Efficacy and safety of rozanolixizumab in patients with generalized myasthenia gravis: A randomized, multicenter, double-blind, placebo-controlled, Phase 3 study (MycarinG)

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Summary

There is an unmet need for targeted treatments for patients with gMG that are well tolerated

MycarinG assessed the efficacy and safety of the FcRn inhibitor rozanolixizumab in patients with gMG

Rozanolixizumab clinically meaningfully and statistically significantly improved MG-ADL, the study primary endpoint, and multiple MG-specific outcome measures compared to placebo

Rozanolixizumab was generally well tolerated

The efficacy and safety data from this study suggest that rozanolixizumab may provide benefit as a treatment option for gMG

Objective

- To assess the efficacy and safety of rozanolixizumab for the treatment of gMG

Introduction

- gMG is a rare, chronic, heterogeneous and unpredictable autoimmune disease that is characterized by muscle weakness and fatigue[1]
- Pathogenic IgG autoantibodies and complement activation impair the normal structure and function of the NMJ, leading to reduced muscle contraction[2,3]
- Unmet needs for treatment remain high; people living with gMG need targeted treatments that are well tolerated and combine a rapid onset of benefit with effective disease control[1,4]
- Rozanolixizumab is a humanized IgG4 monoclonal antibody that inhibits FcRn, reducing the concentration of pathogenic IgG autoantibodies[5]

Methods

- MycarinG (MG0003/NCT03971422) was a Phase 3, double-blind, randomized, placebo-controlled study
- The study included patients aged ≥18 years who were AChR or MuSK autoantibody positive, had MGFA Class II–IVa disease with an MG-ADL score of ≥3 and a QMG score of ≥11, were considered for treatment with additional therapy such as IVIg or plasma exchange and had a body weight of ≥35 kg
- Patients were randomized 1:1:1 to receive weekly rozanolixizumab 7 mg/kg, 10 mg/kg or placebo for 6 weeks, which was followed by an 8-week observation period (**Figure 1**)
- The primary endpoint was CFB to Day 43 in MG-ADL score
- Secondary endpoints included CFB to Day 43 in QMG and MGC and other endpoints included total IgG and anti-AChR autoantibody levels
- Safety and tolerability of rozanolixizumab were also assessed

Results

Patients

- A total of 66 patients were randomized to rozanolixizumab 7 mg/kg, 67 to rozanolixizumab 10 mg/kg and 67 to placebo, with 43 completing the study in both rozanolixizumab groups and 42 in the placebo group (**Figure 1**)
- Baseline characteristics were generally balanced between treatment groups (**Table 1**)

Efficacy

- MG-ADL change from baseline to Day 43 (primary outcome) in both rozanolixizumab groups was clinically meaningful and highly statistically significantly improved compared to placebo (p<0.001 for both doses; **Figure 2**)
- The improvement at Day 43 in QMG (**Figure 3**) and MGC (**Figure 4**) scores in both rozanolixizumab groups was highly statistically significantly greater than in placebo (p<0.001)
- Mean maximum total IgG reduction was 71% for rozanolixizumab 7 mg/kg, 78% for rozanolixizumab 10 mg/kg and 11% for placebo
  - Both doses of rozanolixizumab decreased IgG levels more than placebo during the treatment period (**Figure 5**), including subclasses 1, 2, 3 and 4
- Anti-AChR autoantibody levels decreased over the treatment period in line with the total IgG reduction (**Figure 6**)

Safety

- A higher proportion of TEAEs occurred in the rozanolixizumab 7 mg/kg (81.3%) and 10 mg/kg (82.6%) arms than in the placebo arm (67.2%) (**Table 2**)
  - The majority of TEAEs were mild or moderate in intensity
  - Headache (45.3%, 37.7% and 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%) were the most common TEAEs
  - Most headaches were of mild-to-moderate intensity, with severe headaches adequately managed with over-the-counter medications (non-opioid analgesics such as paracetamol or ibuprofen)
  - The incidence of infections was higher in the rozanolixizumab 10 mg/kg group (30.4%) than in the rozanolixizumab 7 mg/kg (15.6%) and placebo (19.4%) groups
  - Overall, infusions were well-tolerated with low incidence of local injection-site reactions reported
  - No serious or severe infections occurred in either rozanolixizumab group, with most infections of mild severity

