Rozanolixizumab in generalized myasthenia gravis: Responder analyses from the randomized Phase 3 MycarinG study

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Summary

What we did

- MycarinG was a randomized, double-blind, placebo-controlled Phase 3 study of two doses of subcutaneous rozanolixizumab (7 mg/kg and 10 mg/kg) for the treatment of gMG

What we found

- Both doses of rozanolixizumab achieved highly statistically significant and clinically meaningful improvement in MG-ADL score at Day 43, compared with placebo
- MG-ADL, MGC and QMG responder rates were higher for both doses of rozanolixizumab than for placebo
- Both doses of rozanolixizumab also showed greater improvement in MSE rates than placebo

Why it matters

- These data further substantiate the therapeutic benefit of targeting FcRn in the treatment of gMG
- These results suggest that rozanolixizumab has potential as a new treatment option for patients with gMG

Introduction

- gMG is a rare, chronic, unpredictable autoimmune disease caused by pathogenic IgG autoantibodies that disrupt neuromuscular junction components such as AChR and MuSK[1]
- As many as one in three patients do not respond to conventional treatments, highlighting an unmet need for efficacious, well-tolerated treatment options[2]
- Rozanolixizumab is a fully humanized IgG4 mAb that targets the IgG-binding region of FcRn, which accelerates the lysosomal degradation of IgG, including pathogenic autoantibodies[3]

Methods

- MycarinG (MG0003/NCT03971422) was a Phase 3, double-blind, randomized, placebo-controlled study (**Figure 1**)
- Inclusion criteria:
  - Patients with gMG aged ≥18 years
  - AChR or MuSK autoantibody positive
  - MGFA Class II–IVa disease, MG-ADL score of ≥3 and a QMG score of ≥11
  - Considered for additional therapy such as IVIg or PLEX
- Patients were randomized 1:1:1 to receive weekly placebo, rozanolixizumab 7 mg/kg, or rozanolixizumab 10 mg/kg for a 6-week treatment period, followed by an 8-week observation period
- Patients who required rescue therapy were treated as missing at and after that point; patients who discontinued treatment or the study due to TEAEs, COVID-19, or other infections, were included in the analysis
- The primary endpoint was CFB to Day 43 in MG-ADL score
- Other endpoints included the proportion of responders, defined as having ≥2.0-point improvement in MG-ADL (which included a statistically tested MG-ADL composite analysis) or ≥3.0-point improvement in QMG or MGC, which were descriptive
- Additional other endpoints included MSE (MG-ADL score of 0 or 1), Day 43 CFB in MGII scores and sub-scores, Day 43 CFB in MG-QoL 15r (a health-related quality-of-life assessment) and safety

Results

Patients

- Overall, 200 patients were randomized to placebo (n=67), rozanolixizumab 7 mg/kg (n=66), and rozanolixizumab 10 mg/kg (n=67), with 43 completing the study in each rozanolixizumab arm and 42 in the placebo group
- Baseline characteristics were generally balanced between treatment groups (**Table 1**)

Efficacy

- The primary endpoint of CFB in MG-ADL at Day 43 was highly statistically significant and clinically meaningfully improved for both rozanolixizumab doses compared with placebo (p<0.001 for both doses) (**Figure 2**)
- There was a statistically significant increase in the responder rates for MG-ADL in both arms of rozanolixizumab (both p<0.001) when compared with placebo
  - MGC and QMG responder rates were also higher for rozanolixizumab than placebo (**Figure 3**)
- MSE was achieved by a greater proportion of patients in both rozanolixizumab arms than in the placebo arm (**Figure 4**)
- The mean CFB for MG-QoL 15r and MGII scores and sub-scores at Day 43 was greater for both rozanolixizumab dose groups than placebo (**Figure 5**)

Safety

- A higher proportion of patients experienced TEAEs in the rozanolixizumab 7 mg/kg (81.3%) and 10 mg/kg (82.6%) arms than in the placebo arm (67.2%) (**Table 2**)
- Most TEAEs were of mild or moderate intensity, and rates of TEAEs leading to treatment discontinuation were generally low (**Table 2**)
- The most common TEAEs for rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg and placebo were headache (45.3%, 37.7%, 19.4%), diarrhea (25.0%, 15.9% and 13.4%), pyrexia (12.5%, 20.3% and 1.5%) and nausea (7.8%, 11.6% and 7.5%)
- Headaches were mostly mild to moderate; generally, severe headache was well managed with non-opioid analgesics
- Infections were reported in 15.6% of patients in the rozanolixizumab 7 mg/kg group, 30.4% in the rozanolixizumab 10 mg/kg group and 19.4% in the placebo group; there were no severe or serious infections in active treatment arms
- Overall, infusions were well tolerated
- No serious hypersensitivity reactions were reported

