# Efficacy and safety of zilucoplan in myasthenia gravis: Responder analysis from the randomized Phase 3 RAISE trial

Tuan Vu[1], Angela Genge[2], Yessar Hussain[3], Henry J. Kaminski[4], M. Isabel Leite[5], Renato Mantegazza[6], Kimiaki Utsugisawa[7], Melissa Brock[8], Babak Boroojerdi[9], Mark Vanderkelen[10], Guillemette de la Borderie[11], Petra W. Duda[12], James F. Howard Jr.[13], on behalf of the RAISE investigators

[1]Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA; [2]Clinical Research Unit, The Montreal Neurological Institute, Montreal, QC, Canada; [3]Department of Neurology, Dell Medical School, The University of Texas at Austin, Austin, TX, USA; [4]George Washington University, Washington DC, USA; [5]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK; [6]Neuroimmunology and Neuromuscular Diseases Department, Fondazione Istituto Neurologico, PV, Italy; [7]Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan; [8]UCB Pharma, Raleigh, NC, USA; [9]UCB Pharma, Monheim, Germany; [10]UCB Pharma, Braine-l'Alleud, Belgium; [11]UCB Pharma, Brussels, Belgium; [12]UCB Pharma, Cambridge, MA, USA; [13]The University of North Carolina at Chapel Hill, Department of Neurology, Chapel Hill, NC, USA

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## Summary

### What we did

- RAISE was a randomized, double-blind, placebo-controlled Phase 3 study of zilucoplan, a complement C5 inhibitor, in patients with AChR Ab+ gMG

### What we found

- At Week 12:
  - The primary and all key secondary endpoints were met
  - Zilucoplan rapidly, statistically significantly and clinically meaningfully improved MG-ADL score compared with placebo
  - Significantly more patients achieved ≥3-point and ≥5-point improvements in MG-ADL and QMG without rescue therapy with zilucoplan than placebo
- Zilucoplan had a favorable safety profile with no major safety findings and similar incidences of serious adverse events across both treatment arms

### Why it matters

- RAISE demonstrated that zilucoplan was efficacious and well tolerated
- Zilucoplan improved symptoms and disease severity in patients with AChR Ab+ gMG
- Zilucoplan has the potential to be a self-administered treatment option for the management of gMG


## Introduction

- In AChR Ab+ gMG, pathogenic autoantibodies activate the complement cascade, leading to formation of the MAC, damage to the NMJ and loss of AChRs, which impairs muscle contraction[1]
- Zilucoplan is a small (3.5 kDa) macrocyclic peptide that binds to C5 with high affinity and specificity, preventing the cleavage of C5 into C5a and C5b[2]
- Zilucoplan also binds to the domain of C5 that corresponds to C5b and thereby blocks binding of C5b to complement C6[2]
- This dual mechanism of action effectively prevents activation of the terminal complement pathway and formation of the MAC, which leads to damage to the NMJ[2]
- Zilucoplan has shown efficacy and safety in a Phase 2 study in patients with gMG[2]

## Methods

- RAISE (NCT04115293) was a randomized, double-blind, placebo-controlled Phase 3 study to confirm the efficacy and safety of zilucoplan in patients with AChR Ab+ gMG (**Figure 1**)
- Participants were randomized 1:1 to receive either daily self-injected SC zilucoplan 0.3 mg/kg or placebo for 12 weeks
- Key inclusion criteria: Had AChR Ab+ gMG with an MG-ADL score of ≥6; a QMG score of ≥12; aged ≥18 years and <75 years; MGFA Disease Class II–IV; vaccination against *Neisseria meningitidis*; and stable MG-specific medication
- Exclusion criteria: Known positive serology for MuSK antibodies; fixed weakness ('burnt out' MG) based on the investigator assessment; and treatment with IVIg, PLEX, or SCIg 4 weeks prior to baseline visit
- Primary efficacy endpoint was CFB in MG-ADL score at Week 12; key secondary endpoints were CFB in QMG, MGC and MG-QoL 15r scores at Week 12
- Other secondary endpoints were response rates for MG-ADL (≥3-point improvement) and QMG (≥5-point improvement) at Week 12 without rescue therapy, time to administration of rescue therapy over the 12-week treatment period, and achieving MSE (defined as MG-ADL score 0 or 1) at Week 12 without rescue therapy
- Safety assessment included incidence of TEAEs

## Results

### Patients

- Baseline characteristics were generally balanced between treatment arms (**Table 1**)