Figure 1 Study design

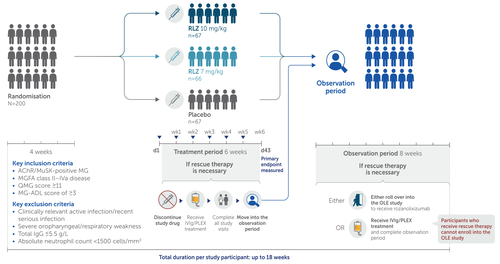


Table 1 Demographic and baseline characteristics

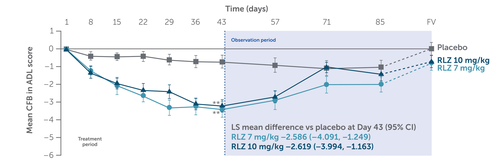
		Placebo (N=67)	RLZ 7 mg/kg (N=66)	RLZ 10 mg/kg (N=67)
Age, years, mean (SD)		50.4 (17.7)	53.2 (14.7)	51.9 (16.5)
Sex, female, n (%)		47 (70.1)	39 (59.1)	35 (52.2)
MGFA class at baseline, n (%)	Class II	23 (34.3)	29 (43.9)	26 (38.8)
	Class III	41 (61.2)	34 (51.5)	39 (58.2)
	Class IVa/b	3 (4.5)	3 (4.5)	2 (3.0)
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 (Inc, Japan)	5 (7.5)	9 (13.7)	6 (9.0)
Race, n (%)	Asian	5 (7.5)	9 (13.6)	7 (10.4)
	Black	1 (1.5)	0	4 (6.0)
	White	46 (68.7)	41 (62.1)	49 (73.1)
	Missing*	14 (20.9)	16 (24.2)	7 (10.4)
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	60 (89.6)	55 (83.3)	57 (85.1)
Duration of disease, years, mean (SD)		9.4 (9.3)	6.9 (6.8)	9.6 (9.9)
MG-ADL score at baseline, mean (SD)		8.4 (3.4)	8.4 (3.8)	8.1 (2.9)
QMG score at baseline, mean (SD)		15.8 (3.5)	15.4 (3.7)	15.6 (3.7)

*Data on race were not permitted to be collected in certain countries.

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 TEAEs	67.2 (45)	81.3 (52)	82.6 (57)
Serious TEAEs	9.0 (6)	7.8 (5)	10.1 (7)
Participant withdrawal from study due to TEAEs	3.0 (2)	3.1 (2)	7.2 (5)
Participant withdrawal of IMP due to TEAEs	3.0 (2)	3.1 (2)	5.8 (4)
Temporary withdrawal of IMP due to TEAEs	1.5 (1)	4.7 (3)	8.7 (6)
Treatment-related TEAEs	32.8 (22)	50.0 (32)	56.5 (39)
Severe TEAEs	4.5 (3)	4.7 (3)	18.8 (13)
All deaths (AEs leading to death)	0	0	0

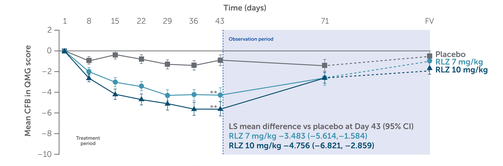
Figure 2 Mean CFB in MG-ADL



Day of visit	1	8	15	22	29	36	43	57	71	85	FV
Placebo n	67	67	66	65	64	61	64	54	49	46	64
RLZ 7 mg/kg n	66	66	62	62	63	63	64	55	52	43	64
RLZ 10 mg/kg n	67	66	64	64	61	60	62	63	59	57	64

**p<0.001 for LS mean CFB for both rozanolixizumab 7 mg/kg and 10 mg/kg treatment groups vs placebo at Day 43.
Final visit could occur on any day up to Day 99.

