Costs and Number Needed to Treat (NNT) to achieve improvements with C5 inhibitors in generalized myasthenia gravis (gMG) from the Japanese healthcare perspective: A network meta-analysis

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Introduction

- gMG is a rare neurological disorder affecting the neuromuscular junction, caused by autoantibodies attacking the post-synaptic membrane.[1]
- Recent therapeutic advances have led to the regulatory approval of three complement C5 inhibitors (zilucoplan, ravulizumab and eculizumab) by the MHLW in Japan, for the treatment of anti-AChR Ab+ gMG.[2-7]
- As the cost burden of C5 inhibitors remains unclear due to the absence of head-to-head data, this study aimed to estimate their therapeutic value and potential cost burden from the Japanese healthcare perspective.

Methods

- A clinical SLR was performed in January 2024 to identify relevant clinical trials in patients with gMG. The pre-defined search strategy included Medline (including In-process), Embase, Cochrane databases. Included studies were among adult patients with gMG. Outcomes of interest were MG-ADL and QMG change from baseline and responders, change from baseline MGC and MG-QoL-15r.
- Following a feasibility assessment, a Bayesian NMA was implemented in JAGS using R (Version 4.2.0).
- A fixed effects model was used to report relative efficacy.
- For each outcome NNT (number needed to treat to achieve one additional positive outcome vs. placebo) and CPIO (cost per improved outcome; NNT was integrated with annual drug costs based on National Health Insurance list prices, as of April 2024) analyses were conducted.
- Positive outcomes were defined as ≥1-point improvement for CFB outcomes, or one additional responder to achieve ≥3 or ≥5-point improvement in MG-ADL or QMG, respectively.
- Results were presented as median posterior estimates with 95% credible intervals.
- All assessments for the NMA were at primary efficacy endpoints; 12-weeks (RAISE) and 26-weeks (REGAIN and CHAMPION MG), and median values were reported for outcomes and associated costs in JPY (millions).

Results

SLR

- Of the 13,425 publications identified through database searches, following screening, 47 RCTs included the relevant gMG population (including mild to moderate, mild to severe, moderate to severe, severe, refractory and exacerbating groups).
- Among the RCTs, three studies were suitable for inclusion in the NMA.
- Each RCT was a Phase III, double-blind, placebo-controlled study with similar inclusion criteria (AChR Ab+ gMG, MG-ADL scores ≥6, MGFA class II-IV); baseline characteristics were generally consistent (Table 1).

