Interpreting patient health-related quality-of-life experience with zilucoplan treatment in generalized myasthenia gravis in RAISE and RAISE-XT

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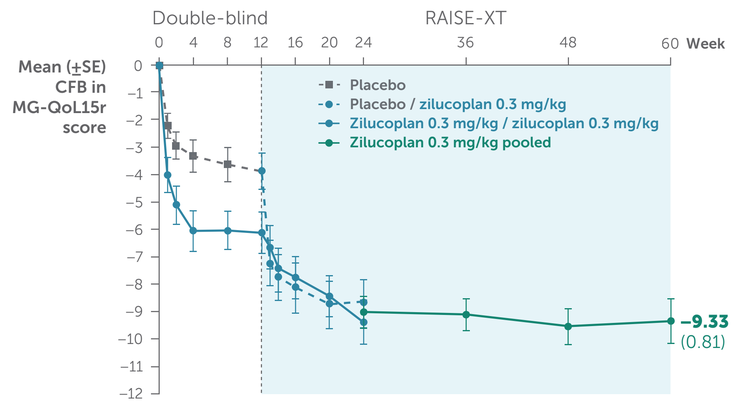
Introduction

- gMG is an autoimmune neuromuscular disease that negatively affects the quality of life of patients[1]
- In the pivotal Phase 3, double-blind, 12-week RAISE study (NCT04115293), treatment with zilucoplan, a potent complement C5 inhibitor, resulted in statistically significant improvements in MG-QoL15r total score versus placebo in patients with anti-AChR Ab+ gMG[2]
  - These improvements were sustained in an ongoing, Phase 3, open-label extension study (RAISE-XT; NCT04225871) up to 60 weeks (**Figure 1**)[3]
  - However, the meaningfulness of these differences for patients can be difficult to interpret
- Rasch modeling is a psychometric framework that transforms categorical data (e.g., PRO responses) into interval-level data, thus enhancing the interpretability of the measurements[4,5]
  - With this approach, the response-likelihood of each response option from each item can be calculated based on patients' quality of life at a given time point and item difficulty, enabling meaningful interpretation of the data
- To interpret the meaningfulness of improvements in MG-QoL15r scale, we determined the most likely response to each item of this scale before and after zilucoplan treatment in RAISE and RAISE-XT using Rasch modeling

Methods

- In RAISE, patients with anti-AChR Ab+ gMG were randomized to self-administer once-daily zilucoplan 0.3 mg/kg or placebo[2]
- Adults who completed the double-blind RAISE or Phase 2 study could enter RAISE-XT to receive daily zilucoplan 0.3 mg/kg[3]
- The primary outcome of RAISE-XT was incidence of TEAEs[3]
- The Rasch Rating Scale Model was used *post hoc* to determine the probability of item responses for the MG-QoL15r scale
- In this analysis, we report the probability of endorsing each item response of MG-QoL15r at:
  - Baseline and Week 12 of RAISE in the zilucoplan and placebo groups
  - Pooled RAISE baseline and Week 60 of RAISE-XT
- The interim data cutoff date was September 8, 2022

Figure 1 Improvements in MG-QoL15r total score were sustained through to Week 60



mITT population, which included all patients who received at least one dose of zilucoplan and had at least one post-dosing MG-ADL score.

Results

- Overall, 200 patients enrolled in RAISE-XT; 174 patients enrolled in RAISE, 166 of whom completed RAISE and entered RAISE-XT and were included in this analysis
- At Week 12, patients treated with zilucoplan were more likely than those treated with placebo to answer "Not at all" for all items, including for the most severe symptoms such as difficulty speaking and personal grooming (**Figure 2**)
- In RAISE-XT, this likelihood increased at Week 60 compared with the baseline (**Figure 3**)
  - The likelihood of answering "Not at all" was highest (a chance higher than 50%) for the seven most severe items at Week 60
- In RAISE-XT, TEAEs occurred in 94.0% (n=188/200) of patients[3]
  - Overall, 32.0% (n=64/200) of patients experienced a serious TEAE, of whom 1.0% (n=2/200) experienced a serious treatment-related TEAE[3]

Summary and conclusions

In this *post hoc* analysis, we assessed the most likely response to each item of a health-related quality-of-life questionnaire before and after zilucoplan treatment in RAISE and RAISE-XT

In RAISE, patients treated with zilucoplan were more likely to respond favorably to all health-related quality-of-life items, including the items that reflect more severe MG such as difficulty talking, than patients treated with placebo

