Repeated cycles of rozanolixizumab treatment in patients with muscle-specific kinase autoantibody-positive generalized myasthenia gravis

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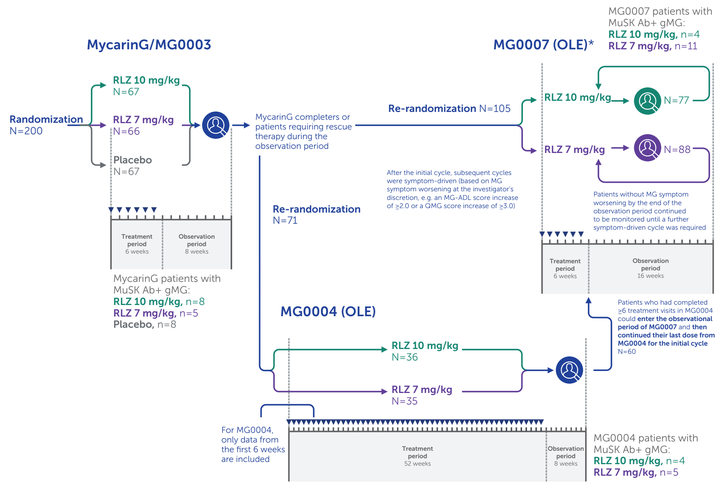
Introduction

- MuSK Ab+ gMG affects 5–8% of patients with MG and is often more severe than AChR Ab+ gMG; treatment of MuSK Ab+ gMG is challenging, with treatments used for AChR Ab+ gMG, such as AChEIs, generally unsatisfactory[1]
- Rozanolixizumab is a humanized IgG4 monoclonal antibody FcRn inhibitor approved by the US FDA for the treatment of adults with AChR or MuSK Ab+ gMG[2,3]
- Here, we assessed efficacy of rozanolixizumab in patients with MuSK Ab+ gMG using data pooled across the Phase 3 MycarinG study (MG0003/NCT03971422)[2] and its OLE studies

Methods

- MycarinG enrolled patients aged ≥18 years with AChR Ab+ or MuSK Ab+ gMG, MGFA Disease Class II–IVa, MG-ADL score ≥3 (for non-ocular symptoms), and QMG score ≥11; randomization was stratified by the presence of AChR or MuSK autoantibodies
- After completing MycarinG, patients could enroll in MG0004 (NCT04124965) and then MG0007 (NCT04650854), or in MG0007 directly (**Figure 1**)
- Data were pooled across MycarinG, MG0004 (first 6 weeks), and MG0007 (interim analysis; data cut-off: July 8, 2022)
  - Efficacy pool: Patients with ≥2 symptom-driven treatment cycles
  - Safety pool: Patients with ≥1 treatment cycle that was followed by an up to 8-week follow-up period (MycarinG and MG0007 data only)
- Efficacy outcomes included change from baseline at Day 43 for each cycle in MG-ADL, MGC and QMG scores, MG-ADL (≥2.0-point improvement from baseline), MGC and QMG (both ≥3.0-point improvement from baseline) responders, MSE response and time to symptom-driven cycle
- Safety and tolerability of rozanolixizumab were also assessed

Figure 1 MycarinG and OLE study design



*After the initial cycle, dose modifications from 10 mg/kg to 7 mg/kg and *vice versa* were permitted at the beginning of each treatment cycle provided the benefit–risk ratio remained favorable for the patient.

Results

Patients

- In total, 196 patients received ≥1 dose of rozanolixizumab; 127 (64.8%) of these patients were included in the efficacy pool (initial rozanolixizumab 7 mg/kg cycle: n=69 [MuSK Ab+: n=9]; initial rozanolixizumab 10 mg/kg cycle: n=58 [MuSK Ab+: n=3])
  - The safety pool included 188 (95.9%) patients (initial rozanolixizumab 7 mg/kg cycle: n=94 [MuSK Ab+: n=9]); initial rozanolixizumab 10 mg/kg cycle: n=94 [MuSK Ab+: n=9])
- Baseline demographics and characteristics for patients in the efficacy pool are reported in **Table 1**

