Efficacy of zilucoplan in patients with generalized myasthenia gravis without prior immunoglobulin or plasma exchange in the RAISE study

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Introduction

- Zilucoplan is a small, 15-amino acid, macrocyclic complement C5 inhibitor peptide with a dual mechanism of action[1,2]
- In the randomized, double-blind, placebo-controlled, Phase 3 RAISE study (NCT04115293), patients with gMG who received zilucoplan showed clinically meaningful improvements in MG-specific outcomes[2]
- Here, we assessed the efficacy of zilucoplan in RAISE patients who received no previous treatment with Ig (either IVIg or SCIg) or PLEX, both of which are typically used for moderate-to-severe exacerbations[3–5]

Methods

- Adults with AChR Ab+ gMG were randomized 1:1 to daily, self-administered SC zilucoplan 0.3 mg/kg or placebo injections for 12 weeks[2] (**Figure 1**)
- Study endpoints included CFB to Week 12 in MG-ADL score (primary endpoint) and QMG score (secondary endpoint)
- We conducted a prespecified, descriptive efficacy analysis of the subgroup of patients who had not received prior Ig or PLEX treatment

Results

- In the overall population, 174 patients were randomized to either zilucoplan 0.3 mg/kg (n=86) or placebo (n=88)
- In total, 54 patients without prior Ig or PLEX treatment were included (zilucoplan 0.3 mg/kg [n=29] or placebo [n=25])
- Baseline characteristics varied between the subgroup without prior Ig or PLEX and the overall population (**Table 1**)
  - The subgroup had a shorter disease duration and was less likely to have had a prior MG crisis or a previous thymectomy
  - The subgroup was more likely to have MGFA Class II disease and less likely to have Class IV disease
- In the subgroup without prior Ig or PLEX:
  - Mean (SE) CFB in MG-ADL score was –4.22 (0.71) with zilucoplan 0.3 mg/kg compared to –2.61 (0.50) with placebo at Week 12 (**Figure 2**)
  - Mean (SE) CFB in QMG score was –6.48 (0.88) with zilucoplan 0.3 mg/kg compared to –3.04 (0.94) with placebo at Week 12 (**Figure 3**)
- CFB in MG-ADL and QMG scores were comparable between the subgroup without prior Ig or PLEX and the overall population
- MG-ADL and QMG responder rates at Week 12 were comparable between the subgroup without prior Ig or PLEX and the overall population (**Figure 4**)
- In the no prior Ig or PLEX subgroup, zilucoplan demonstrated a favorable safety profile and was well tolerated (**Table 2**)

Abbreviations: AChR Ab+, positive for autoantibodies against the acetylcholine receptor; C5, component 5; CFB, change from baseline; CI, confidence interval; gMG, generalized myasthenia gravis; Ig, immunoglobulin; IMP, investigational medicinal product; IVIg, intravenous immunoglobulin; LS, least squares; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America;mITT, modified intention to treat; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous: SCIg, subcutaneous immunoglobulin; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event.

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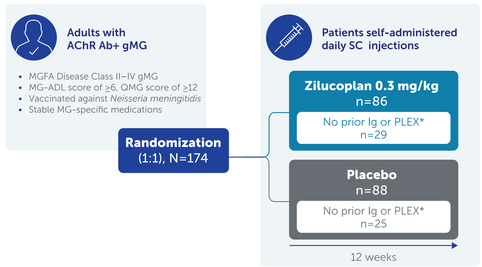
These data were previously presented at the Japanese Society of Neurology and Asian Oceanian Congress of Neurology Annual Meeting in Tokyo, Japan; May 29–June 1, 2024.

Figure 1 Study design



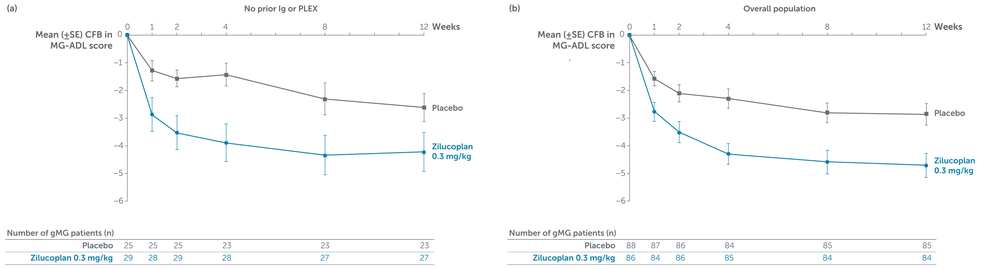
*Prior medications include any medications that started before the first administration of the IMP. Patients were considered 'no prior Ig or PLEX' if they had not received Ig or PLEX therapy prior to the first administration of zilucoplan.

