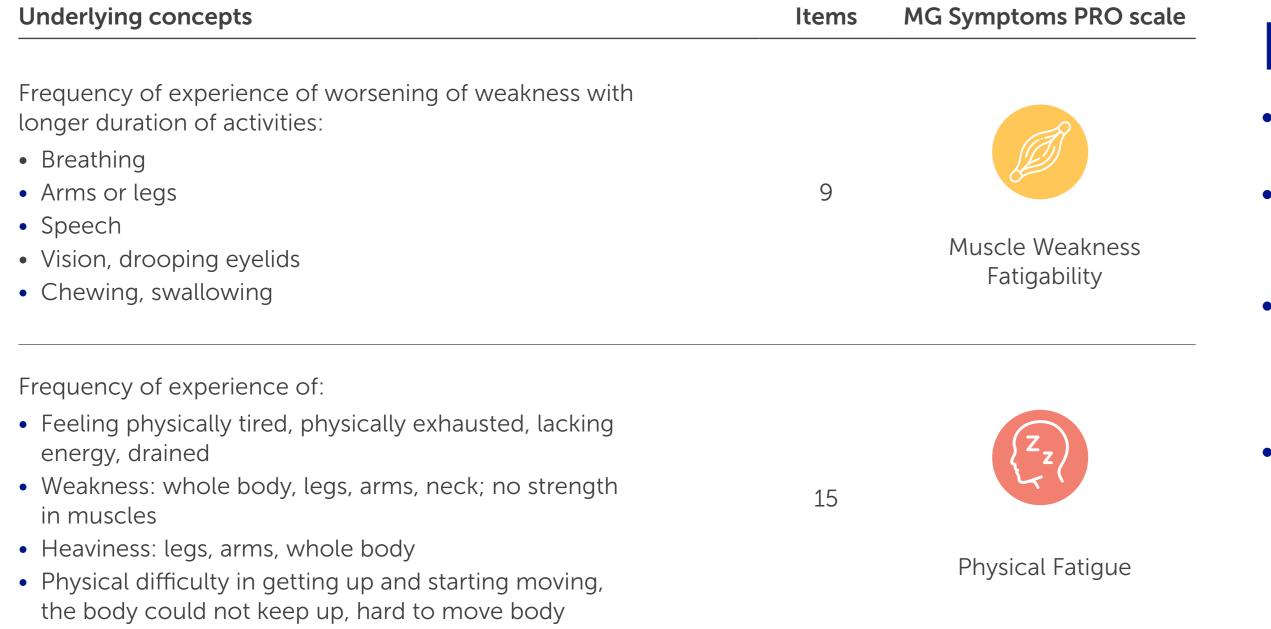# Clinically meaningful improvement in physical fatigue and muscle weakness fatigability with rozanolixizumab: *Post hoc* analysis of MG Symptoms PRO responder rates in the MycarinG study
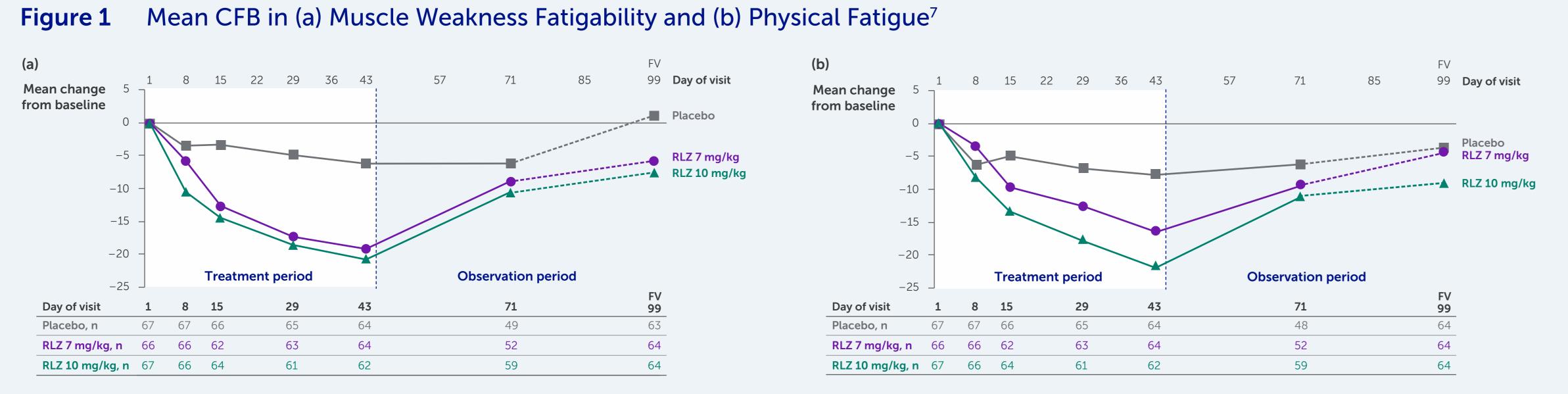
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Ali A. Habib[1], Henry J. Kaminski[2], Julian Grosskreutz[3], Renato Mantegazza[4], Tuan Vu[5], John Vissing[6], Marion Boehnlein[7], Bernhard Greve[7], Fiona Grimson[8], Asha Hareendran[8], Vera Bril[9]

