Interpreting patient experience of rozanolixizumab on bulbar symptoms of generalized myasthenia gravis from the MycarinG clinical trial

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Introduction

- People living with gMG experience fluctuating and variable muscle weakness of the limb and axial, ocular, bulbar and respiratory muscles, as well as muscle weakness fatigability and fatigue; however, each person's experience is different[1,2]
- The MG Symptoms PRO instrument includes 5 scales, developed to understand the important aspects of patients' lived experiences[3]
- The Bulbar Muscle Weakness scale (BMWS) in the MG Symptoms PRO assesses weakness of bulbar muscles (e.g., difficulties with speech, swallowing and chewing).[3,4]
- Whereas other clinical assessment tools for MG have single items evaluating these symptoms, the BMWS evaluates a patient's experience of the severity (none, mild, moderate, severe) of 10 bulbar symptoms[4] most relevant to patients based on findings from qualitative research involving adults with gMG[3]
  - Calculated scores for the BMWS can range from 0 to 100, with higher BMWS scores indicating more severe symptoms[4]
- MycarinG (NCT03971422) was a Phase 3 study of rozanolixizumab, a humanized IgG4 monoclonal antibody FcRn inhibitor, in people living with gMG. Three MG Symptoms PRO scales were selected as secondary endpoints: Physical Fatigue, Muscle Weakness Fatigability, and BMWS[5]
  - At Day 43, MG Symptoms PRO BMWS scores showed significant improvement in the bulbar symptom severity for patients receiving rozanolixizumab compared with placebo (**Figure 1**)
- The objective of this post hoc analysis was to show how the patient-relevant content of the MG Symptoms PRO scale could be used to provide an interpretation of the changes in the MG Symptoms PRO BMWS score observed in MycarinG that is meaningful to patients

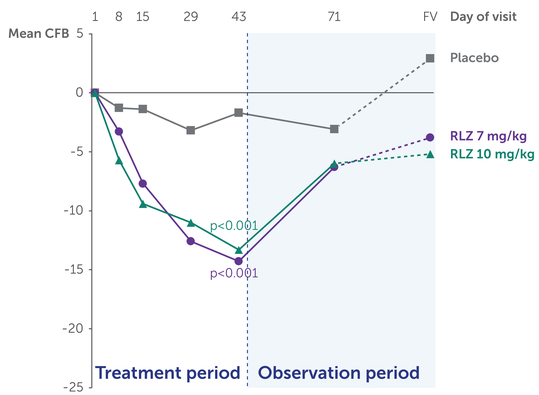
Methods

- MycarinG enrolled patients aged ≥18 years with AChR Ab+ or MuSK Ab+ gMG, MGFA Disease Class II-IVa, MG-ADL score ≥3 (for nonocular symptoms) and QMG score ≥11[5]
- Patients were randomly assigned to receive one cycle (6 weekly infusions) of rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg, or placebo
- Secondary endpoints included CFB to Day 43 in MG Symptoms PRO scales, including the BMWS
  - MG Symptoms PRO scales were assessed at Days 1, 8, 15, 29, 43, 71, and 99
- The MG Symptoms PRO scales were developed with the Rasch model; a mathematical model that expresses the probability of a respondent to give a response to a specific item as a function of the respondent level of the measured attribute (i.e., the targeted concept) and the level of this attribute that is characterized by the item
  - The Rasch model has been used previously in the context of other commonly used scales in MG: MG-ADL, QMG, and MGC[6-9]
- The mean MG Symptoms PRO scales observed in each treatment arm (rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg, and placebo) at Day 1 and Day 43 were mapped to this frame of reference to determine the most likely response to the MG Symptoms PRO scales for each group of patients at these timepoints