Efficacy

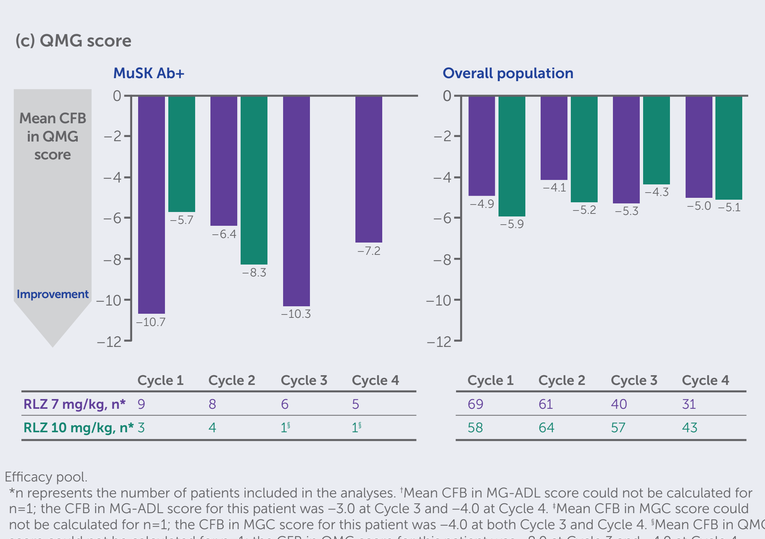
- Clinically meaningful improvement from baseline in MG-ADL score was observed for the MuSK Ab+ and overall populations at Day 43 in Cycle 1; consistent improvement was observed following repeated treatment cycles (**Figure 2a**)
  - Clinically meaningful improvements from baseline were also observed for MGC and QMG scores at Day 43 (**Figure 2b–c**)
- High rates of MG-ADL, MGC and QMG responders among patients with MuSK Ab+ gMG and in the overall population were observed at Day 43 in Cycle 1 and consistently reported following repeated cycles of treatment (**Figure 3**)
- In the overall population, MSE was consistently reached in >26.1% of patients treated with rozanolixizumab 7 mg/kg and >20.7% of patients treated with rozanolixizumab 10 mg/kg across Cycles 1–4 (**Figure 4**)
  - In patients with MuSK Ab+ gMG, MSE was achieved in >25.0% of patients treated with rozanolixizumab 7 mg/kg and >33.3% of patients treated with rozanolixizumab 10 mg/kg across Cycles 1 and 2 (**Figure 4**)
- The estimated median (Q1, Q3) treatment-free interval to the first symptom-driven cycle was 63 days (36, 105) for the overall population and 75 days (36, 209) for patients with MuSK Ab+ gMG[a]

Table 1 Baseline demographics and characteristics

		RLZ 7 mg/kg		RLZ 10 mg/kg		RLZ total	
		Overall population* (n=69)	MuSK Ab+ subgroup† (n=9)	Overall population* (n=58)	MuSK Ab+ subgroup† (n=3)	Overall population* (N=127)	MuSK Ab+ subgroup† (N=12)
Age, years, mean (SD)		**52.0** (14.3)	**47.8** (8.4)	**48.9** (18.3)	**43.7** (18.3)	**50.6** (16.2)	**46.8** (10.8)
Sex, female, n (%)		**40** (58.0)	**6** (66.7)	**36** (62.1)	**3** (100.0)	**76** (59.8)	**9** (75.0)
Thymectomy at baseline, yes, n (%)‡		**33** (47.8)	**2** (22.2)	**22** (37.9)	**0**	**55** (43.3)	**2** (16.7)
MG-ADL score at baseline, mean (SD)		**9.1** (3.8)	**10.2** (3.6)	**8.4** (2.9)	**8.7** (3.2)	**8.8** (3.4)	**9.8** (3.5)
QMG score at baseline, mean (SD)		**16.0** (3.8)	**17.8** (4.7)	**16.0** (3.7)	**15.7** (4.6)	**16.0** (3.8)	**17.3** (4.5)
Duration of disease, years, mean (SD)		**7.9** (8.4)	**10.4** (8.7)	**8.5** (8.9)	**7.9** (6.0)	**8.2** (8.6)	**9.8** (8.0)
Geographic region, n (%)	North America	**19** (27.5)	**1** (11.1)	**9** (15.5)	**0**	**28** (22.0)	**1** (8.3)
	Europe	**40** (58.0)	**6** (66.7)	**44** (75.9)	**2** (66.7)	**84** (66.1)	**8** (66.7)
	Asia (excl. Japan)	**2** (2.9)	**1** (11.1)	**1** (1.7)	**0**	**3** (2.4)	**1** (8.3)
	Japan	**8** (11.6)	**1** (11.1)	**4** (6.9)	**1** (33.3)	**12** (9.4)	**2** (16.7)