[1]MDA ALS and Neuromuscular Center, University of California, Irvine, Irvine, CA, USA; [2]Department of Neurology & Rehabilitation Medicine, George Washington University, Washington, DC, USA; [3]Precision Neurology of Neuromuscular Diseases, Department of Neurology, University of Lübeck, Lübeck, Germany; [4]Department of Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS, Istituto Nazionale Neurologico Carlo Besta, Milan, Italy; [5]Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA; [6]Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [7]UCB Pharma, Monheim, Germany; [8]UCB Pharma, Slough, UK; [9]University Health Network, Toronto, ON, Canada

Introduction

- gMG is a chronic autoimmune disease affecting the neuromuscular junction, characterized by muscle fatigability, where symptoms worsen with sustained activity[1]
- Physical fatigue in gMG is associated with sensations ranging from tiredness to an overwhelming, debilitating and sustained sense of exhaustion, which can have a major impact on aspects of the day-to-day lives of patients such as physical, functional, social and mental activities[1–3]
  - Physical fatigue is strongly associated with reduced quality of life and the most common goal for symptom management expressed by patients with gMG is to reduce fatigue[4,5]
- Rozanolixizumab is a humanized IgG4 mAb FcRn inhibitor indicated for the treatment of adults with AChR Ab+ or MuSK Ab+ gMG[6]
- In the Phase 3, randomized, placebo-controlled, double-blind MycarinG study (MG0003/NCT03971422), one 6-week cycle of rozanolixizumab was generally well tolerated and provided clinically meaningful improvements in MG-ADL scores at Day 43[7]
  - Three MG Symptoms PRO scales were included as secondary endpoints in the MycarinG study
- The MG Symptoms PRO:
  - Measures core symptoms of MG based on findings from qualitative and quantitative research involving adults with gMG[2]
  - Includes scales that measure physical fatigue and muscle weakness fatigability (**Table 1**) – key aspects of patients' experiences with gMG that are not evaluated in the MG-ADL assessment
  - Is reliable, valid and sensitive to change[8]
- At Day 43 in MycarinG, compared with those receiving placebo, patients receiving rozanolixizumab achieved statistically significant improvements in Muscle Weakness Fatigability, Physical Fatigue (**Figure 1**) and Bulbar Muscle Weakness

Table 1   MG Symptoms PRO scales assessed in MycarinG[2]