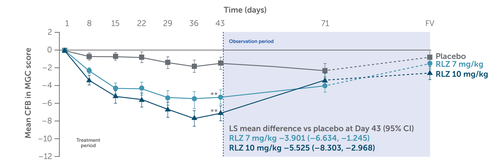
Figure 3 Mean CFB to Day 43 in QMG



Day of visit	1	8	15	22	29	36	43	71	FV
Placebo n	67	67	66	65	64	59	64	47	63
RLZ 7 mg/kg n	66	66	62	62	63	63	64	51	64
RLZ 10 mg/kg n	67	66	64	64	60	59	62	58	63

**p<0.001 for LS mean CFB for both rozanolixizumab 7 mg/kg and 10 mg/kg treatment groups vs placebo at Day 43.
Final visit could occur on any day up to Day 99.

Figure 4 Mean CFB to Day 43 in MGC



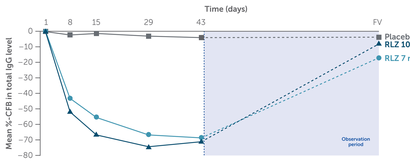
Day of visit	1	8	15	22	29	36	43	71	FV
Placebo n	67	67	66	65	64	60	64	47	63
RLZ 7 mg/kg n	66	66	62	62	63	63	64	52	64
RLZ 10 mg/kg n	67	66	64	60	64	59	62	58	63

**p<0.001 for LS mean CFB for both rozanolixizumab 7 mg/kg and 10 mg/kg treatment groups vs placebo at Day 43.
Final visit could occur on any day up to Day 99.

Conclusions

- The primary objective was met with a clinically meaningful and highly statistically significant improvement in MG-ADL at Day 43
  - Both doses also showed clinically meaningful and highly statistically significant improvements in MGC and QMG scores over placebo
- Rozanolixizumab had an acceptable safety profile and was generally well tolerated
- These results suggest that rozanolixizumab has potential as a new treatment option for patients with generalized myasthenia gravis and further substantiate the therapeutic benefit of targeting FcRn for patients with gMG

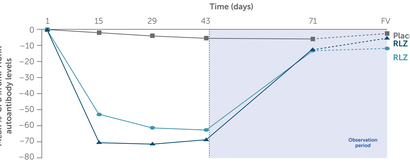
Figure 5 Mean percent CFB in total IgG level



Day of visit	1	8	15	29	43	FV
Placebo n	67	67	65	63	60	56
RLZ 7 mg/kg n	64	61	57	59	62	55
RLZ 10 mg/kg n	69	57	63	61	62	62

Final visit could occur on any day up to Day 99.

Figure 6 Mean percent CFB in anti-AChR autoantibody levels



Day of visit	1	15	29	43	71	FV
Placebo n	53	49	50	48	37	44
RLZ 7 mg/kg n	54	45	51	49	40	46
RLZ 10 mg/kg n	58	46	47	53	48	50

Final visit could occur on any day up to Day 99.

Rozanolixizumab is not approved for treatment of MG by any health authority.

Abbreviations: AChR, acetylcholine receptor; AE, adverse event; CFB, change from baseline; 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; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities Of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; NMJ, neuromuscular junction; OLE, open-label extension; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; RLZ, rozanolixizumab; SD, standard deviation; TEAE, treatment-emergent adverse event; Wk, week.