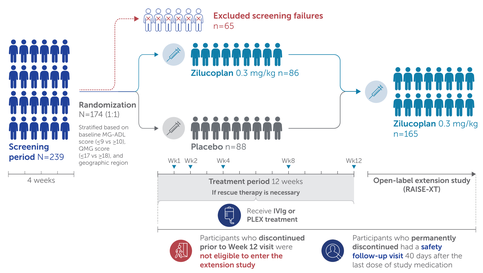
### Efficacy

- The primary efficacy endpoint was met: A highly statistically significant and clinically meaningful improvement from baseline in MG-ADL (LS mean difference [95% CI]: −2.09 [−3.24, −0.95]; p<0.001) was observed for zilucoplan vs placebo at Week 12 (**Figure 2**)
  - All key secondary efficacy endpoints were also met[3]
- A significantly higher proportion of zilucoplan patients achieved a ≥3-point improvement in MG-ADL without rescue therapy (MCID = 2-point difference) compared with placebo (**Figure 3a**)
  - Logistic regression analysis: 73.1% vs 46.1% (OR [95% CI] = 3.184 [1.662, 6.101]; p<0.001)
- A significantly higher proportion of zilucoplan patients achieved a ≥5-point improvement in QMG without rescue therapy (MCID = 3-point difference) compared with placebo (**Figure 3b**)
  - Logistic regression analysis: 58.0% vs 33.0% (OR [95% CI] = 2.865 [1.518, 5.409]; p=0.0012)
- More patients in the zilucoplan arm achieved MSE at Week 12 without rescue therapy compared with placebo (p=0.0885, not significant) (**Table 2**)
- Fewer patients received rescue therapy by Week 12 in the zilucoplan group (5%) vs placebo (12%) (logrank p=0.1003) (**Table 2**)

### Safety

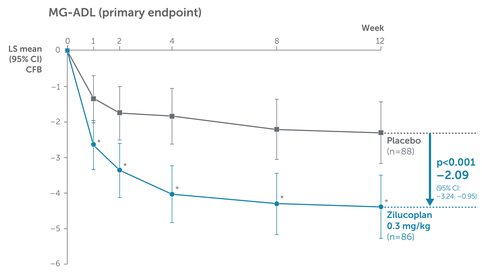
- Incidences of TEAEs are shown in **Table 3**
- The incidences of serious TEAEs were similar across both treatment arms (**Table 3**)
- The higher incidence of TEAEs in the zilucoplan arm was mainly driven by injection-site reactions, upper respiratory tract infections and diarrhea (**Table 3**)
- No *Neisseria* infections were observed
- TEAEs leading to discontinuation were:
  - Zilucoplan: One each of aphthous ulcer, mouth ulceration, COVID-19, hepatic enzyme increase
  - Placebo: One each of hyperemesis gravidarum and cerebral hemorrhage
- One death occurred in each treatment group (COVID-19, zilucoplan; cerebral hemorrhage, placebo); neither death was considered treatment related

**Figure 1** RAISE study design




Zilucoplan and placebo were self-administered as a once-daily SC injection. Patients were enrolled from East Asia, Europe and North America.

**Figure 2** Change from baseline to Week 12 in MG-ADL




*p<0.05 (nominal) vs placebo.

Treatment group differences were assessed using an MMRM analysis of ANCOVA, where treatment failures (rescue therapy, death or myasthenic crisis) were imputed with baseline or the last available value, whichever was worse.

A 2-point change in MG-ADL score is considered clinically meaningful.[4]

## Conclusions

- Zilucoplan rapidly, statistically significantly and clinically meaningfully improved MG-ADL score vs placebo, and improvement was sustained through to Week 12
- Significantly higher proportions of patients receiving zilucoplan achieved ≥3-point and ≥5-point improvements in MG-ADL and QMG without rescue therapy vs placebo, respectively
- More patients achieved MSE at Week 12 with zilucoplan vs placebo, while fewer patients received rescue therapy with zilucoplan vs placebo
- Zilucoplan had a favorable safety profile with no major safety findings and good tolerability, confirming the results of the Phase 2 study
  - All patients in the zilucoplan arm who completed the 12-week treatment period entered the ongoing RAISE-XT extension study (NCT04225871)
- Zilucoplan, a complement C5 inhibitor, improved MG symptoms and disease severity, and has the potential to be a new, self-administered, convenient option for the management of patients with AChR Ab+ gMG