Underlying concepts	Items	MG Symptoms PRO scale
Frequency of experience of worsening of weakness with longer duration of activities: • Breathing • Arms or legs • Speech • Vision, drooping eyelids • Chewing, swallowing	9	Muscle Weakness Fatigability
Frequency of experience of: • Feeling physically tired, physically exhausted, lacking energy, drained • Weakness: whole body, legs, arms, neck; no strength in muscles • Heaviness: legs, arms, whole body • Physical difficulty in getting up and starting moving, the body could not keep up, hard to move body	15	Physical Fatigue

Methods

- Enrolled patients were aged ≥18 years with AChR Ab+ or MuSK Ab+ gMG
- Patients received one 6-week cycle of once-weekly rozanolixizumab 7 mg/kg or 10 mg/kg, or placebo
- To complement the analysis of statistically significant improvements in mean CFB (secondary endpoint), responder definitions to understand the meaningfulness of these changes were developed (**Table 2**)
  - *Post hoc* analyses of blinded data from Day 29 of the MycarinG study, including anchor- and distribution-based methods, resulted in a range of values for each scale
  - Triangulation of these findings resulted in the selection of preliminary reference values for meaningful within-patient improvement
- *Post hoc* exploratory analyses to interpret the meaningfulness of the CFB results utilized cumulative distribution function plots of responses to depict the effect of treatment across the study sample by showing all magnitudes of changes[9,10]
- An Empirical Cumulative Distribution Function (eCDF) plot is a graphical tool used to visualize the distribution of the proportion of patients at each point along the scale score continuum who experience change at that level or lower
  - This approach helps visually compare the separation between groups across all levels of the PRO change score so that a variety of responder definitions can be considered simultaneously
- The proportion of responders across treatment groups was explored for the preliminary reference value and the higher (most stringent) threshold

Table 2   Estimated thresholds for meaningful within-patient symptom improvement (responders)

	Meaningful within-patient improvement estimates	
	Reference value*	Range of values
Muscle Weakness Fatigability	−16.67	−13.89 to −27.78
Physical Fatigue	−20.00	−16.67 to −26.67

Preliminary reference values* and the range of values from all anchor- and distribution-based methods are presented.
The sum of the responses to the items composing each scale undergoes linear transformation to generate a score of 0–100.