Efficacy pool.
*Includes patients with AchR Ab+ and MuSK Ab+ gMG. †MuSK antibody status was captured from historical data case report form. ‡Captured from medical history and procedure history case report form.

Figure 2 Mean CFB at Day 43 in (a) MG-ADL (b) MGC and (c) QMG score



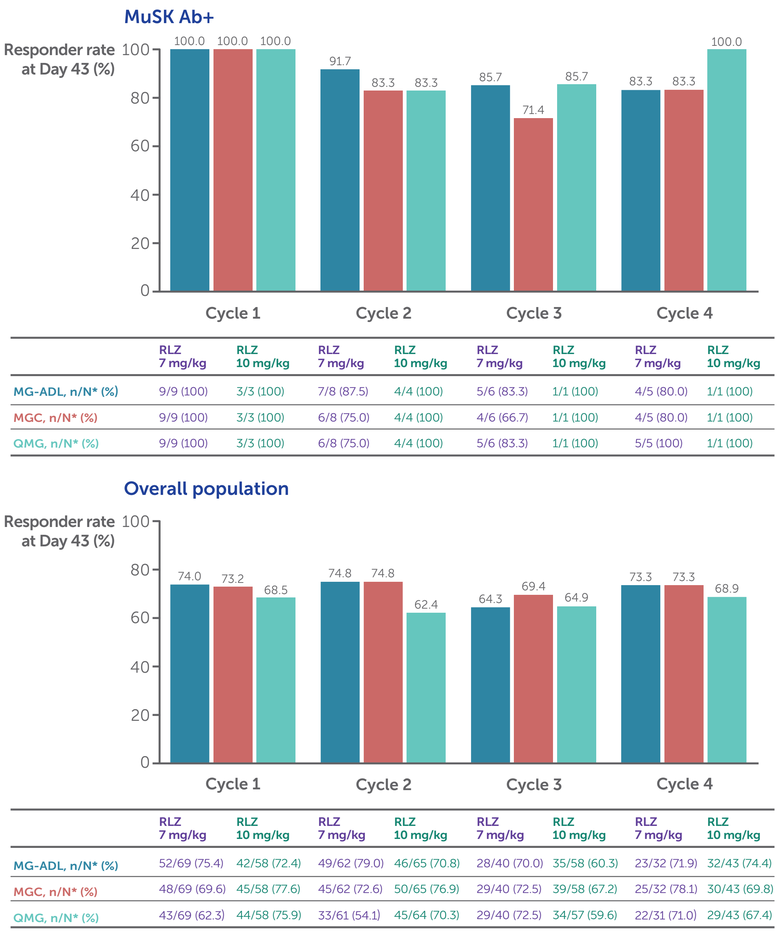
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 1	Cycle 2	Cycle 3	Cycle 4
RLZ 7 mg/kg, n*	9	8	6	5	69	62	40	32
RLZ 10 mg/kg, n*	3	4	1‡	1‡	58	65	58	43

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 1	Cycle 2	Cycle 3	Cycle 4
RLZ 7 mg/kg, n*	9	8	6	5	69	61	40	32
RLZ 10 mg/kg, n*	3	4	1‡	1‡	58	65	57	43

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 1	Cycle 2	Cycle 3	Cycle 4
RLZ 7 mg/kg, n*	9	8	6	5	69	61	40	31
RLZ 10 mg/kg, n*	3	4	1‡	1‡	58	64	57	43

Efficacy pool.
*n represents the number of patients included in the analyses. †Mean CFB in MG-ADL score could not be calculated for n=1; the CFB in MG-ADL score for this patient was −3.0 at Cycle 3 and −4.0 at Cycle 4. ‡Mean CFB in MGC score could not be calculated for n=1; the CFB in MGC score for this patient was −4.0 at both Cycle 3 and Cycle 4. §Mean CFB in QMG score could not be calculated for n=1; the CFB in QMG score for this patient was −8.0 at Cycle 3 and −4.0 at Cycle 4.