Table 1 Baseline characteristics and disease history

	No prior Ig or PLEX		Overall population	
	Placebo (n=25)	Zilucoplan 0.3 mg/kg (n=29)	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)
Age, years, mean (SD)	**57.7** (14.8)	**53.4** (15.2)	**53.3** (15.7)	**52.6** (14.6)
Female, n (%)	**12** (48.0)	**16** (55.2)	**47** (53.4)	**52** (60.5)
Body weight, kg, mean (SD)	**90.8** (26.9)	**89.7** (23.5)	**88.2** (26.6)	**90.1** (22.9)
White, n (%)	**21** (84.0)	**25** (86.2)	**62** (70.5)	**66** (76.7)
MGFA Disease Class, n (%)				
IIa/b	**11** (44.0)	**10** (34.5)	**27** (30.7)	**22** (25.6)
IIIa/b	**14** (56.0)	**18** (62.1)	**57** (64.8)	**60** (69.8)
IVa/b	**0**	**1** (3.4)	**4** (4.5)	**4** (4.7)
MG-ADL score, mean (SD)	**9.8** (2.8)	**10.6** (2.7)	**10.9** (3.4)	**10.3** (2.5)
QMG score, mean (SD)	**17.8** (3.5)	**18.7** (3.4)	**19.4** (4.5)	**18.7** (3.6)
Age at onset, years, mean (SD)	**52.2** (17.4)	**47.3** (16.8)	**44.0** (18.7)	**43.5** (17.4)
Duration of disease, years, mean (SD)	**4.9** (4.7)	**5.9** (8.1)	**9.0** (10.4)	**9.3** (9.5)
Prior MG crisis, n (%)	**1** (4.0)	**1** (3.4)	**29** (33.0)	**28** (32.6)
Thymoma diagnosis, n (%)	**1** (4.0)	**9** (31.0)	**18** (20.5)	**21** (24.4)
Previous thymectomy, n (%)	**0**	**10** (34.5)	**37** (42.0)	**45** (52.3)
Prior corticosteroids, n (%)	**19** (76.0)	**21** (72.4)	**74** (84.1)*	**77** (89.5)*
Prior NSISTs, n (%)	**12** (48.0)	**13** (44.8)	**67** (76.1)*	**59** (68.6)*

mITT population unless otherwise stated. *Safety set.

Figure 2 Mean CFB in MG-ADL score for the (a) no prior Ig or PLEX subgroup and (b) the overall population



Number of gMG patients (n)

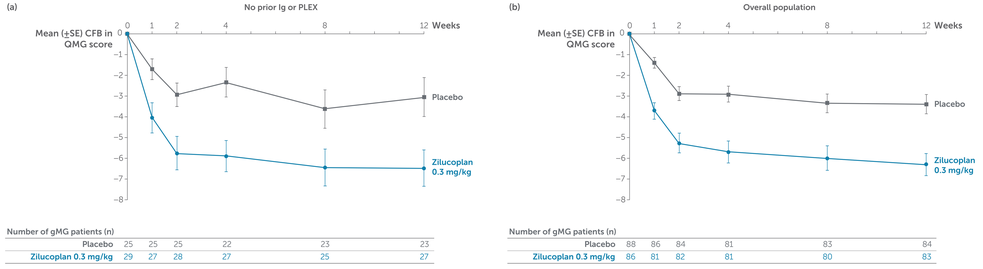
	0	1	2	4	8	12 Weeks
Placebo	25	25	25	23	23	23
Zilucoplan 0.3 mg/kg	29	28	29	28	27	27

Number of gMG patients (n)

	0	1	2	4	8	12 Weeks
Placebo	88	87	86	84	85	85
Zilucoplan 0.3 mg/kg	86	84	86	85	84	84

mITT population.
RAISE primary endpoint: CFB in MG-ADL score at Week 12. LS mean CFB in MG-ADL score: zilucoplan 0.3 mg/kg –4.39 (95% CI: –5.28 to –3.50) vs placebo –2.30 (–3.17 to –1.43); LS mean difference –2.09 (–3.24 to –0.95; p=0.0004).[2]