Table 1 Baseline patient characteristics and disposition

		Placebo (n=67)	RLZ 7 mg/kg (n=66)	RLZ 10 mg/kg (n=67)
Age, years, mean (SD)		50.4 (17.7)	53.2 (14.7)	51.9 (16.5)
Sex, female, n (%)		47 (70.1)	39 (59.1)	35 (52.2)
Body weight, n (%)	<50 kg	4 (6.0)	7 (10.6)	1 (1.5)
	50 to <70 kg	16 (23.9)	19 (28.8)	26 (38.8)
	70 to <100 kg	35 (52.2)	26 (39.4)	22 (32.8)
	≥100 kg	12 (17.9)	14 (21.2)	18 (26.9)
Geographic region, n (%)	North America	21 (31.3)	21 (31.8)	18 (26.9)
	Europe	41 (61.2)	36 (54.5)	43 (64.2)
	Asia (incl. Japan)	5 (7.5)	9 (13.6)	6 (9.0)
Race, n (%)	Asian	5 (7.5)	9 (13.6)	7 (10.4)
	Black	1 (1.5)	0	4 (6.0)
	Native Hawaiian/ other Pacific Islander	1 (1.5)	0	0
	White	46 (68.7)	41 (62.1)	49 (73.1)
	Missing*	14 (20.9)	16 (24.2)	7 (10.4)
Disease duration, years, mean (SD)	Age at initial MG diagnosis	41.4 (19.1)	46.6 (16.0)	42.6 (19.1)
	Duration of disease	9.4 (9.3)	6.9 (6.8)	9.6 (9.9)
MGFA disease class at baseline, n (%)	Class II	23 (34.3)	29 (43.9)	26 (38.8)
	Class III	41 (61.2)	34 (51.5)	39 (58.2)
	Class IVa/b†	3 (4.5)	3 (4.5)	2 (3.0)
Baseline medications, n (%)	Corticosteroids for systemic use	38 (56.7)	43 (65.2)	48 (71.6)
	Immunosuppressants	33 (49.3)	32 (48.5)	38 (56.7)
	Parasympathomimetics (AChEIs)	60 (89.6)	55 (83.3)	57 (85.1)

*Data on race were not permitted to be collected in certain countries.
†Only 1 patient, who was randomized to the placebo group, had Class IVb disease.

Table 2 Overview of TEAEs

Preferred term	Placebo (n=67) n (%)	RLZ 7 mg/kg (n=64) n (%)*	RLZ 10 mg/kg (n=69) n (%)*
Any TEAE	45 (67.2)	52 (81.3)	57 (82.6)
Serious TEAEs	6 (9.0)	5 (7.8)	7 (10.1)
Patient withdrawal from study due to TEAEs	2 (3.0)	2 (3.1)	5 (7.2)
Patient withdrawal of IMP due to TEAEs	2 (3.0)	2 (3.1)	4 (5.8)
Treatment-related TEAEs†	22 (32.8)	32 (50.0)	39 (56.5)
Severe TEAEs	3 (4.5)	3 (4.7)	13 (18.8)
All deaths (AEs leading to death)	0	0	0

*Two patients in the 7 mg/kg group who incorrectly received 10 mg/kg were analyzed in the 10 mg/kg group for safety analyses.
†Treatment-related TEAEs, as assessed by investigators. Assessed in the safety set.

