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The long-term effectiveness of zilucoplan in myasthenia gravis: Predictive modeling in a US real-world database

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Introduction

- MG is a rare autoimmune neuromuscular disease marked by fluctuating muscle weakness; exacerbations can require hospitalization[1,2]
- Recently, targeted immunotherapies have emerged, including **zilucoplan**,[3] a daily self-injected treatment **approved in 2023 by the FDA**, EMA, and PMDA for the treatment of patients with anti-AChR Ab+ gMG
- The efficacy of zilucoplan was demonstrated in the RAISE trial (NCT04115293), using MG-ADL as the primary outcome[3]
- **Currently, zilucoplan's long-term real-world effectiveness cannot be evaluated because the open-label extension study, RAISE-XT (NCT04225871), has no placebo comparator.[4] Additionally, due to the time since approval, real-world usage data are not yet available**
  - **Innovative methods, including external control arm (ECA) and simulation, may offer alternatives to address these gaps**
- **This study leverages these approaches to assess the long-term effectiveness of zilucoplan when added to SoC in real-world settings, as measured by risk of severe exacerbation over 2 years**

Methods

- Data sources were:
  - **RAISE study** and its extension, **RAISE-XT**
  - **MyRealWorld MG** (MRWMG; patient-reported global database)
  - **MarketScan** (US claims database)
- The selected outcome of **severe exacerbations was a composite event defined as (i) hospitalizations for myasthenic exacerbation or crisis or (ii) acute rescue therapy use**
  - The primary endpoint was time to next severe exacerbation
- This study used a two-step methodology (**Figure 1**)
  - Step 1: Estimating treatment effect. The 2-year HR for severe exacerbations was calculated by comparing the zilucoplan-treated arm from RAISE and RAISE-XT with an ECA built in MRWMG by (**Figure 2**):
    - Replicating most inclusion and exclusion criteria of RAISE
    - Adjusting for differences in patients' baseline characteristics between the 'unadjusted' ECA and the treated arm through weighting
    - Fitting a weighted Cox proportional hazards model on time to severe exacerbation, including stratification factors from RAISE available in MRWMG (baseline MG-ADL and geographic region)
  - Step 2: Bridging Efficacy to Effectiveness. The risk of severe exacerbations in real-world settings over 2 years across multiple scenarios was simulated using the treatment effect estimated in Step 1 and a validated predictive model in MarketScan by (**Figure 1**):
    - Creating a real-world cohort from incident MG cases, then separating into four subgroups based on treatment escalation (**Figure 2**)
    - Training and validating a predictive Cox model to estimate the probability of severe exacerbations under SoC
    - Simulating event-free survival for each patient under two treatment condition groups: (i) under SoC by applying the predictive model and (ii) under zilucoplan as add-on to SoC by applying the predictive model combined with the estimated treatment effect
- Additional details on the Methods can be found via the QR code

Results

- Step 1:
  - The zilucoplan-treated arm included **82 patients** from RAISE/RAISE-XT and the ECA included **241 patients** from MRWMG
  - The variables included in the weighting (age at index date, sex, region, disease duration, baseline MG-ADL and MGFA class) were successfully balanced (**Figure 3**)
  - Throughout follow-up, the zilucoplan-treated arm maintained a consistently higher severe exacerbation-free survival than the ECA, with an adjusted HR (CI) for time to severe exacerbation for zilucoplan vs SoC of 0.14 (0.07–0.29) ($p \leq 0.001$) over 2 years (**Figure 4**). This HR translates to an 86% risk reduction of severe exacerbation over 2 years, assuming proportional hazards
- Step 2:
  - The MarketScan real-world cohort included **2,243 incident MG patients** meeting all eligibility criteria, stratified by therapy: **CS (n=1,528), NSIST (n=695), and biologics/rescue therapy (n=304)**. The prevalence of severe exacerbation increased progressively across the three cohorts (8.6%, 16.7% and 21.1%, respectively)
  - The predictive model was validated on discrimination and calibration metrics in MarketScan
  - For all scenarios, the risk of severe exacerbation at 2 years was lower for patients under zilucoplan+SoC than SoC alone. A greater risk difference at 2 years was observed in later stages. All scenarios showed overlapped CIs, with larger CIs for the simulated SoC group than the simulated zilucoplan add-on to SoC group (**Figure 5**)