Results

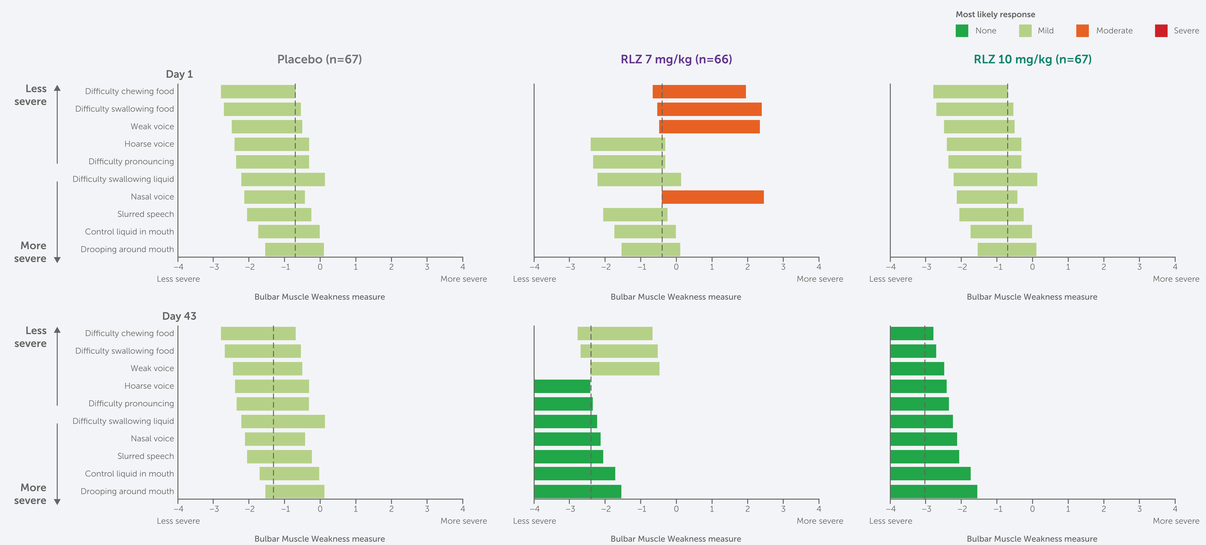
- Two hundred patients were enrolled and randomized to receive placebo (n=67), rozanolixizumab 7 mg/kg (n=66), or rozanolixizumab 10 mg/kg (n=67)[5]
- **Figure 2** lists the most likely responses to individual items of the MG Symptoms PRO BMWS in order of severity
- At baseline, patients reported experiencing mild or moderate bulbar symptoms. The rozanolixizumab 7 mg/kg group reported more moderate symptoms than the other groups, the reason for this is unknown
  - Patients with MGFA Class IVb or V disease, who would be more likely to experience severe bulbar symptoms, were not included in the study
- At Day 43, the placebo group continued to experience mild bulbar symptoms. In contrast, most patients treated with rozanolixizumab experienced symptom improvement, reporting no or mild bulbar symptoms at Day 43
- Similar outcomes were reported across the Physical Fatigue and Muscle Weakness Fatigability scales (data not shown)

Figure 1 Mean CFB in MG Symptoms PRO BMWS Score in MycarinG[5]



Day	1	8	15	29	43	71	FV
Placebo, n	67	67	66	65	64	49	64
RLZ 7 mg/kg, n	66	66	62	63	64	52	64
RLZ 10 mg/kg, n	67	66	64	61	62	59	64

Figure 2 Most Likely Response to the Items of the MG Symptoms PRO BMWS at Day 1 and Day 43 by Treatment Arm



The items are ordered according to their severity (as per the estimation from the initial Rasch model). The gray dotted lines represent the observed means of overall bulbar symptom severity observed in the study for the treatment group at the visit. The colored bars show the most likely response to the item.

Summary and conclusions

- The 10 items in the MG Symptoms PRO BMWS were developed with input from people living with gMG and evaluate changes that reflect patients' actual experience of these symptoms
- In the Phase 3 MycarinG study of rozanolixizumab, statistically significant improvements in BMWS scores from baseline to Day 43 were observed for both rozanolixizumab treatment groups versus placebo
- These results can be translated to fully understand patient-relevant aspects of bulbar symptoms after treatment
- Patients who received rozanolixizumab experienced improvements in bulbar symptoms, with most experiencing mild to moderate symptoms at baseline and either no or mild symptoms after treatment. Symptom severity was unchanged in patients who received placebo

	MG Symptoms PRO BMWS items	Patients receiving rozanolixizumab typically…	Patients receiving placebo typically…
Less severe	Difficulty chewing food	Experienced no or mild symptoms	Experienced mild symptoms
	Difficulty swallowing food		
	Weak voice		
	Hoarse voice	No longer experienced these symptoms	Experienced mild symptoms
	Difficulty pronouncing		
	Difficulty swallowing liquids		
	Nasal voice		
	Slurred speech		
	Difficulty controlling liquids in mouth		
More severe	Drooping around mouth		

This *post hoc* analysis of the MG Symptoms PRO results from MycarinG further supports the meaningfulness of the positive clinical trial results and may help facilitate communication about patient experience with rozanolixizumab

For more detailed explanations about the use of Rasch, a modern scientific approach for the evaluation of outcome measures, please see the following references: Browne JP, Cano SJ. A Rasch measurement theory approach to improve the interpretation of patient-reported outcomes. *Med Care*. 2019;57(Suppl 5 Suppl 1):S18-S23; and data supplement to van Nes SI, et al. Appendix e-1 supplemental data: Explaining Rasch to neurologists: Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology*. 2011;76(4):337-345.

Abbreviations: AChR Ab+, positive for autoantibodies against the acetylcholine receptor; BMWS, Bulbar Muscle Weakness scale; CFB, change from baseline; FcRn, neonatal Fc receptor; FV, final visit; (g)MG, (generalized) myasthenia gravis; IgG, immunoglobulin G; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MuSK Ab+, positive for autoantibodies against muscle-specific kinase; PRO, patient-reported outcome; QMG, Quantitative Myasthenia Gravis; RLZ, rozanolixizumab.

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