Outcomes from RAISE: A randomized, placebo-controlled, double-blind, Phase 3 trial of zilucoplan in generalized myasthenia gravis

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Summary

Need for improved, targeted treatment options for patients with generalized MG (gMG)

RAISE assessed the efficacy, safety, and tolerability of the complement inhibitor zilucoplan (0.3 mg/kg daily) in patients with AChR-autoantibody positive gMG

Compared with placebo, zilucoplan:

- Rapidly improved MG-ADL from baseline to Week 12
- Improved all other key MG-specific secondary efficacy outcome measures (QMG, MGC, MG-QoL 15r) from as early as Week 1. Results were statistically significant and clinically meaningful at Week 12
- Statistically significantly improved responder rates based on MG-ADL (≥3 points) and QMG (≥5 points)

In subgroups defined by demographics and disease characteristics at baseline, response to zilucoplan mirrored effects observed in the overall population

Zilucoplan showed a favorable safety and tolerability profile with no major safety findings

Zilucoplan has the potential to be a novel treatment option for patients with gMG

Objective

- To determine the efficacy, safety, and tolerability of subcutaneous self-administered zilucoplan in patients with gMG

Introduction

- gMG is a chronic, unpredictable and debilitating rare disease. Almost half of patients do not achieve an adequate response, are intolerant to conventional treatment, or require chronic treatment with intravenous immunoglobulin or plasma separation procedures[1,2]
- In AChR+ gMG, pathogenic autoantibodies activate the complement cascade, leading to formation of membrane attack complex and loss of AChRs, which impairs muscle contraction[3]
- Zilucoplan is a small macrocyclic peptide that binds dually to C5 and C5b and inhibits its cleavage[4], which showed promising efficacy and safety in a Phase 2 study in patients with gMG[5]

Methods

- RAISE (NCT04115293) was a Phase 3, multinational, randomized, double-blind, placebo-controlled study of zilucoplan in patients with AChR+ gMG (**Figure 1**)
- Patients were randomized to receive daily subcutaneous doses of 0.3 mg/kg zilucoplan or matched placebo, self-injected over 12 weeks
- Eligible patients were aged ≥18 years, had MGFA Class II–IV gMG, were positive for AChR autoantibodies, had an MG-ADL score of ≥6 and a QMG score of ≥12, and were vaccinated against *Neisseria meningitidis*
- Exclusions included: Thymectomy <12 months prior to baseline or scheduled during study; abnormal thyroid function; history of meningococcal disease; or known positive serology for muscle-specific tyrosine kinase antibodies
- The primary endpoint was CFB to Week 12 in MG-ADL score
- Secondary efficacy endpoints included CFB to Week 12 in QMG, MGC and MG-QoL 15r scores, and MG-ADL and QMG responder rates defined as ≥3-point and ≥5-point improvements without rescue therapy from baseline respectively
- Safety was assessed mainly by incidence of TEAEs

Results

Patients

- Recruitment and randomization are shown in **Figure 1**
- Patient demographics and baseline disease characteristics were generally balanced between treatment arms (**Table 1**)

Efficacy

- Zilucoplan highly statistically significantly and clinically meaningfully reduced MG-ADL from baseline to Week 12, with an LS mean difference (95% CI) of −2.12 (−3.26, −0.97) vs placebo (p<0.001; **Figure 2**)
- LS mean differences for zilucoplan vs placebo at Week 12 for key secondary efficacy endpoints were also statistically significant and clinically meaningful: −3.07 (−4.48, −1.66; p<0.001) for QMG, −3.20 (−5.24, −1.16; p=0.0023) for MGC and −2.51 (−4.46, −0.55; p=0.0122) for MG-QoL 15r (**Figure 2**)
  - Rapid separation of zilucoplan and placebo curves for the primary and key secondary efficacy endpoints started at Week 1 and increased through Week 4, with stabilization thereafter up to Week 12 (nominal p<0.05 for LS mean difference for all visits after baseline; **Figure 2**)
- MG-ADL and QMG response rates for each level of improvement are shown in **Figure 3**
  - Additionally, logistic regression analyses show 73.1% of zilucoplan patients achieved a 3-point improvement in MG-ADL vs 46.1% in the placebo arm (OR [95% CI] = 3.182 [1.660, 6.098]; p<0.001). A ≥5-point improvement in QMG was seen in 58.0% of patients receiving zilucoplan vs 33.1% in the placebo arm (OR [95% CI] = 2.869 [1.520, 5.418]; p=0.0012)
- MG-ADL results in subgroups based on demographics or disease characteristics at baseline mirrored those seen in the overall population
  - Mean CFB in MG-ADL at Week 12 with zilucoplan vs placebo for: Age (<65 years: −4.56 vs −2.75; ≥65 years: −5.14 vs −3.08), gender (male: −5.12 vs −2.85; female: −4.43 vs −2.84), baseline MG-ADL (≤9: −3.88 vs −2.48; ≥10: −5.24 vs −3.06) and region (North America: −4.67 vs −3.61; Europe: −4.74 vs −2.31; Asia: −4.71 vs −1.00)