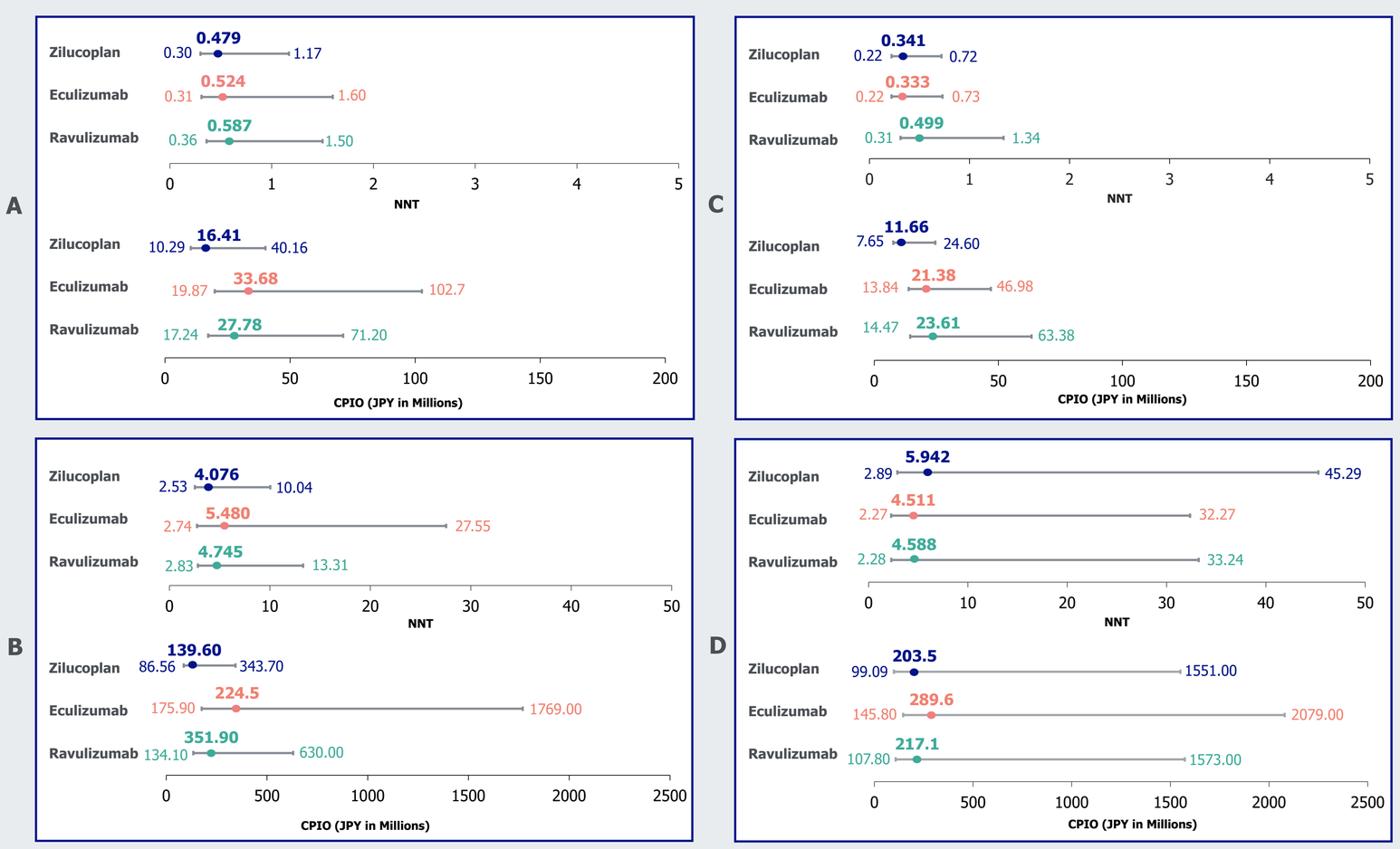
NMA

- Zilucoplan was associated with the lowest NNT for MG-ADL change from baseline and responders, and MG-QoL-15r change from baseline (Figure 1A, 1B, and Figure 2).
- Eculizumab was associated with lowest NNT for QMG change from baseline and responders, and MGC change from baseline (Figure 1C, 1D and Figure 3).
- Zilucoplan was associated with the lowest CPIO across all endpoints compared to ravulizumab and eculizumab (Figure 1-3).

Table 1. Baseline characteristics of the included trials

Characteristic	RAISE (NCT04115293)	REGAIN (NCT01997229)	CHAMPION-MG (NCT03920293)
Treatment	Zilucoplan vs. placebo	Eculizumab vs. placebo	Ravulizumab vs. placebo
Study design	Phase III randomized double-blind trial	Phase III randomized double-blind trial	Phase III randomized double-blind trial
Study population	• Adults with AChR Ab+ gMG • MG-ADL score ≥6 • MGFA class II–IV • QMG score ≥12	• Adults with AChR Ab+ gMG • MG-ADL score ≥6 • MGFA class II–IV • Refractory patients	• Adults with AChR Ab+ gMG • MG-ADL score ≥6 • MGFA class II-IV
Sample size	N=174 • Zilucoplan: n=86 • Placebo: n=88	N=125 • Eculizumab: n=62 • Placebo: n=63	N=175 • Ravulizumab: n=86 • Placebo: n=89
Key baseline characteristics	• Time since gMG diagnosis (years): 9.1 • MG-ADL: 10.6 • QMG: 19.1 • MGFA II: 28% • MGFA III: 67% • MGFA IV: 5%	• Time since gMG diagnosis (years): 9.6 • MG-ADL: 10.2 • QMG: 17.1 • MGFA II: 38% • MGFA III: 53% • MGFA IV: 10%	• Time since gMG diagnosis (years): 9.9 • MG-ADL: 9.0 • QMG: 14.7 • MGFA II: 45% • MGFA III: 49% • MGFA IV: 6%
Population used for the NMA	Overall trial population	Overall trial population	Overall trial population

Figure 1. NNT and CPIO for zilucoplan, eculizumab and ravulizumab for MG-ADL change from baseline (A) and responders (B), and QMG change from baseline (C) and responders (D)



Note: The CPIO analyses presented in Figure 1-3 combined the NNT concept with cost data to provide a comprehensive assessment of both financial impact and therapeutic effectiveness. Annual drug costs for the maintenance phase of treatment were used, estimated based on dosing information from each medication's official package insert. A standard patient body weight of 65.3 kg was used for dosage calculations. The annual costs calculated based on National Health Insurance List prices as of April 2024 were: Zilucoplan: JPY 34,248,680 (Drug Price: JPY 93,832/23 mg), Eculizumab: JPY 64,214,137 (Drug Price: JPY 615,752/300 mg), Ravulizumab: JPY 47,318,567 (Drug Price: JPY 659,985/300 mg).

Summary and conclusions

Zilucoplan, ravulizumab and eculizumab are complement C5 inhibitors approved for the treatment of gMG in Japan.