In RAISE-XT, the likelihood of zilucoplan-treated patients responding favorably to the health-related quality-of-life items further increased to Week 60

These findings demonstrate that patients treated with zilucoplan generally no longer experienced the more severe gMG symptoms and support the interpretation that changes in the total MG-QoL15r score were clinically meaningful

Figure 2 At Week 12, patients treated with zilucoplan were more likely to answer favorably for all MG-QoL15r items than those treated with placebo

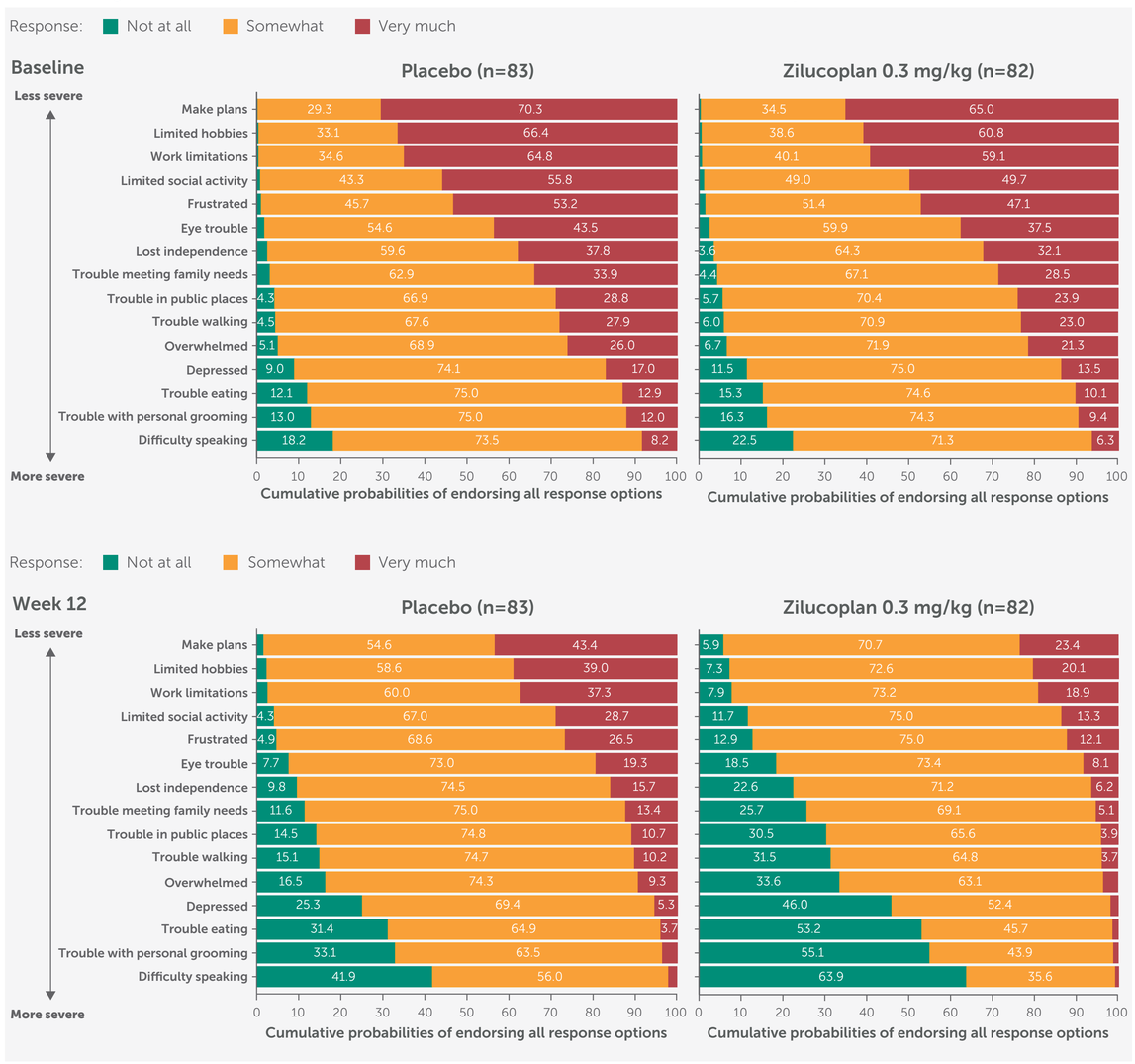
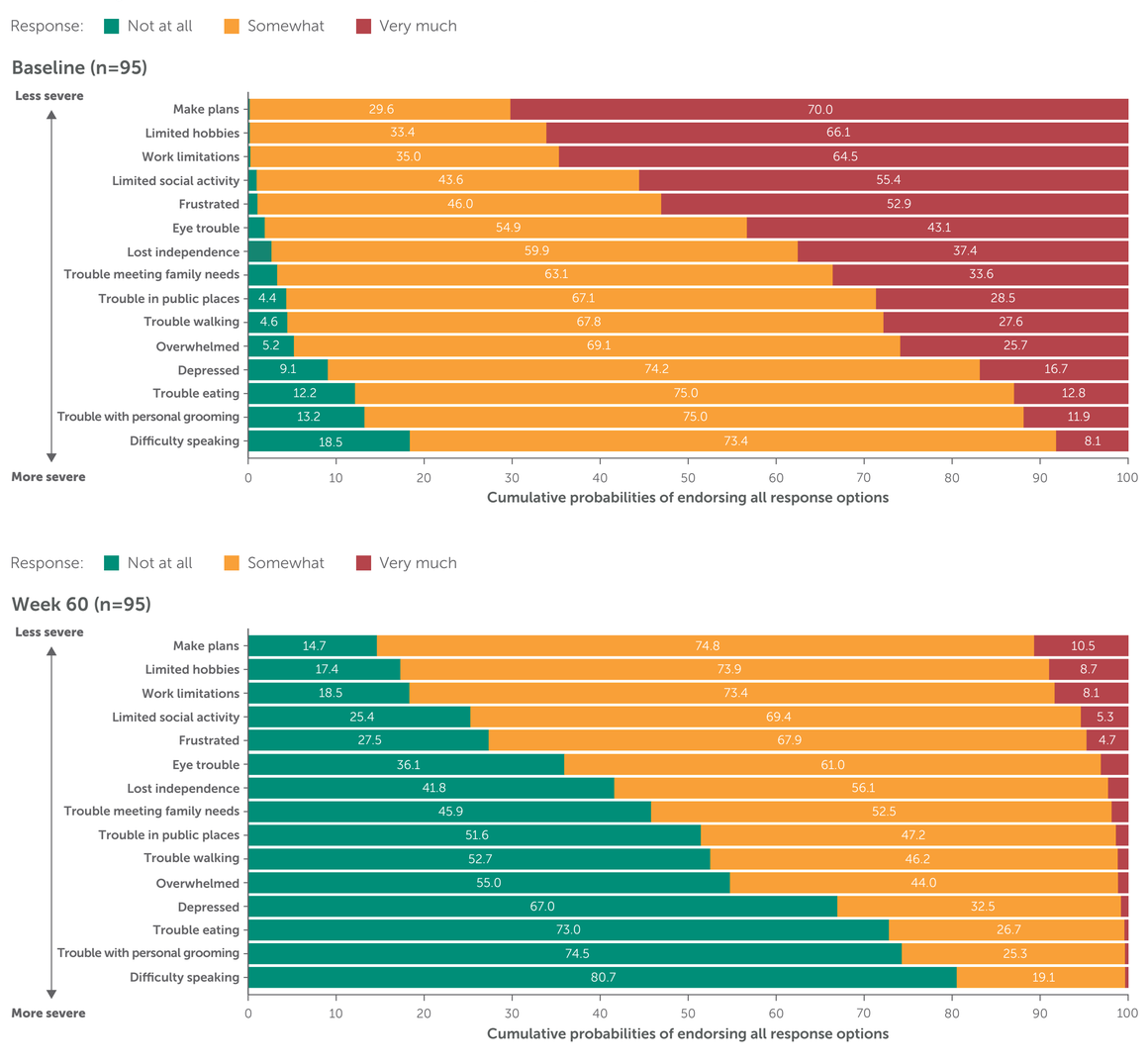


Figure 3 At Week 60, patients treated with zilucoplan were more likely to answer favorably for all MG-QoL15r items compared with the RAISE baseline



ITT population, which included all randomized patients enrolled in the RAISE study and was used to derive the Rasch model. Only patients who had an available MG-QoL15r total score at both baseline and Week 12 (**Figure 2**) or Week 60 (**Figure 3**) were included. More severe: items endorsed mainly in patients with severe gMG; less severe: items endorsed by patients even with mild gMG.

Abbreviations: Ab+, antibody positive; AChR, acetylcholine receptor; C5, component 5; CFB, change from baseline; (g)MG, (generalized) myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL15r, Myasthenia Gravis Quality of Life 15-item revised; (m)ITT, (modified) intention-to-treat; PRO, patient-reported outcome; SE, standard error; TEAE, treatment-emergent adverse event.

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