CO226

Matching-Adjusted Indirect Comparison of Zilucoplan Versus Cemdisiran and Gefurulimab in Generalized Myasthenia Gravis (gMG)

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Introduction

- Generalized myasthenia gravis (gMG) is an autoimmune disease of the neuromuscular junction characterized by impaired neuromuscular transmission, resulting in skeletal muscle weakness and fatigue.[1]
- Complement C5 inhibitors represent an important treatment approach in gMG; however, comparative evidence across these therapies is limited by the absence of head-to-head trials.[2-4]

Objective

- To estimate the comparative efficacy of zilucoplan versus cemdisiran and gefurulimab using unanchored matching-adjusted indirect comparisons (MAICs).

Methods

- A systematic literature review identified relevant trials evaluating zilucoplan (RAISE/RAISE-XT; NCT04115293/NCT04225871), cemdisiran (NIMBLE; NCT05070858), and gefurulimab (PREVAIL; NCT05556096) in patients with gMG.[2-4]
- Feasibility assessment confirmed sufficient population and outcome overlap to allow for comparison by MAICs.
- Zilucoplan patient-level data were reweighted to match aggregate baseline characteristics from NIMBLE and PREVAIL.
- Base-case matching prioritized clinically relevant prognostic characteristics while maintaining adequate effective sample size (ESS) and stable weights; alternative specifications were evaluated in sensitivity analyses.
- NIMBLE and PREVAIL assessed outcomes at approximately 6 months (cemdisiran at week 24, gefurulimab at week 26), whereas RAISE placebo-controlled period ended at week 12. Week 24 RAISE-XT data were therefore used for the ~6-month unanchored MAICs, as no common placebo comparator was available.
- Endpoints were MG-ADL response (≥3-point improvement) and QMG response (≥5-point improvement),[3-4] summarized as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was determined through the non-inclusion of null values in the 95% CIs.

Results

Feasibility and population adjustment

- Baseline differences were observed between RAISE and the NIMBLE and PREVAIL populations, with greater baseline disease severity in RAISE, particularly for MG-ADL and QMG scores (Table 1 and Table 2).
- Baseline QMG was excluded from the base-case matching specifications as its inclusion substantially reduced ESS and resulted in less stable weights. Race was also excluded from the base-case matching; scenarios including baseline QMG and race were among those in the sensitivity analyses (Supplementary Tables 1 and 2).
- Base-case reweighting achieved ESS of 59/86 and 66/86 for the cemdisiran and gefurulimab comparisons, respectively, with stable weights and alignment of the included characteristics with the target trial populations (Tables 1 and 2, Supplementary Figures 1 and 2).

Table 1. Selected parameters before and after reweighting: zilucoplan vs. cemdisiran

Parameter	NIMBLE Cemdisiran (n=64)	RAISE Zilucoplan (before matching) (n=86)	SMD*	RAISE Zilucoplan (after matching) (ESS=59/86)
Age, years, mean (SD)	52.70 (15.70)	52.63 (14.55)	0.005	54.27
Race – White, n (%)	35 (54.70%)	66 (76.70%)	-0.465	79.00%
Sex – Female, n (%)	36 (56.20%)	52 (60.50%)	-0.086	55.43%
MG duration, years, mean (SD)	8.10 (8.69)	9.34 (9.47)	-0.136	8.10
MG crisis (0), n (%)	39 (60.90%)	58 (67.40%)	-0.136	65.33%
Baseline MG-ADL score, mean (SD)	8.90 (2.40)	10.31 (2.51)	-0.574	8.90
Baseline QMG score, mean (SD)	15.50 (4.90)	18.71 (3.64)	-0.744	17.21
Baseline MGC score, mean (SD)	17.20 (5.80)	20.13 (6.01)	-0.496	17.20
Baseline MG-QoL-15r, mean (SD)	15.90 (5.80)	18.56 (6.55)	-0.430	15.90

**Absolute SMD values <0.1 indicate minimal imbalance; values ≥0.1 indicate increasing imbalance between populations. ESS: effective sample size; MGC: Myasthenia Gravis Composite; MG: Myasthenia gravis; MG-ADL: Myasthenia Gravis Activities of Daily Living; MG-QoL-15r: Myasthenia Gravis Quality of Life 15-item Revised; QMG: Quantitative Myasthenia Gravis; SD: Standard deviation; SMD: Standardized mean difference.*

Table 2. Selected parameters before and after reweighting: zilucoplan vs. gefurulimab

Parameter	PREVAIL Gefurulimab (n=131)	RAISE Zilucoplan (before matching) (n=86)	SMD*	RAISE Zilucoplan (after matching) (ESS=66/86)
Age, years, mean (SD)	53.00 (14.42)	52.63 (14.55)	0.026	53.00
Race – White, n (%)	69 (52.70%)	66 (76.74%)	-0.504	80.28%
Sex – Female, n (%)	78 (59.50%)	52 (60.47%)	-0.019	59.50%
MG duration, years, mean (SD)	9.20 (8.45)	9.34 (9.47)	-0.016	9.20
Baseline MG-ADL score, mean (SD)	9.00 (2.29)	10.31 (2.51)	-0.545	9.00
Baseline QMG score, mean (SD)	14.90 (4.38)	18.71 (3.64)	-0.946	17.69

**Absolute SMD values <0.1 indicate minimal imbalance; values ≥0.1 indicate increasing imbalance between populations. ESS: effective sample size; MG: Myasthenia gravis; MG-ADL: Myasthenia Gravis Activities of Daily Living; QMG: Quantitative Myasthenia Gravis; SD: Standard deviation; SMD: Standardized mean difference.*

Comparative efficacy

Zilucoplan demonstrated significantly greater odds of QMG response vs. cemdisiran

- At week 24, the odds of achieving a ≥3-point MG-ADL improvement numerically favoured zilucoplan vs. cemdisiran but were not statistically significant (OR 2.07; 95% CI 0.73–5.83) (Figure 1A).
- At week 24, zilucoplan was associated with significantly greater odds of achieving a ≥5-point QMG improvement vs. cemdisiran (OR 4.26; 95% CI 1.82–9.97) (Figure 1A).