Figure 3 MG-ADL, MGC and QMG response rate at Day 43 (RLZ total and by dose)

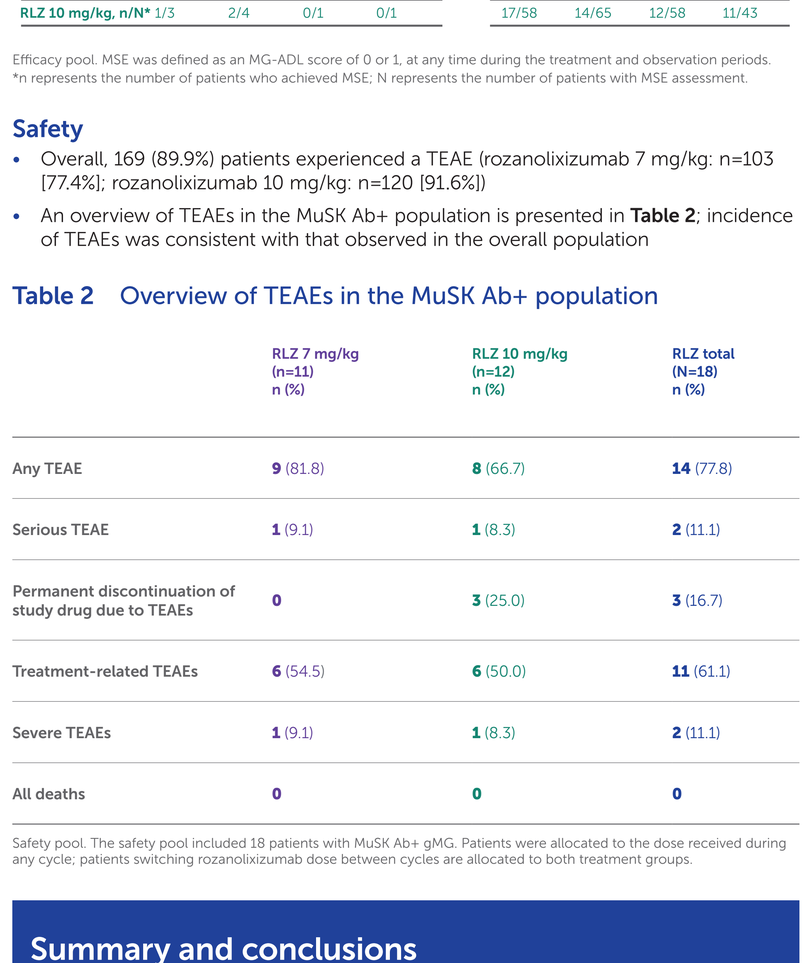


	RLZ 7 mg/kg	RLZ 10 mg/kg	RLZ 7 mg/kg	RLZ 10 mg/kg	RLZ 7 mg/kg	RLZ 10 mg/kg	RLZ 7 mg/kg	RLZ 10 mg/kg
MG-ADL, n/N* (%)	9/9 (100)	3/3 (100)	7/8 (87.5)	4/4 (100)	5/6 (83.3)	1/1 (100)	4/5 (80.0)	1/1 (100)
MGC, n/N* (%)	9/9 (100)	3/3 (100)	6/8 (75.0)	4/4 (100)	4/6 (66.7)	1/1 (100)	4/5 (80.0)	1/1 (100)
QMG, n/N* (%)	9/9 (100)	3/3 (100)	6/8 (75.0)	4/4 (100)	5/6 (83.3)	1/1 (100)	5/5 (100)	1/1 (100)