Results

- A total of 200 patients received either rozanolixizumab 7 mg/kg (n=66), 10 mg/kg (n=67) or placebo (n=67)[7]
- Rozanolixizumab had an acceptable safety profile and was generally well tolerated, with similar occurrences of TEAEs across both rozanolixizumab doses[7]
- At Day 43, eCDF plots illustrate that the proportion of responders in both rozanolixizumab treatment groups was higher compared with the placebo group at both the reference value and the higher threshold for meaningful within-patient symptom improvement (**Figure 2**)
- At Day 43, meaningful improvement in Bulbar Muscle Weakness (reference value: −20.00, higher threshold: −26.67) was achieved by:
  - 10.9%, 26.6% and 32.3% of patients receiving placebo, rozanolixizumab 7 mg/kg and 10 mg/kg at the reference value
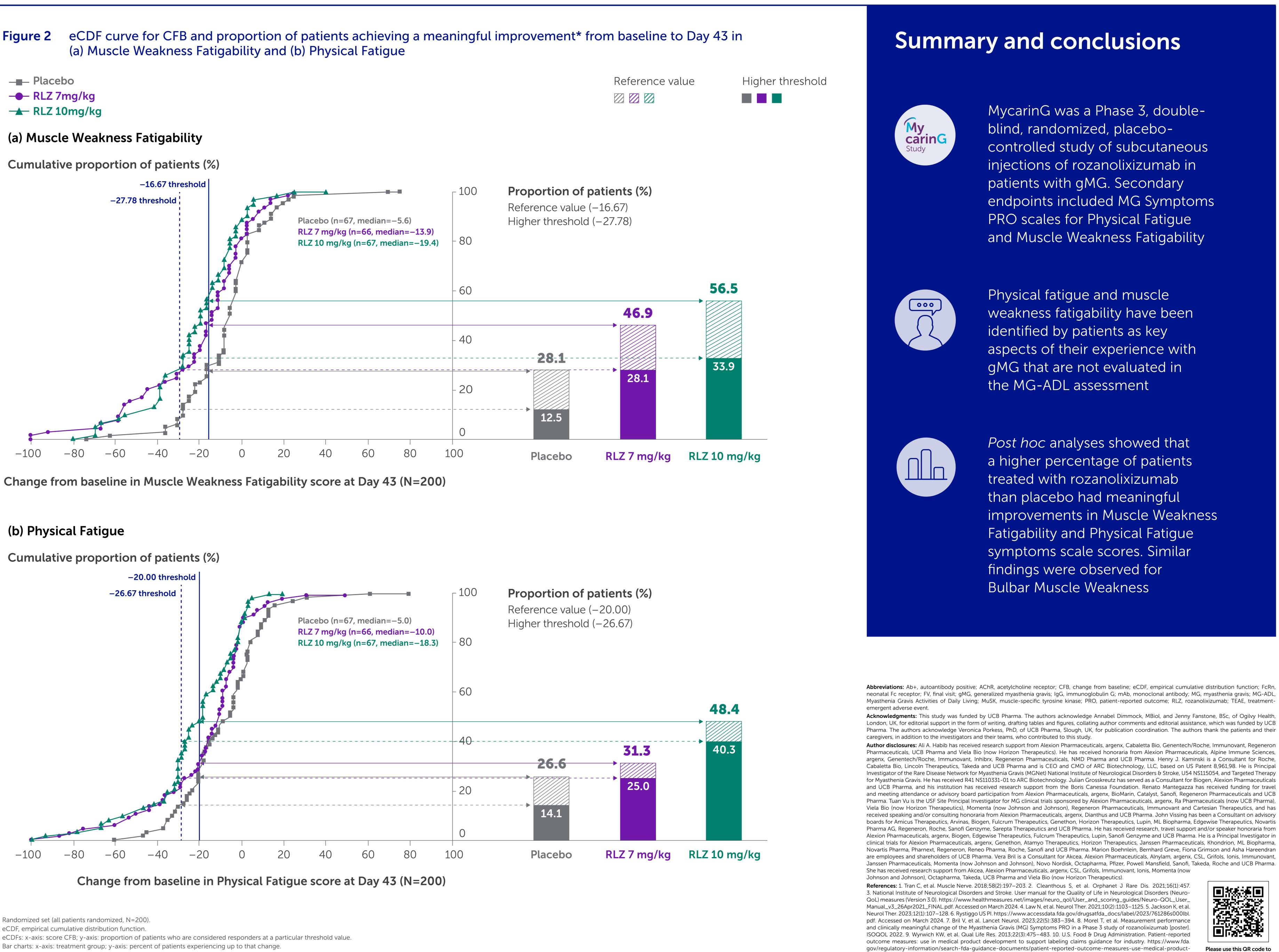 - 4.7%, 21.9% and 22.6% of patients receiving placebo, rozanolixizumab 7 mg/kg and 10 mg/kg at the higher threshold

Figure 1   Mean CFB in (a) Muscle Weakness Fatigability and (b) Physical Fatigue[7]

(a)

Day of visit	1	8	15	29	43	57	71	FV 99
Placebo, n	67	67	66	65	64		48	64
RLZ 7 mg/kg, n	66	66	66	63	63		52	64
RLZ 10 mg/kg, n	67	66	64	61	62		59	64

(b)

Day of visit	1	8	15	29	43	57	71	FV 99
Placebo, n	67	67	66	65	64		48	64
RLZ 7 mg/kg, n	66	66	66	63	64		52	64
RLZ 10 mg/kg, n	67	66	64	61	62		59	64

Figure 2   eCDF curve for CFB and proportion of patients achieving a meaningful improvement* from baseline to Day 43 in (a) Muscle Weakness Fatigability and (b) Physical Fatigue

