# Effect of zilucoplan on fatigue in generalized myasthenia gravis in the Phase 3 RAISE and RAISE-XT studies

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## Introduction

- Fatigue has a marked negative impact on the day-to-day lives of patients with MG, and is strongly associated with a reduced quality of life[1]
- Zilucoplan, a complement C5 inhibitor, showed clinically meaningful and statistically significant improvements in MG-specific outcomes in patients with AChR Ab+ gMG in Phase 2[2] and Phase 3 (RAISE)[3] randomized, double-blind, placebo-controlled studies
  - In RAISE, mean change from baseline to Week 12 in MG-ADL score was significantly improved with zilucoplan compared to placebo (LSM difference: −2.09 [−3.24, −0.95]; p=0.0004);[3] further treatment with zilucoplan in RAISE-XT demonstrated continued improvements that were sustained through to Week 60
  - Statistically significant improvements in the zilucoplan group versus placebo were observed in fatigue at Week 12 in RAISE[3]
- Long-term data from RAISE-XT will enhance our understanding of the effect of zilucoplan on fatigue in patients with gMG as measured by the Neuro-QoL Short Form fatigue scale
  - Neuro-QoL Short Form fatigue raw scores can be converted into T-scores, which allow for clinically meaningful thresholds and severity thresholds to be applied[4,5]

## Methods

- In RAISE (NCT04115293), adults with AChR Ab+ gMG (MGFA Disease Class II–IV) were randomized 1:1 to receive daily subcutaneous self-administered injections of zilucoplan 0.3 mg/kg or placebo for 12 weeks
- Patients who completed RAISE, or the qualifying Phase 2 study (NCT03315130), were eligible to enroll in RAISE-XT (NCT04225871), an ongoing, Phase 3, multicenter, OLE study of zilucoplan 0.3 mg/kg (interim data cut-off September 8, 2022)
- The primary outcome of RAISE-XT was incidence of TEAEs
- In this *post-hoc* analysis of RAISE and RAISE-XT, we report:
  - CFB in Neuro-QoL Short Form fatigue T-scores over time
  - Proportion of Neuro-QoL Short Form fatigue T-score responders compared with placebo at Week 12 in RAISE
  - Fatigue severity transition from RAISE baseline to Week 60
- Neuro-QoL Short Form fatigue data were not collected during the Phase 2 study

## Results

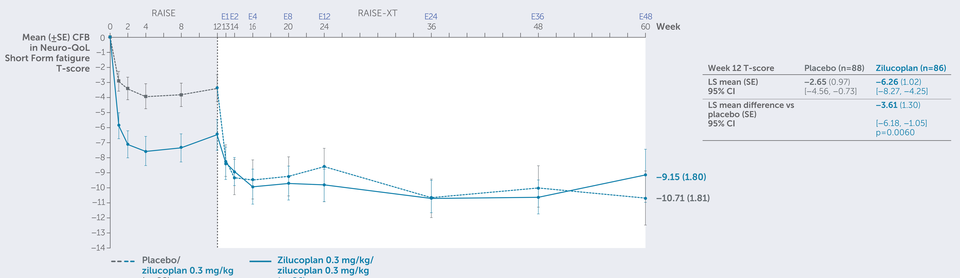
- In RAISE, 174 patients were randomized to receive zilucoplan 0.3 mg/kg (n=86) or placebo (n=88)
  - After Week 12, all patients who completed RAISE (166 [95.4%]) entered RAISE-XT to receive zilucoplan 0.3 mg/kg
- Patient demographics and baseline disease characteristics are presented in **Table 1**
- In the overall RAISE-XT population (N=200), TEAEs occurred in 188 (94.0%) patients; the most common TEAEs were worsening of MG (n=52 [26.0%]) and COVID-19 (n=49 [24.5%])
  - Serious TEAEs occurred in 64 (32.0%) patients
- Mean Neuro-QoL Short Form fatigue T-scores improved from RAISE baseline to Week 12 in those receiving zilucoplan, with an LSM difference (SE) of −3.61 (1.30) from placebo (p=0.0060) (**Figure 1**)
  - This difference is considered clinically meaningful as it surpasses the established within-patient change threshold of −3.5[5]
  - At Week 12 of RAISE, a higher proportion of patients receiving zilucoplan had clinically meaningful reductions in fatigue baseline versus placebo (**Figure 2**)
- During RAISE-XT, rapid improvements were observed within 1 week in patients who switched from placebo to zilucoplan (placebo-switch group; **Figure 1**)
  - T-scores improved further for both the placebo-switch and zilucoplan groups and were sustained through to Week 60
- There were significant positive correlations between Neuro-QoL Short Form fatigue scale T-scores and MG-ADL, QMG and MG-QoL 15r scores at double-blind study baseline, Week 12 and Week 60 (data not shown)
- At RAISE baseline, the fatigue severity of most patients was moderate or severe (n=66 [78.6%]), whilst at Week 60, most patients had mild or no fatigue (n=55 [65.5%]; **Figure 3**)
  - These findings were consistent across the placebo-switch and zilucoplan groups