	RLZ 7 mg/kg	RLZ 10 mg/kg	RLZ 7 mg/kg	RLZ 10 mg/kg	RLZ 7 mg/kg	RLZ 10 mg/kg	RLZ 7 mg/kg	RLZ 10 mg/kg
MG-ADL, n/N* (%)	52/69 (75.4)	42/58 (72.4)	49/62 (79.0)	46/65 (70.8)	28/40 (70.0)	35/58 (60.3)	23/32 (71.9)	32/43 (74.4)
MGC, n/N* (%)	48/69 (69.6)	45/58 (77.6)	45/62 (72.6)	50/65 (76.9)	29/40 (72.5)	39/58 (67.2)	25/32 (78.1)	30/43 (69.8)
QMG, n/N* (%)	43/69 (62.3)	44/58 (75.9)	33/61 (54.1)	45/64 (70.3)	29/40 (72.5)	34/57 (59.6)	22/31 (71.0)	29/43 (67.4)

Efficacy pool.
*n represents the number of patients who were responders at Day 43; N represents the number of patients who completed the outcome measure assessment at Day 43.

Figure 4 MSE at Day 43



	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 1	Cycle 2	Cycle 3	Cycle 4
RLZ 7 mg/kg, n/N*	4/9	2/8	1/6	1/5	18/69	20/62	13/40	13/32
RLZ 10 mg/kg, n/N*	1/3	2/4	0/1	0/1	17/58	14/65	12/58	11/43

Efficacy pool. MSE was defined as an MG-ADL score of 0 or 1, at any time during the treatment and observation periods.
*n represents the number of patients who achieved MSE; N represents the number of patients with MSE assessment.

Safety

- Overall, 169 (89.9%) patients experienced a TEAE (rozanolixizumab 7 mg/kg: n=103 [77.4%]; rozanolixizumab 10 mg/kg: n=120 [91.6%])
- An overview of TEAEs in the MuSK Ab+ population is presented in **Table 2**; incidence of TEAEs was consistent with that observed in the overall population

Table 2 Overview of TEAEs in the MuSK Ab+ population

	RLZ 7 mg/kg (n=11) n (%)	RLZ 10 mg/kg (n=12) n (%)	RLZ total (N=18) n (%)
Any TEAE	**9** (81.8)	**8** (66.7)	**14** (77.8)
Serious TEAE	**1** (9.1)	**1** (8.3)	**2** (11.1)
Permanent discontinuation of study drug due to TEAEs	**0**	**3** (25.0)	**3** (16.7)
Treatment-related TEAEs	**6** (54.5)	**6** (50.0)	**11** (61.1)
Severe TEAEs	**1** (9.1)	**1** (8.3)	**2** (11.1)
All deaths	**0**	**0**	**0**

Safety pool. The safety pool included 18 patients with MuSK Ab+ gMG. Patients were allocated to the dose received during any cycle; patients switching rozanolixizumab dose between cycles are allocated to both treatment groups.

Summary and conclusions

Rozanolixizumab efficacy in patients with MuSK Ab+ gMG was maintained over repeated treatment cycles and multiple endpoints, consistent with findings in the overall population

Rozanolixizumab represents a novel treatment option for patients with MuSK Ab+ gMG, a subtype of MG that can be severe and challenging to treat[1]

Rozanolixizumab was well tolerated and had an acceptable safety profile over repeated cycles of treatment in patients with MuSK Ab+ gMG and the overall population

Footnotes: [a]Calculated using data from an additional efficacy pool (N=167; MuSK Ab+ gMG: n=16), which included patients who had received rozanolixizumab treatment and had initiated or were waiting for the next symptom-driven treatment cycle based on gMG symptom worsening. Patients without a symptom-driven cycle after rozanolixizumab treatment (waiting for a symptom-driven cycle) are censored at time of dropping-out, data cut-off date or end of the study (MycarinG or MG0007).

Abbreviations: AChEI, acetylcholinesterase inhibitor; AChR Ab+, positive for autoantibodies against the acetylcholine receptor; CFB, change from baseline; FcRn, neonatal Fc receptor; FDA, Food and Drug Administration; (g)MG, (generalized) myasthenia gravis; IgG4, immunoglobulin G4; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MSE, minimal symptom expression; MuSK Ab+, positive for autoantibodies against muscle-specific kinase; OLE, open-label extension; Q[x], quartile [x]; QMG, Quantitative Myasthenia Gravis; RLZ, rozanolixizumab; SD, standard deviation; TEAE, treatment-emergent adverse event; US, United States.

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