Summary and conclusions

This study leveraged an external control arm and simulations to assess zilucoplan's long-term effectiveness in MG

Zilucoplan, as add-on to SoC, significantly reduced the risk of severe exacerbations over 2 years compared with a SoC external control arm from MRWMG

Simulations in real-world data suggested that zilucoplan reduced the long-term risk of severe exacerbations with benefit across different MG SoC therapy scenarios

This study combines real-world data and clinical trial results to anticipate zilucoplan's effectiveness in various MG SoC therapy scenarios. This innovative approach provides early clinical insights, which may support physicians to make informed treatment decisions for diverse patient profiles as zilucoplan enters real-world practice

Figure 1 Overview of the two-step methodology

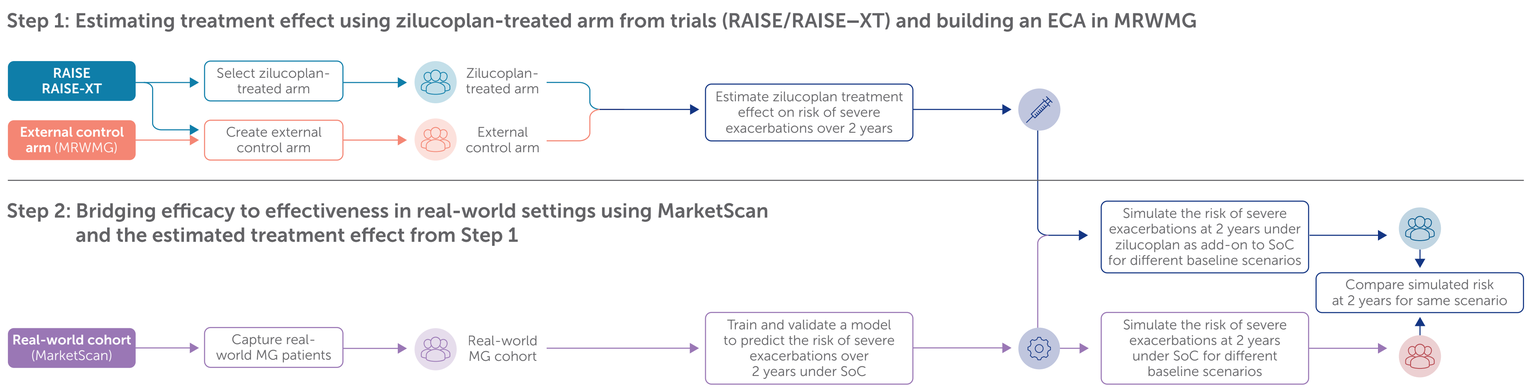
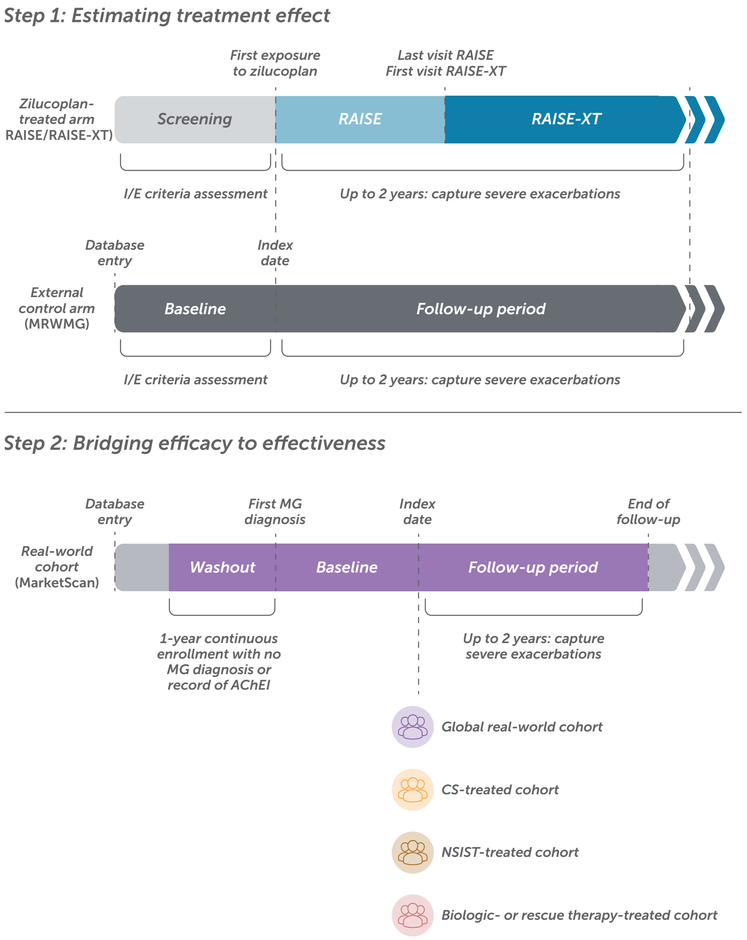