**Table 1** Patient demographics and baseline disease characteristics

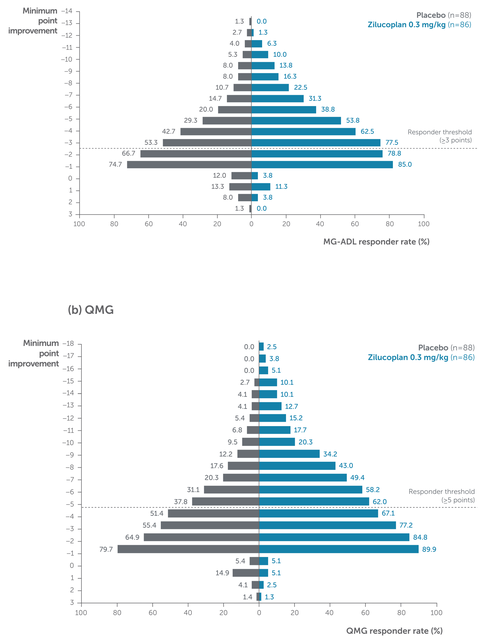
| | | Placebo (n=88) | Zilucoplan 0.3 mg/kg (n=86) |
|---|---|---|---|
| Age, years, mean (SD) | | 53.3 (15.7) | 52.6 (14.6) |
| Sex, male, n (%) | | 41 (46.6) | 34 (39.5) |
| Geographic region, n (%) | North America | 46 (52.3) | 45 (52.3) |
| | Europe | 33 (37.5) | 34 (39.5) |
| | East Asia | 9 (10.2) | 7 (8.1) |
| MGFA disease class, n (%) | II (IIa, IIb) | 27 (30.7) | 22 (25.6) |
| | III (IIIa, IIIb) | 57 (64.8) | 60 (69.8) |
| | IV (IVa, IVb) | 4 (4.5) | 4 (4.7) |
| MG-ADL score, mean (SD) | | 10.9 (3.4) | 10.3 (2.5) |
| QMG score, mean (SD) | | 19.4 (4.5) | 18.7 (3.6) |
| MGC score, mean (SD) | | 21.6 (7.2) | 20.1 (6.0) |
| MG-QoL 15r score, mean (SD) | | 18.9 (6.8) | 18.6 (6.6) |
| Prior thymectomy, n (%) | | 37 (42.0) | 45 (52.3) |
| Duration of disease, years, mean (SD) | | 9.0 (10.4) | 9.3 (9.5) |
| Treatment refractory,* n (%) | | 44 (50.0) | 44 (51.2) |
| MG medications at baseline,† n (%) | Cholinesterase inhibitor | 73 (83.0) | 74 (86.0) |
| | Corticosteroids | 51 (58.0) | 59 (68.6) |
| | Azathioprine, MMF | 35 (39.8) | 30 (34.9) |
| | Cyclosporin, methotrexate, tacrolimus | 15 (17.0) | 12 (14.0) |

mITT population unless otherwise stated; mITT population includes all randomized participants who received at least one dose of study drug and have at least one post-dosing MG-ADL score.

*A participant is considered 'treatment refractory' if they have had treatment for at least 1 year with two or more of the following therapies: Prednisone, azathioprine, mycophenolate, cyclosporin, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids; OR history of treatment with at least one of the above therapies for 1 year or more and required chronic PLEX, IVIg or SCIg at least every 3 months for the 12 months prior to enrollment.

†Safety set. Includes all participants who received at least one dose of study drug with participants analyzed based on the actual study treatment received.

**Figure 3** Change from baseline in (a) MG-ADL response and (b) QMG response at Week 12




A Holm procedure was used for Family 2 secondary endpoints: Time to receive rescue therapy, achievement of MSE, achievement of a ≥3-point reduction in MG-ADL score, achievement of a ≥5-point reduction in QMG score (all at Week 12).

**Table 2** MSE and first receipt of rescue therapy

| | | Placebo (n=88) | Zilucoplan 0.3 mg/kg (n=86) | p-value |
|---|---|---|---|---|
| MSE (MG-ADL 0 or 1) without rescue therapy at Week 12, %* | | 5.8 | 14.0 | 0.0885 |
| First receipt of rescue therapy | Cumulative number (proportion) of events at Week 12, n (%) | 10 (12) | 4 (5) | 0.1003 |

*Percentages are estimated using multiple imputation as for the primary endpoint.

**Table 3** Overview of TEAEs

| | | Placebo (n=88) n (%) | Zilucoplan 0.3 mg/kg (n=86) n (%) |
|---|---|---|---|
| Any TEAE | | 62 (70.5) | 66 (76.7) |
| | Injection-site bruising | 8 (9.1) | 14 (16.3) |
| | Headache | 14 (15.9) | 13 (15.1) |
| | Upper respiratory tract infections | 6 (6.8) | 12 (14.0) |
| | Diarrhea | 2 (2.3) | 9 (10.5) |
| | Myasthenia gravis | 8 (9.1) | 9 (10.5) |
| | Serious TEAE | 13 (14.8) | 11 (12.8) |
| | TEAE resulting in permanent withdrawal from IMP* | 2 (2.3) | 4 (4.7) |
| | Treatment-related TEAE | 22 (25.0) | 28 (32.6) |
| | Severe TEAE | 11 (12.5) | 10 (11.6) |
| Death | | 1 (1.1) | 1 (1.2) |
| | COVID-19 | 0 | 1 (1.2) |
| | Cerebral hemorrhage | 1 (1.1) | 0 |

TEAEs listed are those that occurred in >10% in any treatment arm.

*Includes deaths.

Safety set. Safety set includes all participants who received at least one dose of study drug with participants analyzed based on the actual study treatment received.

Zilucoplan is an investigational new product and has not been approved by any authority.

**Abbreviations:** Ab, autoantibody; AChR, acetylcholine receptor; ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; C(x), complement component (x); gMG, generalized myasthenia gravis; IMP, investigational medicinal product; IVIg, intravenous immunoglobulin; LS, least squares; MAC, membrane attack complex; MCID, minimal clinically important difference; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QoL 15r, Myasthenia Gravis Quality of Life 15-item revised scale; mITT, modified intention-to-treat; MMF, mycophenolate mofetil; MMRM, mixed model repeated measures; MSE, Minimal Symptom Expression; MuSK, muscle-specific kinase; NMJ, neuromuscular junction; OR, odds ratio; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SD, standard deviation; TEAE, treatment-emergent adverse event; Wk, week

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