Figure 1 MycarinG study design

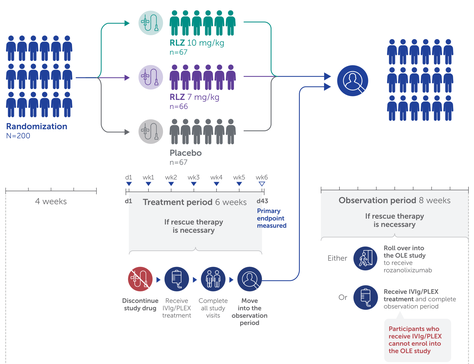


Figure 2 MycarinG primary endpoint: LS mean MG-ADL score CFB at Day 43

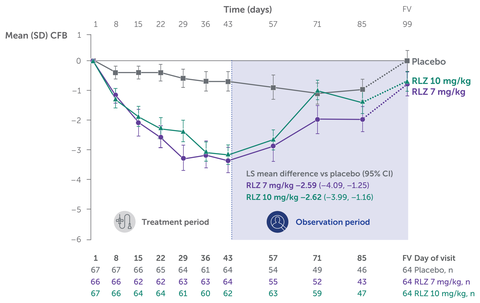
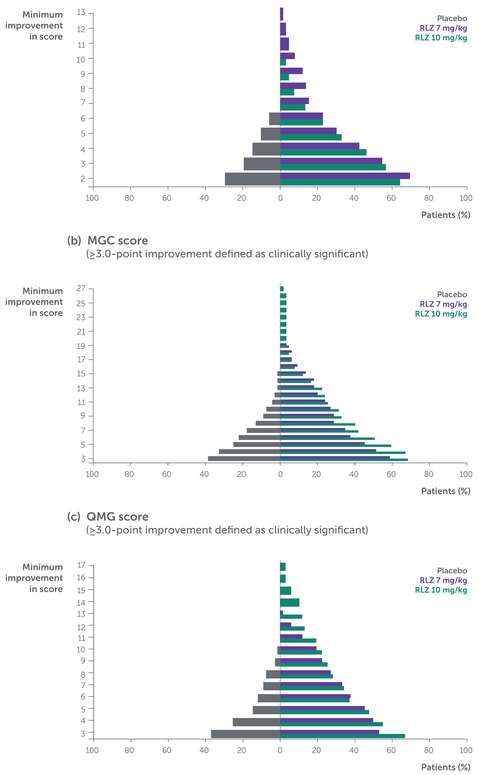


Figure 3 Day 43 response in (a) MG-ADL, (b) MGC, and (c) QMG



*Responder rates for MG-ADL were compared between RLZ treatment groups and placebo utilizing odds ratios based on a logistic regression analysis, with OR (CI) of 7.918 (2.068, 30.314) for 7 mg/kg and 7.191 (1.911, 27.055) for 10 mg/kg (both p<0.001).

Conclusions

- Both rozanolixizumab doses resulted in highly statistically significant and clinically meaningful improvements in MG-ADL CFB to Day 43 compared with placebo
- Additionally, MG-ADL, MGC and QMG responder rates were higher for both doses of rozanolixizumab than for placebo
- Rozanolixizumab had an acceptable safety profile and was generally well tolerated, with similar occurrences of TEAEs between both rozanolixizumab doses
- These results indicate that rozanolixizumab offers potential as a new treatment option for patients with gMG, and further substantiate the therapeutic benefit of targeting FcRn for patients with gMG

Figure 4 MSE

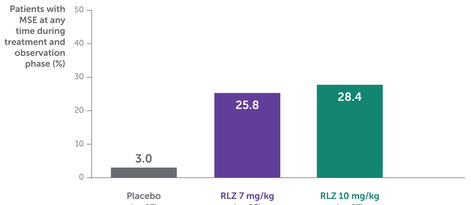


Figure 5 Mean CFB at Day 43 in (a) MG-QoL 15r and (b) MGII scores and sub-scores

Rozanolixizumab is an investigational new product and has not been approved by any authority.

Abbreviations: AChEI, acetylcholinesterase inhibitor; AChR, acetylcholine receptor; AE, adverse event; CFB, change from baseline; CI, confidence interval; d, day; FcRn, neonatal Fc receptor; FV, final visit; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; IMP, investigational medicinal product; IVIg, intravenous immunoglobulin; LS, least squares; mAb, monoclonal antibody; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MGII, Myasthenia Gravis Impairment Index; MG-QoL 15r, Myasthenia Gravis Quality of Life 15–item revised scale; MSE, Minimal Symptom Expression; MuSK, muscle-specific kinase; OLE, open-label extension; OR, odds ratio; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; RLZ, rozanolixizumab; SD, standard deviation; TEAE, treatment-emergent adverse event; wk, week.

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