Figure 2 Study designs



Step 1: Study design of zilucoplan-treated arm (RAISE/RAISE-XT) and external control arm (MRWMG). The inclusion and exclusion criteria from the RAISE trial were replicated in the MRWMG cohort, with the MG-ADL >6 threshold serving as the index date. This allowed for the construction of a comparator group for zilucoplan-treated patients.
Step 2: Study design of real-world cohort (MarketScan) where incident patients were captured. Treatment escalations were defined as the first record of treatment initiation such as CS, NSIST, biologic and chronic rescue therapy per patient if no previous treatment was captured or if previous treatment records indicated an earlier stage. These proxies of escalations were used to create four different cohorts, each representing a distinct scenario based on therapy initiation to simulate effectiveness.

Figure 3 The propensity score density displayed a moderate overlap before weighting, which increased after weighting

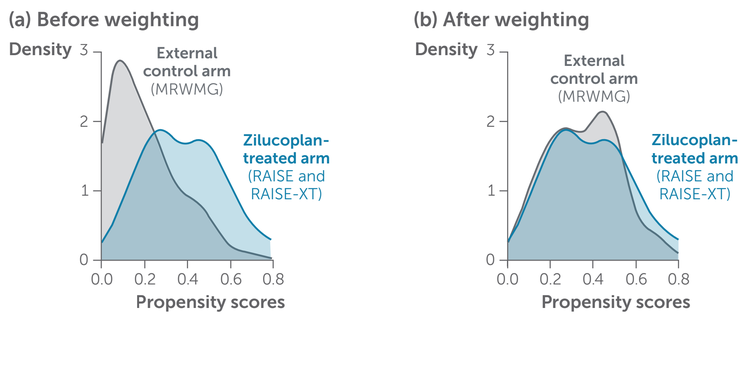
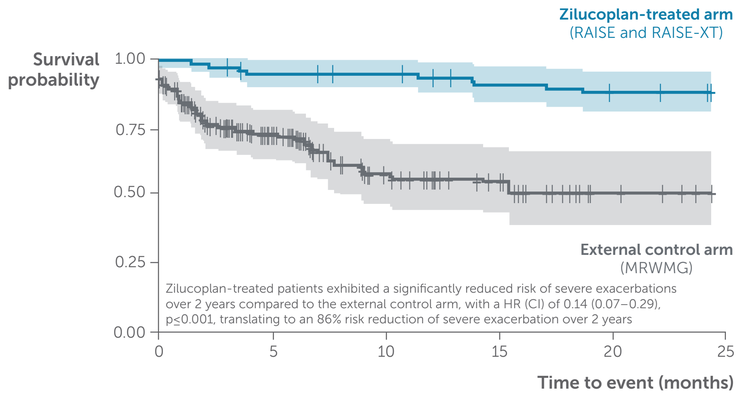
