Effect of zilucoplan on disease fluctuation in patients with generalized myasthenia gravis in the Phase 3 RAISE study

AANEM 2023, Phoenix, AZ, USA; November 1–4, 2023

Angela Genge[1], Channa Hewamadduma[2,3], Yessar Hussain[4], Raphaëlle Beau Lejdstrom[5], Babak Boroojerdi[6], Fiona Grimson[7], Natasa Savic[5], James F. Howard Jr[8] on behalf of the RAISE study group

[1]Clinical Research Unit, The Montreal Neurological Institute, Montreal, QC, Canada; [2]Academic Neuroscience Unit, Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK; [3]Sheffield Institute for Translational Neuroscience (SITRAN), Sheffield, UK; [4]Department of Neurology, Dell Medical School, The University of Texas at Austin, Austin, TX, USA; [5]UCB Pharma, Bulle, Switzerland; [6]UCB Pharma, Monheim, Germany; [7]UCB Pharma, Slough, UK; [8]Department of Neurology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Introduction

- MG is an autoimmune disease characterized by fluctuating muscle weakness and fatigue[1]

- Complement-mediated architectural destruction of the NMJ by pathogenic autoantibodies is a major mechanism involved in gMG pathology[2]

- Zilucoplan is a small peptide C5 inhibitor with a dual mechanism of action: it prevents C5 cleavage to C5a and C5b and hinders the formation of C5b6, should any C5b be formed, thereby preventing activation of the terminal complement pathway and formation of the MAC[3,4]

- In RAISE (NCT04115293), a Phase 3 study in patients with AChR+ gMG, zilucoplan statistically significantly and clinically meaningfully improved MG-ADL score from baseline to Week 12 and other MG-specific outcomes compared with placebo[4]

- In this *post-hoc* analysis, we assessed the effect of zilucoplan on gMG disease fluctuations

Methods

- RAISE was a randomized, multicenter, double-blind, placebo-controlled Phase 3 study to confirm the efficacy, safety, and tolerability of zilucoplan in patients with AChR+ gMG[4]

  – Adults with AChR+ gMG (MGFA Disease Class II–IV) were randomized 1:1 to receive daily subcutaneous zilucoplan 0.3 mg/kg or placebo for 12 weeks

  – The primary efficacy endpoint was CFB to Week 12 in MG-ADL score

- Here we assessed:

  – MG worsening (defined as ≥3-point or ≥5-point increase from baseline in MG-ADL or QMG scores in the mITT population at any point during the study, regardless of investigators' judgment)

  – TEAEs and MG-related TEAEs (defined post-hoc as any adverse event of 'myasthenia gravis', 'myasthenia gravis crisis', or 'muscular weakness')

  – Rescue therapy in patients with MG-related TEAEs

  – Hospitalizations due to MG-related TEAEs

  – CFB in MG-ADL and QMG scores at Week 12 among patients who received rescue therapy (IVIg or PLEX administered concomitantly with zilucoplan)

Results

- Patient demographics and baseline characteristics were generally well balanced across treatment groups (**Table 1**)

- Fewer patients in the zilucoplan group than in the placebo group experienced MG worsening (**Figure 1**)

- The most frequently reported TEAEs in the zilucoplan group were injection-site bruising, headache, MG-related TEAEs, and diarrhea (**Table 2**)

- A similar proportion of patients experienced MG-related TEAEs in the zilucoplan and placebo groups (**Figure 2**)

  – Of these, only 2/10 (20%) zilucoplan patients required rescue therapy compared with 9/9 (100%) placebo patients

  – The proportion of patients hospitalized due to MG-related TEAEs was lower in the zilucoplan group (3/86, 3.5%) compared with the placebo group (5/88, 5.7%)

- No cases of MG crisis were reported in either the zilucoplan or placebo groups

- Of patients who received rescue therapy, the mean CFB to Week 12 in MG-ADL score was greater in the zilucoplan group (−2.3) compared with the placebo group (−0.3); the same trend was observed for QMG score (mean CFB −1.7 and −0.1, respectively)