Zilucoplan demonstrated significantly greater odds of MG-ADL and QMG responses vs. gefurulimab

- Zilucoplan (at week 24) was associated with significantly greater odds of achieving a ≥3-point MG-ADL improvement (OR 3.92; 95% CI 1.62–9.48) and a ≥5-point QMG improvement (OR 4.08; 95% CI 1.97–8.45) vs. gefurulimab (at week 26) (Figure 1B).

Sensitivity analyses

- All sensitivity analyses directionally favoured zilucoplan (Supplementary Tables 3 and 4). The QMG response estimate remained statistically significant in most sensitivity scenarios for the cemdisiran comparison.
- For the gefurulimab comparisons, statistical significance varied depending on the baseline characteristics included in the matching and the corresponding ESS.

Summary and conclusions

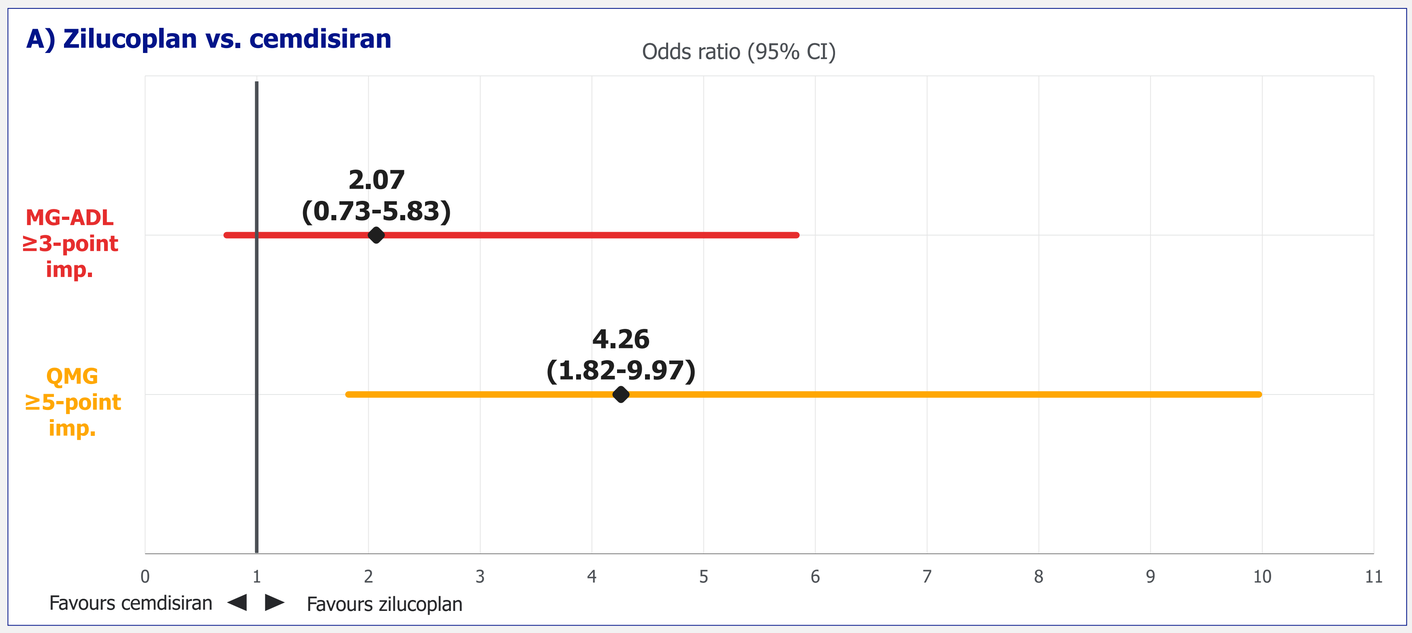
The odds of achieving a ≥3-point MG-ADL improvement and a ≥5-point QMG improvement with zilucoplan (at week 24) was significantly greater vs. gefurulimab (at week 26).

Zilucoplan demonstrated significantly greater odds of achieving a ≥5-point QMG improvement vs. cemdisiran at week 24.

The studies had significant baseline differences and, although efforts were made to adjust for these, residual confounding might remain.

Whilst acknowledging uncertainty, these population-adjusted findings from an unanchored MAIC approach provide an indication of superior comparative efficacy of zilucoplan compared with cemdisiran and gefurulimab.

Figure 1. Unanchored MAIC for MG-ADL (≥3-point) and QMG (≥5-point) response for zilucoplan vs. cemdisiran at week 24 (panel A) and zilucoplan (at week 24) vs. gefurulimab (at week 26) (panel B)



CI: confidence interval; MAIC: matching-adjusted indirect comparison; MG-ADL: Myasthenia Gravis Activities of Daily Living; QMG: Quantitative Myasthenia Gravis.

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Abbreviations: CI, confidence interval; ESS, effective sample size; gMG, generalized myasthenia gravis; IPD, individual patient data; KOL, key opinion leader; MAIC, matching-adjusted indirect comparison; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MG-QoL-15r, Myasthenia Gravis Quality of Life 15-item revised; OR, odds ratio; QMG, Quantitative Myasthenia Gravis; SD, standard deviation; SLR, systematic literature review; SMD, standardized mean difference.

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