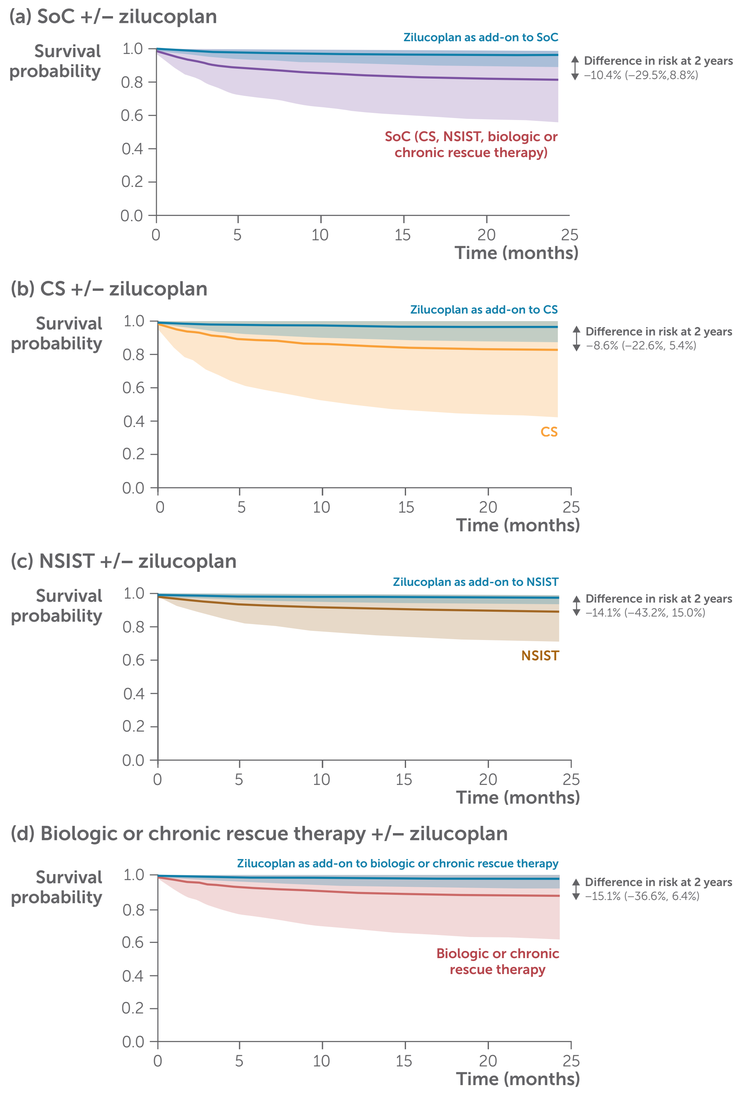


Figure 4 The zilucoplan-treated arm maintained a consistently higher severe exacerbation-free survival than the ECA



Number at risk						
Zilucoplan-treated arm (RAISE and RAISE-XT)	82	75	73	67	64	–
External control arm (MRWMG)	75	25	10	6	2	–

Figure 5 Simulation of the risk of severe exacerbation, and the differences in risk of severe exacerbation over 2 years under different scenarios



Abbreviations: Ab+, antibody positive; AChEI, acetylcholinesterase inhibitor; AChR, acetylcholine receptor; CI, confidence interval; CS, corticosteroid; ECA, external control arm; EMA, European Medicines Agency; FDA, Food and Drug Administration; gMG, generalized myasthenia gravis; HR, hazard ratio; I/E, inclusion/exclusion; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MRWMG, MyRealWorld MG; NSIST, non-steroidal immunosuppressant therapy; PMDA, Pharmaceuticals and Medical Devices Agency; SoC, standard of care; US, United States.

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