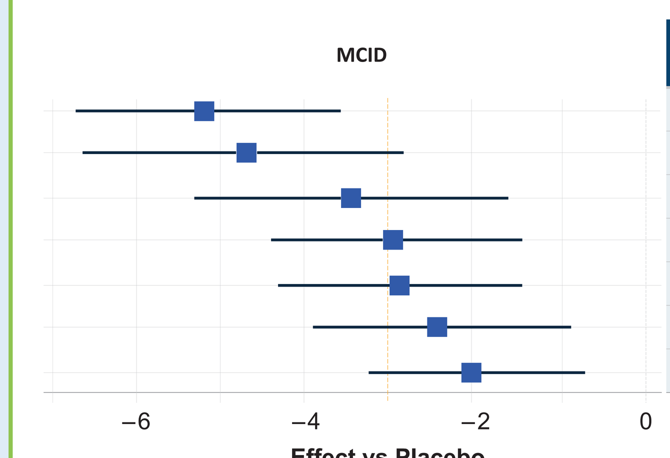
TABLE 3. Probabilities to be the best treatment from the NMA efficacy analysis

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
Efgartigimod IV	**90%**	**79%**	28%	**83%**
Ravulizumab	1%	2%	1%	1%
Rozanolixizumab 10 mg/kg	8%	10%	**39%**	9%
Rozanolixizumab 7 mg/kg	0%	6%	26%	4%
Zilucoplan	1%	0%	4%	0%
Inebilizumab	0%	0%	0%	0%
Nipocalimab	0%	3%	2%	3%
Placebo	0%	0%	0%	0%

QMG Change From Baseline (Figure 2)

- Compared with placebo, all active treatments achieved significantly larger improvement in change from baseline in QMG
- Mean QMG improvement with efgartigimod and rozanolixizumab 10 mg/kg and 7 mg/kg had exceeded the commonly cited minimal clinically important difference (MCID) value of ≥3-point improvement from baseline in QMG

FIGURE 2. Effect of treatments compared with placebo in QMG change from baseline

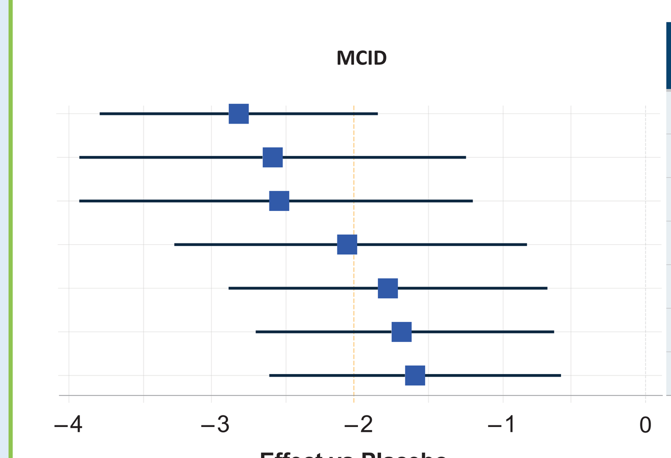


Treatment	Treatment Difference (Mean)	CrI (95%)
Efgartigimod	−5.20	(−6.77, −3.61)
Rozanolixizumab 10 mg/kg	−4.73	(−6.63, −2.81)
Rozanolixizumab 7 mg/kg	−3.45	(−5.37, −1.58)
Zilucoplan	−2.94	(−4.47, −1.41)
Nipocalimab	−2.89	(−4.36, −1.45)
Inebilizumab	−2.41	(−3.97, −0.83)
Ravulizumab	−2.00	(−3.26, −0.72)

MG-ADL Change From Baseline (Figure 3)

- Compared to placebo, all active treatments achieved significantly larger improvement in change from baseline in MG-ADL
- Mean MG-ADL improvement with efgartigimod, rozanolixizumab 10 mg/kg and 7 mg/kg, and zilucoplan had exceeded the commonly cited MCID value of ≥2-point improvement from baseline in MG-ADL

FIGURE 3. Effect of treatments compared with placebo in MG-ADL change from baseline