Safety

- The incidence of TEAEs was 76.7% in the zilucoplan arm (66 patients) and 70.5% in the placebo arm (62 patients) (**Table 2**)
  - No *Neisseria* infections were observed
  - The most frequently reported TEAEs were injection-site bruising (16.3% and 9.1% for zilucoplan and placebo), headache (15.1% and 15.9%), diarrhea (10.5% and 2.3%), and MG worsening (10.5% and 9.1%)
  - In the zilucoplan group, 4 (4.7%) patients discontinued treatment due to a TEAE (1 each of aphthous ulcer, mouth ulceration, COVID-19, hepatic enzyme increase), and 2 (2.3%) patients discontinued from the placebo group due to a TEAE (1 each of hyperemesis gravidarum and cerebral hemorrhage)
  - Two patients died, due to COVID-19 (zilucoplan) and a cerebral hemorrhage (placebo). Neither death was considered treatment-related
- The incidence of serious TEAEs was 12.8% in the zilucoplan arm (11 patients) and 14.8% in the placebo arm (13 patients)

Figure 1 Study design

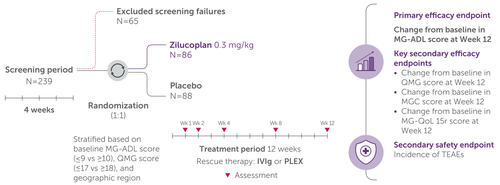


Table 2 Overview of TEAEs (safety set)

Preferred term	Placebo (N=88) n (%)	Zilucoplan 0.3 mg/kg (N=86) n (%)
Any TEAE	62 (70.5)	66 (76.7)
Serious TEAE	13 (14.8)	11 (12.8)
TEAE resulting in permanent withdrawal from IMP	2 (2.3)	4 (4.7)
Treatment-related TEAE	22 (25.0)	28 (32.6)
Severe TEAE	11 (12.5)	10 (11.6)
Deaths	1 (1.1)	1 (1.2)

Conclusions

- Zilucoplan highly statistically significantly and clinically meaningfully improved MG-ADL from baseline vs placebo in patients with AChR+ gMG
- Zilucoplan significantly improved all key secondary endpoints vs placebo
- Zilucoplan had a favorable safety profile with no major safety findings and good tolerability, confirming the results of the Phase 2 study

Figure 2 Change from baseline to Week 12 in MG-ADL, QMG, MGC and MG-QoL 15r (mITT population)

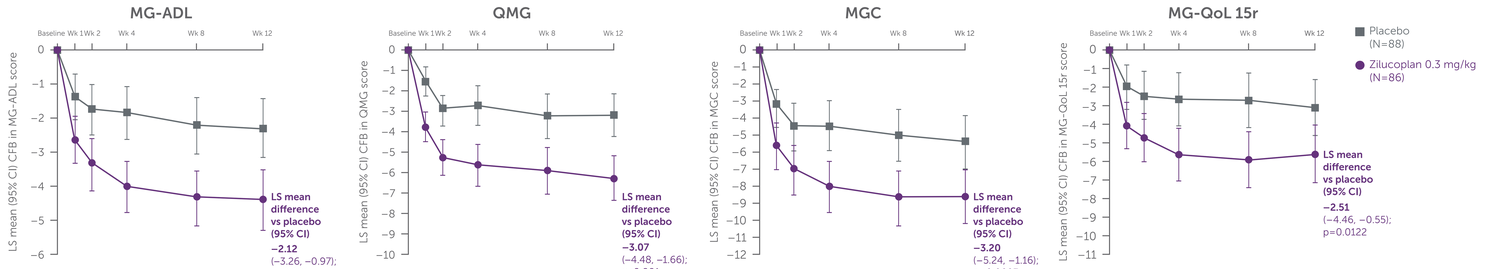
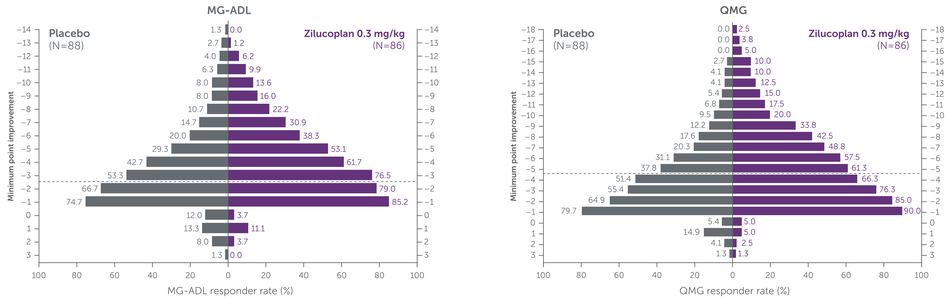