(a) Muscle Weakness Fatigability

Change from baseline in Muscle Weakness Fatigability score at Day 43 (N=200)

Placebo (n=67, median=−5.6)
RLZ 7 mg/kg (n=66, median=−13.9)
RLZ 10 mg/kg (n=67, median=−19.4)

Proportion of patients (%)
Reference value (−16.67)
Higher threshold (−27.78)

(b) Physical Fatigue

Change from baseline in Physical Fatigue score at Day 43 (N=200)

Placebo (n=67, median=−5.0)
RLZ 7 mg/kg (n=66, median=−10.0)
RLZ 10 mg/kg (n=67, median=−18.3)

Proportion of patients (%)
Reference value (−20.00)
Higher threshold (−26.67)

Randomized set (all patients randomized, N=200).
eCDF, empirical cumulative distribution function.
eCDFs: x-axis: score CFB; y-axis: proportion of patients who are considered responders at a particular threshold value.
Bar charts: x-axis: treatment group; y-axis: percent of patients experiencing up to that change.
*Defined using the preliminary reference value and the higher (most stringent) threshold of the range of values for each scale.

Summary and conclusions

- MycarinG was a Phase 3, double-blind, randomized, placebo-controlled study of subcutaneous injections of rozanolixizumab in patients with gMG. Secondary endpoints included MG Symptoms PRO scales for Physical Fatigue and Muscle Weakness Fatigability

- Physical fatigue and muscle weakness fatigability have been identified by patients as key aspects of their experience with gMG that are not evaluated in the MG-ADL assessment

- *Post hoc* analyses showed that a higher percentage of patients treated with rozanolixizumab than placebo had meaningful improvements in Muscle Weakness Fatigability and Physical Fatigue symptoms scale scores. Similar findings were observed for Bulbar Muscle Weakness

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Table 1 MG Symptoms PRO scales assessed in MycarinG[1]

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1. Cleanthous S, et al. Orphanet J Rare Dis. 2021;16(1):457.
MG, myasthenia gravis; PRO, patient reported outcomes.

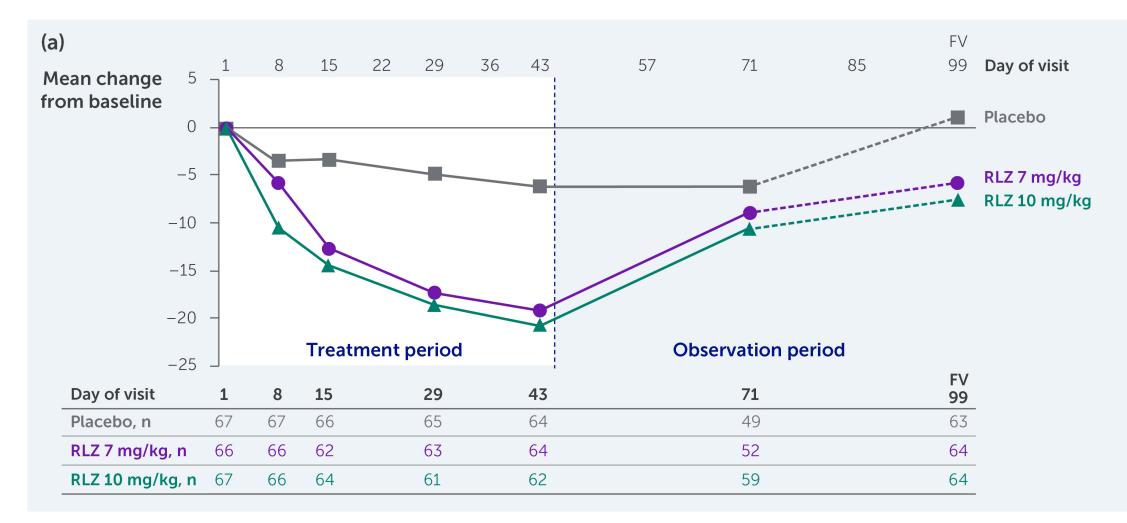# Figure 1 Mean CFB in (a) Muscle Weakness Fatigability and (b) Physical Fatigue[1]