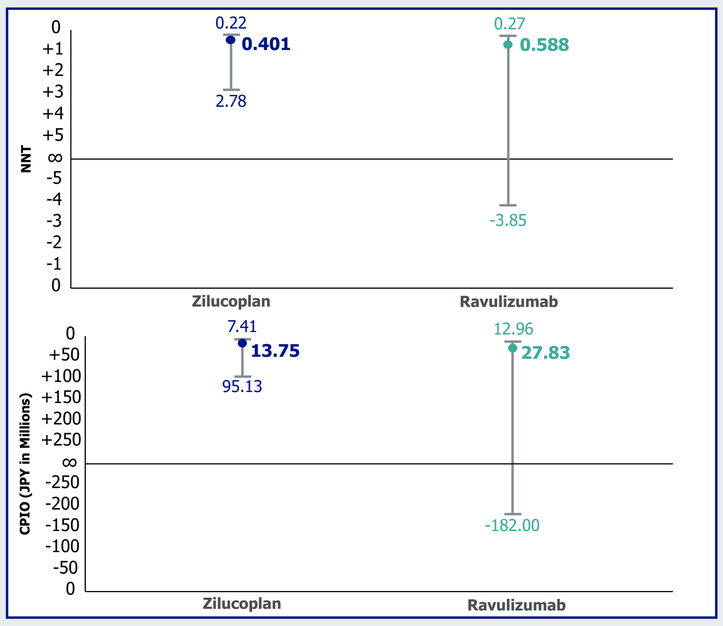
This research assessed the potential cost-benefit of zilucoplan, ravulizumab and eculizumab for the treatment of gMG from a Japanese healthcare perspective.

Zilucoplan demonstrated the lowest NNT for MG-ADL change from baseline and responders, and MG-QoL-15r change from baseline

Zilucoplan was consistently associated with the lowest CPIO across all endpoints compared to ravulizumab and eculizumab, indicative of potential cost benefit

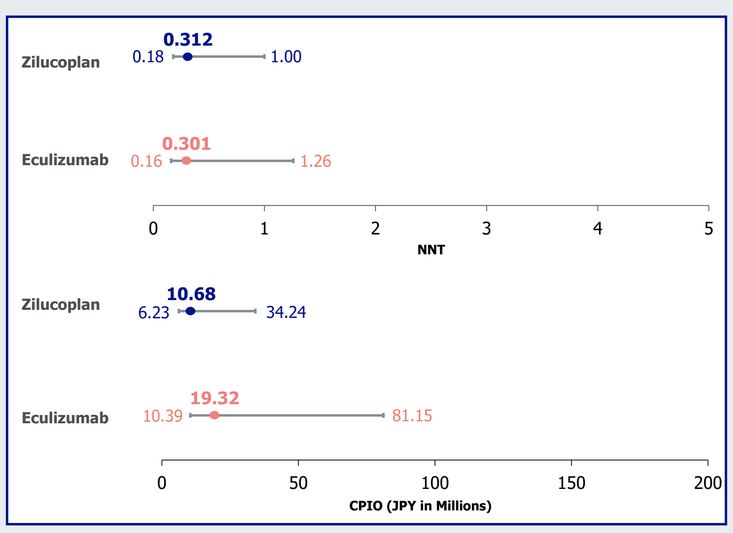
These findings may have important implications for clinical decision-making and resource allocation in gMG management in Japan and the National Health Insurance system.

Figure 2. NNT and CPIO for zilucoplan and ravulizumab for MG-QoL-15r change from baseline



Note: The benefit of ravulizumab over placebo was not statistically significant, resulting in an NNT range from -3.85 to 0.27 and wide variability in cost implications, including instances where placebo outperformed ravulizumab. Practically, this indicates no meaningful difference between the two treatments in the analyzed outcome and suggests that, theoretically, an infinite number of patients might need to be treated to observe any benefit in favor of ravulizumab.

Figure 3. NNT and CPIO for zilucoplan and eculizumab for MGC change from baseline



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Abbreviations:

anti-AChR Ab+: anti–acetylcholine receptor antibody–positive, C5: complement component 5, CPIO: cost per improved outcome, CrI: credible interval, gMG: generalized myasthenia gravis, JPY: Japanese Yen, MG-ADL: MG Activities of Daily Living, MGC: Myasthenia Gravis Composite, MGFA: myasthenia gravis foundation of America, MG-QoL-15r: the 15-item myasthenia gravis quality of life questionnaire, MHLW: Ministry of Health, Labour and Welfare; NMA: network meta analysis, NNT: number needed to treat, QMG: Quantitative Myasthenia Gravis, RCTs: randomised controlled trials, SLR: systematic literature review

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Disclosures:

MO declares the following conflicts of interest: Served as consultant for Nobelpharma, UCB Japan. Received lecture fees from Takeda Pharmaceutical Company Ltd., Mitsubishi Tanabe Pharma Corporation, Sumitomo Pharma Co, Chugai Pharmaceutical Co, AbbVie GK, Biogen Japan Ltd., Novartis Japan., Alexion Pharmaceuticals, Inc. AU has received honoraria from Alexion Pharmaceuticals, UCB and Argenx. VM and AC are employed by Parexel. HB, KS, EY, KT, KT and YO are employed by UCB.

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