Figure 3 Mean CFB in QMG score for the (a) no prior Ig or PLEX subgroup and (b) the overall population



Number of gMG patients (n)

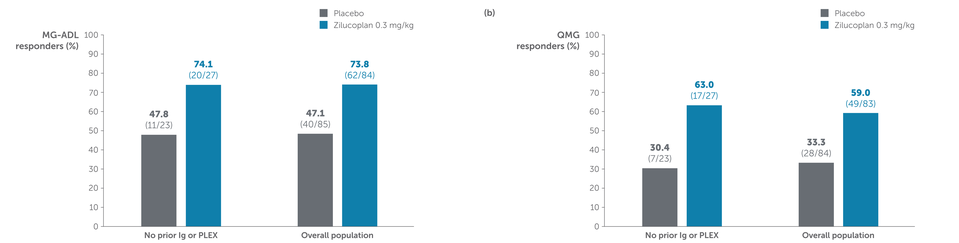
	0	1	2	4	8	12 Weeks
Placebo	25	25	25	22	23	23
Zilucoplan 0.3 mg/kg	29	27	28	27	25	27

Number of gMG patients (n)

	0	1	2	4	8	12 Weeks
Placebo	88	86	84	81	83	84
Zilucoplan 0.3 mg/kg	86	81	82	81	80	83

mITT population.
RAISE secondary endpoint: CFB in QMG score at Week 12. LS mean CFB in QMG score: zilucoplan 0.3 mg/kg –6.19 (95% CI –7.29 to –5.08) vs placebo –3.25 (–4.32 to –2.17); LS mean difference –2.94 (–4.39 to –1.49; p<0.0001).[2]

Figure 4 (a) MG-ADL and (b) QMG responders at Week 12



mITT population. Percentages are based on the number of patients with available data at Week 12. MG-ADL responders: ≥3-point decrease in MG-ADL score from baseline; QMG responders: ≥5-point decrease in QMG score from baseline.

Summary and conclusions

In the RAISE study, the subgroup of patients without prior Ig or PLEX treatment had a shorter duration of disease and was more likely to have mild gMG (MGFA Class II)

In line with the overall population, zilucoplan treatment showed relevant improvements in MG-specific outcomes in gMG patients without prior Ig or PLEX treatment

Zilucoplan demonstrated a favorable safety profile and was well tolerated in gMG patients without prior Ig or PLEX treatment

Given the comparable safety and efficacy to the overall population, these data support earlier use of zilucoplan in the treatment paradigm and suggest that zilucoplan has potential as a second-line treatment in patients with gMG

Table 2 Overview of TEAEs

n (%)	No prior Ig or PLEX		Overall population	
	Placebo (n=25)	Zilucoplan 0.3 mg/kg (n=29)	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)
Any TEAE*	**17** (68.0)	**20** (69.0)	**62** (70.5)	**66** (76.7)
Headache	**3** (12.0)	**4** (13.8)	**14** (15.9)	**13** (15.1)
Diarrhea	**2** (8.0)	**4** (13.8)	**2** (2.3)	**9** (10.5)
Injection-site bruising	**1** (4.0)	**4** (13.8)	**8** (9.1)	**14** (16.3)
Serious TEAE	**3** (12.0)	**2** (6.9)	**13** (14.8)	**11** (12.8)
Treatment-related serious TEAE†	**0**	**1** (3.4)	**1** (1.1)	**4** (4.7)
TEAE resulting in permanent withdrawal from IMP‡	**2** (8.0)	**3** (10.3)	**2** (2.3)	**4** (4.7)
Treatment-related TEAE	**7** (28.0)	**9** (31.0)	**22** (25.0)	**28** (32.6)
Severe TEAE	**2** (8.0)	**2** (6.9)	**11** (12.5)	**10** (11.6)
TEAE leading to death§	**1** (4.0)	**1** (3.4)	**1** (1.1)	**1** (1.2)

Safety set. *Specific TEAEs listed are the three most commonly occurring in the subgroup without prior Ig or PLEX. †Treatment-related serious TEAE in the subgroup without prior Ig or PLEX was one (3.4%) event of worsening aphthous mouth ulceration in the zilucoplan 0.3 mg/kg group. ‡Includes all deaths. §Neither death (cerebral hemorrhage [placebo] nor COVID-19 [zilucoplan]) was considered treatment related.