(a)

Day of visit	1	8	15	29	43	71	FV 99
Placebo, n	67	67	66	65	64	49	63
RLZ 7 mg/kg, n	66	66	62	63	64	52	64
RLZ 10 mg/kg, n	67	66	64	61	62	59	64

1. Bril V, et al. Lancet Neurol. 2023;22(5):383–394.
CFB, change from baseline; RLZ, rozanolixizumab.

Figure 1 Mean CFB in (a) Muscle Weakness Fatigability and (b) Physical Fatigue[1]

(b)

Mean change from baseline

Day of visit	1	8	15	29	43	71	FV 99
Placebo, n	67	67	66	65	64	48	64
RLZ 7 mg/kg, n	66	66	62	63	64	52	64
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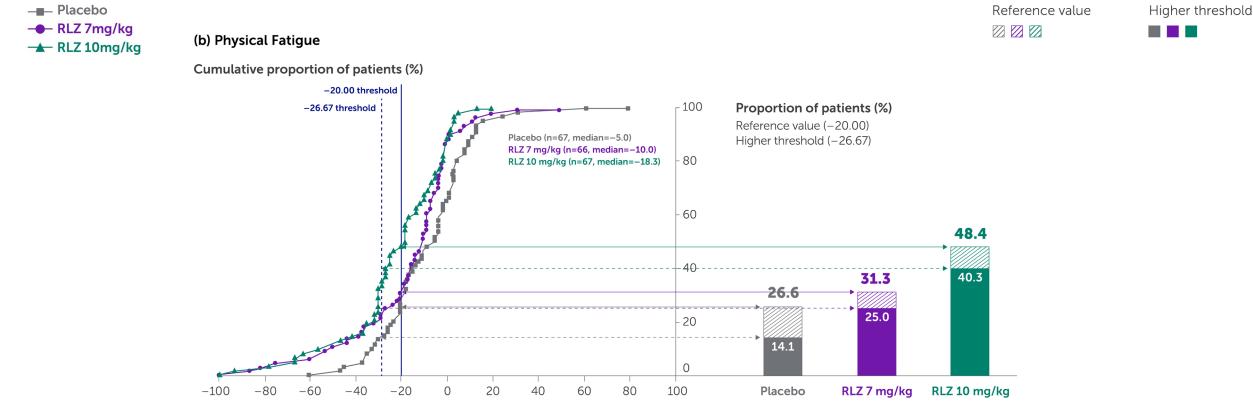

Placebo
RLZ 7mg/kg
RLZ 10mg/kg

Reference value

Higher threshold

(a) Muscle Weakness Fatigability

Cumulative proportion of patients (%)

−16.67 threshold
−27.78 threshold

Placebo (n=67, median=−5.6)
RLZ 7 mg/kg (n=66, median=−13.9)
RLZ 10 mg/kg (n=67, median=−19.4)

Proportion of patients (%)
Reference value (−16.67)
Higher threshold (−27.78)

56.5
46.9
28.1
33.9
28.1
12.5

Placebo   RLZ 7 mg/kg   RLZ 10 mg/kg

−100 −80 −60 −40 −20 0 20 40 60 80 100

Change from baseline in Muscle Weakness Fatigability score at Day 43 (N=200)

Randomized set (all patients randomized, N=200)
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(b) Physical Fatigue

Placebo (n=67, median=−5.0)
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Proportion of patients (%)
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Change from baseline in Physical Fatigue score at Day 43 (N=200)

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Post hoc analyses showed that a higher percentage of patients treated with rozanolixizumab than placebo had meaningful improvements in Muscle Weakness Fatigability and Physical Fatigue symptoms scale scores. Similar findings were observed for Bulbar Muscle Weakness

gMG, generalized myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; PRO, patient reported outcomes.