Table 1 Patient demographics and baseline disease characteristics

		Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
Age, years, mean (SD)		53.3 (15.7)	52.6 (14.6)
Sex, male, n (%)		41 (46.6)	34 (39.5)
Weight, kg, mean (SD)		88.2 (26.6)	90.1 (22.9)
Geographic region, n (%)	North America	46 (52.3)	45 (52.3)
	Europe	33 (37.5)	34 (39.5)
	East Asia	9 (10.2)	7 (8.1)
MGFA disease class, n (%)	II (IIa, IIb)	27 (30.7)	22 (25.6)
	III (IIIa, IIIb)	57 (64.8)	60 (69.8)
	IV (IVa, IVb)	4 (4.5)	4 (4.7)
MG-ADL score, mean (SD)		10.9 (3.4)	10.3 (2.5)
QMG score, mean (SD)		19.4 (4.5)	18.7 (3.6)
MGC score, mean (SD)		21.6 (7.2)	20.1 (6.0)
MG-QoL 15r score, mean (SD)		18.9 (6.8)	18.6 (6.6)
Prior thymectomy, n (%)		37 (42.0)	45 (52.3)
Duration of disease, years, mean (SD)		9.0 (10.4)	9.3 (9.5)
Treatment refractory*, n (%)		44 (50.0)	44 (51.2)
MG medication at baseline†, n (%)	Cholinesterase inhibitor	73 (83.0)	74 (86.0)
	Corticosteroids	51 (58.0)	59 (68.6)
	Azathioprine, MMF	35 (39.8)	30 (34.9)
	Cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab	15 (17.0)	12 (14.0)

mITT population unless otherwise stated. The mITT population includes all randomized participants who received at least one dose of study drug and have at least one post-dosing MG-ADL score. *A participant is considered 'treatment refractory' if they have had treatment for at least one year with two or more of the following therapies: Prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids. †History of treatment with at least one of the above therapies for one year or more and required chronic PLEX, IVIg or SCIg at least every 3 months for the 12 months prior to enrollment.
‡Safety set. Includes all participants who received at least one dose of study drug with subjects analyzed based on the actual study treatment received.

Figure 3 Responder analyses for changes in MG-ADL and QMG scores from baseline without rescue therapy at Week 12 (mITT population)



Zilucoplan is not approved for treatment of myasthenia gravis by any health authority.

Abbreviations: AChR: acetylcholine receptor; C5, complement protein 5; CFB, change from baseline; CI, confidence interval; COVID-19, coronavirus disease 2019; gMG, generalized myasthenia gravis; 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; MG-QoL 15r, Myasthenia Gravis Quality of Life 15-item revised; mITT, modified intent-to-treat; MMF, mycophenolate mofetil; OR, odds ratio; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SCIg, subcutaneous immunoglobulin; SD, standard deviation; TEAE, treatment-emergent adverse event; Wk, Week.

References: [1] Gilhus NE. *N Engl J Med*. 2016;375:2570-2581. doi:10.1056/NEJMra1602678 [2] Howard JF Jr, et al. *Lancet Neurol*. 2017;16:976-986. doi:10.1016/S1474-4422(17)30369-1 [3] Gilhus NE, Verschuuren JJ. *Lancet Neurol*. 2015;14:1023-1036. doi:10.1016/S1474-4422(15)00145-3 [4] Howard JF Jr, et al. *Muscle Nerve*. 2020;61:468-479. doi:10.1002/mus.26742 [5] Howard JF Jr, et al. *JAMA Neurol*. 2020;77:582-592.

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