References: 1. Juel VC, *et al. Orphanet J Rare Dis* 2007;2:44. 2. Meizer N, *et al. J Neurol* 2016;263:1473–94. 3. Phillips W, *et al. F1000Res* 2016;5:F1000 Faculty Rev-513. 4. Gilhus NE, *et al. Nat Rev Dis Primers* 2019;5:30. 5. Kiessling P, *et al. Sci Trans Med* 2017;9 pii:eaan1208. **Author disclosures:** Vera Bril is a Consultant for Grifols, CSL, UCB Pharma, Argenx, Takeda, Alnylam, Octapharma, Pfizer, Powell Mansfield, Alcea, Ionis, Immunovant, Sanofi, Momenta (now Jb3), Roche, Janssen, Alexion and Novo Nordisk. She has received research support from Alexion, Grifols, CSL, UCB Pharma, Argenx, Takeda, Octapharma, Alcea, Momenta, Immunovant, Ionis and Viela Bio (now Horizon). Julian Grosskreutz has served as a Consultant for Biogen, Alexion and UCB Pharma, and his institution has received research support from the Boris Canessa Foundation. Ali A. Habib has received research support from Argenx, Alexion, Viela Bio, UCB Pharma, Genentech, Regeneron and Sanofi. He has received consulting fees/honoraria from Argenx, Alexion and UCB Pharma. Renato Mantegazza has received funding for travel and meeting attendance or advisory board participation from Alexion, Argenx, Biomarin, Catalyst, Sanofi, Regeneron and UCB Pharma. Kimiaki Utsugisawa has served as a paid Consultant for UCB Pharma, Argenx, Janssen Pharma, Viela Bio, Chugai Pharma, Hanall BioPharma and Mitsubishi Tanabe Pharma and has received speaker honoraria from Argenx, Alexion Pharmaceuticals and the Japan Blood Products Organization. John Vissing has been a Consultant on advisory boards for Sanofi Genzyme, Sarepta Therapeutics, Viela Bio, Novartis Pharma AG, Fulcrum Therapeutics, Stealth Biotherapeutics, Roche, Biogen, Lupin, Genethon, Amicus Therapeutics, Zogenix, Regeneron, UCB Pharma, Arvinas, Mi, Biopharma, Horizon Therapeutics and Lundbeck Pharma. He has received research, travel support, and/or speaker honoraria from Sanofi Genzyme, Argenx, Alexion Pharmaceuticals, Biogen, Lupin, Stealth Biotherapeutics, Edgewise Therapeutics, Fulcrum Therapeutics and UCB-Pharma. He is a Principal Investigator in clinical trials for Sanofi Genzyme, Roche, Horizon Therapeutics, Argenx, Novartis Pharma, Alexion Pharmaceuticals, Stealth Biotherapeutics, UCB Pharma, Genethon, Mi, Biopharma, Renexo Pharma, Pharnext, Janssen Pharmaceuticals, Khondrion, Regeneron and Dynacure. Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion, Argenx, RaYCB Pharma. Horizon/Viela Bio, Janssen/Momenta, Sanofi, Regeneron and Cartesian Therapeutics, and receives speaking and consulting honoraria from Alexion, Argenx and UCB Pharma. Henry Kaminski is a Consultant for Roche, Cabeleta Bio, Lincoln Therapeutics, Takeda and UCB Pharma, and is CEO and CMO of ARC Biotechnology. LLC based on US Patent 8,961,98. He is Principal Investigator of the Rare Disease Network for Myasthenia Gravis (MGNet), National Institute of Neurological Disorders & Stroke, U54 NS115054 and Targeted Therapy for Myasthenia Gravis. He has received R41 NS115331-01 to ARC Biotechnology. Marion Boehnlein, Ali Bozorg, Maryam Gayfieva and Franz Woltering are employees and shareholders of UCB Pharma. Artur Drużdż and Sabrina Sacconi have nothing to disclose. **Acknowledgments:** The authors thank the patients and their caregivers, in addition to the investigators and their teams who contributed to this study. This study was funded by UCB Pharma. The authors acknowledge David Onoja, Ogilvy Health, London, UK, for editorial assistance, which was funded by UCB Pharma. The authors acknowledge Veronica Porkess, PhD, of UCB Pharma, Slough, UK, for publication coordination.

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