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

| | | Placebo (n=88) | Zilucoplan 0.3 mg/kg (n=86) | Total (N=174) |
|---|---|---|---|---|
| | Age, years, mean (SD) | **53.3** (15.7) | **52.6** (14.6) | **53.0** (15.1) |
| | Sex, male, n (%) | **41** (46.6) | **34** (39.5) | **75** (43.1) |
| MGFA Disease Class, n (%) | II | **27** (30.7) | **22** (25.6) | **49** (28.2) |
| | III | **57** (64.8) | **60** (69.8) | **117** (67.2) |
| | IV | **4** (4.5) | **4** (4.7) | **8** (4.6) |
| | MG-ADL, mean (SD) | **10.9** (3.4) | **10.3** (2.5) | **10.6** (3.0) |
| | QMG score, mean (SD) | **19.4** (4.5) | **18.7** (3.6) | **19.1** (4.1) |
| | Prior thymectomy, n (%) | **37** (42.0) | **45** (52.3) | **82** (47.1) |
| | Prior MG crisis, n (%) | **29** (33.0) | **28** (32.6) | **57** (32.8) |
| | Duration of disease, years, mean (SD) | **9.0** (10.4) | **9.3** (9.5) | **9.2** (9.9) |
| | Age at onset, years, mean (SD) | **44.0** (18.7) | **43.5** (17.4) | **43.8** (18.0) |
| | Cholinesterase inhibitors | **84** (95.5) | **84** (97.7) | **168** (96.6) |
| Prior gMG therapies (safety set), n (%) | Corticosteroids | **74** (84.1) | **77** (89.5) | **151** (86.8) |
| | Azathioprine, MMF | **54** (61.4) | **49** (57.0) | **103** (59.2) |
| | Cyclosporin, cyclophosphamide, methotrexate, tacrolimus, rituximab | **31** (35.2) | **26** (30.2) | **57** (32.8) |

RAISE mITT population, which included all randomized patients who received at least one dose of the study drug and had at least one post-dosing MG-ADL score. Safety set included all patients who received at least one dose of zilucoplan in RAISE.

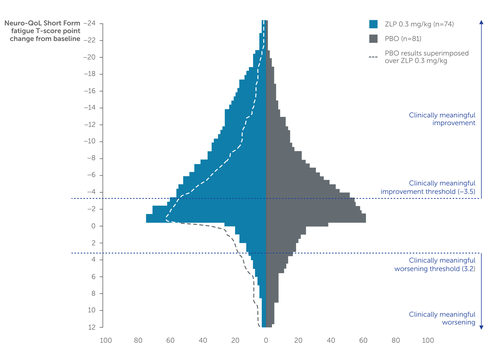
**Figure 1** Change from RAISE baseline to Week 60 in Neuro-QoL Short Form fatigue T-scores




| Week 12 T-score | Placebo (n=88) | Zilucoplan (n=86) |
|---|---|---|
| LS mean (SE) | −2.65 (0.97) | **−6.26** (1.02) |
| 95% CI | [−4.56, −0.73] | [−8.27, −4.25] |
| LS mean difference vs placebo (SE) | | **−3.61** (1.30) |
| 95% CI | | [−6.18, −1.05] p=0.0060 |

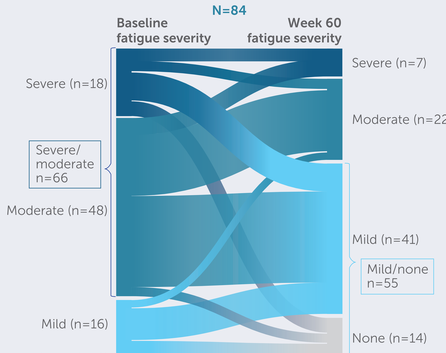
The analysis set for mean change from RAISE baseline to Week 60 in Neuro-QoL Short Form fatigue T-scores includes patients from RAISE and RAISE-XT who were included in the RAISE mITT population. Statistical analysis of Week 12 Neuro-QoL Short Form fatigue T-scores was performed using the mITT population in RAISE.

**Figure 2** Responder analysis in Neuro-QoL Short Form fatigue T-scores at Week 12 in RAISE




The analysis was performed using the Neuro-QoL analysis set, which is defined as all patients who had a Neuro-QoL Short Form fatigue T-score at RAISE baseline and at Week 12.
Thresholds for clinically meaningful improvement and clinically meaningful worsening were defined as point changes of −3.5 and 3.2, respectively, in Neuro-QoL Short Form fatigue T-scores from RAISE baseline.[5]

**Figure 3** Fatigue severity transition from RAISE baseline to Week 60




The analysis set includes patients from RAISE and RAISE-XT who were included in the RAISE mITT population and had available Neuro-QoL Short Form fatigue data at RAISE baseline and Week 60.
The fatigue severity level thresholds for T-scores were defined as: none ("no problems"), <45; mild problems, 45–55; moderate problems, 56–65; and severe problems, >65).[4]

## Summary and conclusions

In this *post-hoc* analysis of data from the Phase 3 RAISE study and its OLE, RAISE-XT, we evaluated the effect of the complement C5 inhibitor zilucoplan on fatigue up to 60 weeks in patients with AChR Ab+ gMG

Zilucoplan demonstrated a favorable long-term safety profile and was well tolerated

Improvements in Neuro-QoL Short Form fatigue T-scores were observed with zilucoplan from Week 1, with a clinically meaningful, significant difference from placebo in CFB to Week 12 of RAISE

The majority of patients had moderate or severe fatigue at baseline, whilst at Week 60, the majority experienced mild or no fatigue, demonstrating meaningful improvements in fatigue severity

These data show that zilucoplan led to rapid, clinically meaningful and significant improvements in fatigue that were sustained over long-term treatment in patients with gMG

**Abbreviations:** AChR Ab+, positive for autoantibodies against the acetylcholine receptor; C5, component 5; CFB, change from baseline; CI, confidence interval; COVID-19, coronavirus disease 2019; E, extension; IgMG, (generalized) myasthenia gravis; LSM, least squares mean; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL 15r, Myasthenia Gravis Quality of Life 15-item revised; mITT, modified intention-to-treat; MMF, mycophenolate mofetil; Neuro-QoL, Quality of Life in Neurological Disorders; OLE, open-label extension; PBO, placebo; QMG, Quantitative Myasthenia Gravis; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; ZLP, zilucoplan.

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