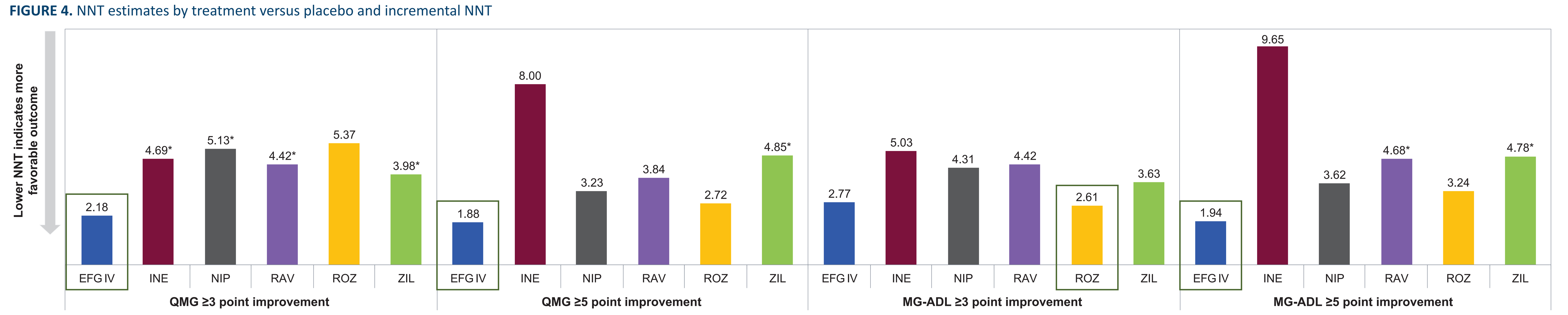


Treatment	Treatment Difference (Mean)	CrI (95%)
Efgartigimod	−2.85	(−3.82, −1.86)
Rozanolixizumab 10 mg/kg	−2.60	(−3.97, −1.24)
Rozanolixizumab 7 mg/kg	−2.57	(−3.95, −1.22)
Zilucoplan	−2.09	(−3.32, −0.86)
Inebilizumab	−1.81	(−2.93, −0.68)
Ravulizumab	−1.70	(−2.74, −0.64)
Nipocalimab	−1.63	(−2.65, −0.62)

Results of NNT

- Efgartigimod IV was associated with significantly lower NNT compared with inebilizumab, nipocalimab, ravulizumab and zilucoplan in achieving a ≥3-point improvement in QMG; with ravulizumab and zilucoplan for achieving a ≥5-point improvement in MG-ADL; and with zilucoplan for achieving a ≥5-point improvement in QMG. No significant differences across treatments in the NNT to achieve a ≥3-point improvement in MG-ADL score (**Figure 4**)

FIGURE 4. NNT estimates by treatment versus placebo and incremental NNT



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

KEY TAKEAWAYS

- This comparative effectiveness analysis provides timely insights into the clinical profiles of currently available gMG treatments in the U.S. and extends beyond prior NMAs by incorporating phase 3 data for nipocalimab and inebilizumab on QMG and MG-ADL outcomes. Inebilizumab is currently under FDA review for this indication.[12-14]
- Efgartigimod IV showed greater treatment effect than ravulizumab, rozanolixizumab, zilucoplan, inebilizumab, and nipocalimab on assessed measures; however, some differences were not statistically significant.
- In the absence of head-to-head comparisons, this assessment provides valuable insights to guide clinical decision-making in gMG.

LIMITATIONS

- Cross-trial differences were harmonized as much as possible: for outcomes defined by QMG or MG-ADL thresholds (≥3 or ≥5), analyses were based on anti-AChR Ab+ patients in ADAPT, CHAMPION, RAISE and MINT; anti-AChR Ab+ or anti-MuSK Ab+ patients in MycarinG; and anti-AChR Ab+, anti-MuSK Ab+, or LRP4+ patients in VIVACITY-MG3. However, residual differences remain
- The varying dosing strategies and trial designs led to inherent differences in assessment timepoints between the trials, which the current methodology cannot fully address

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ABBREVIATIONS

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

DISCLOSURES

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