Table 1   Baseline demographic and disease characteristics

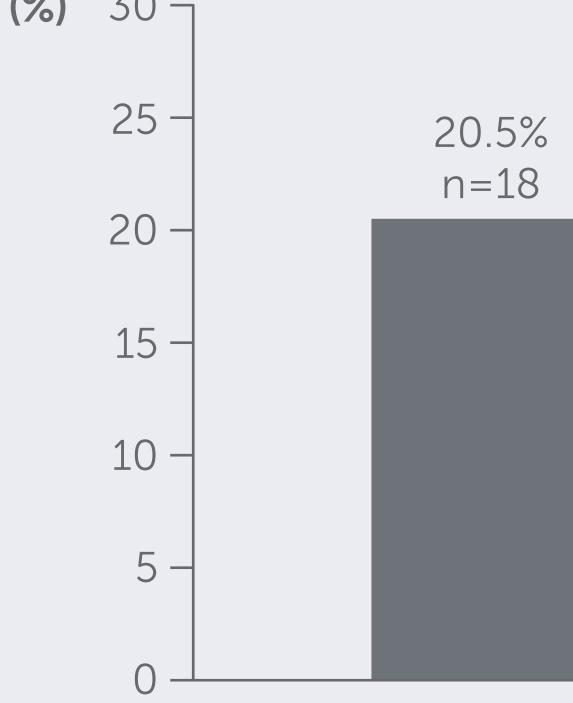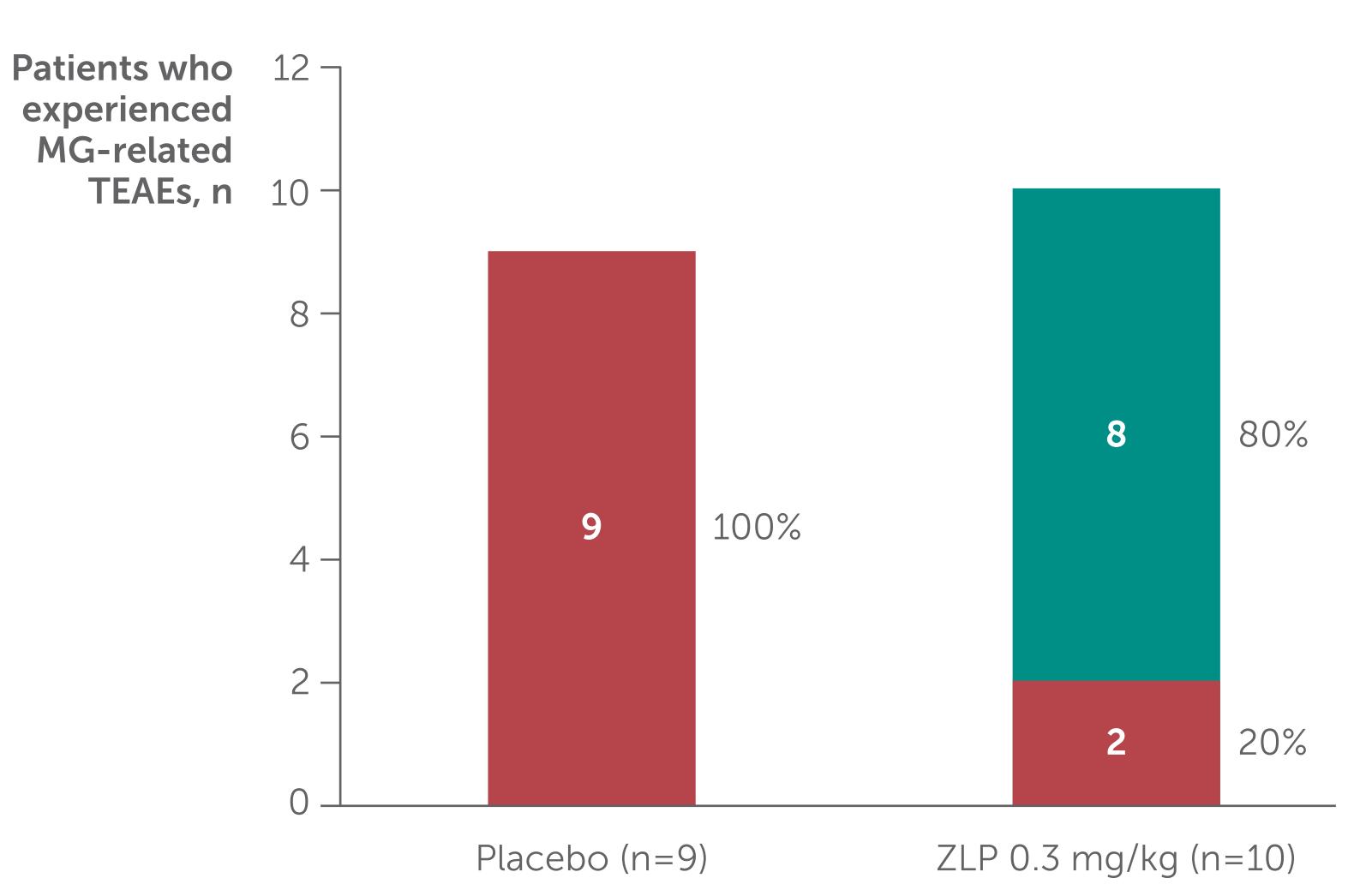|		Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)
	Age, years, mean (SD)	53.3 (15.7)	52.6 (14.6)
	Sex, male, n (%)	41 (46.6)	34 (39.5)
MGFA Disease Class, n (%)	II (IIa, IIb)	27 (30.7)	22 (25.6)
	III (IIIa, IIIb)	57 (64.8)	60 (69.8)
	IV (IVa, IVb)	4 (4.5)	4 (4.7)
	MG-ADL score, mean (SD)	10.9 (3.4)	10.3 (2.5)
	QMG score, mean (SD)	19.4 (4.5)	18.7 (3.6)
	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)
	Diagnosed with thymoma, n (%)	18 (20.5)	20 (23.3)
	Cholinesterase inhibitor	73 (83.0)	74 (86.0)
MG medication at baseline, n (%)†	Corticosteroids	51 (58.0)	59 (68.6)
	Azathioprine, MMF	35 (39.8)	29 (33.7)
	Cyclosporin, methotrexate, tacrolimus	15 (17.0)	12 (14.0)

mITT population unless otherwise stated. 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 ≥1 year with ≥2 of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporin, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroid; OR history of treatment with ≥1 of the above therapies for ≥1 year 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 participants analyzed based on the actual study treatment received.

Figure 1   MG worsening at any time during the study

≥3-point increase in MG-ADL

≥5-point increase in QMG

≥3-point increase in MG-ADL or ≥5-point increase in QMG

*Nominal p-value <0.05, based on Chi-square test of ZLP 0.3 mg/kg vs placebo.

Table 2   Overview of TEAEs

		Placebo (n=88) n (%)	Zilucoplan 0.3 mg/kg (n=86) n (%)
Any TEAE		**62 (70.5)**	**66 (76.7)**
Injection-site bruising		8 (9.1)	14 (16.3)
Headache		14 (15.9)	13 (15.1)
MG-related TEAE*		9 (10.2)	10 (11.6)
Diarrhea		2 (2.3)	9 (10.5)
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	Total	1 (1.1)	1 (1.2)
	COVID-19/ COVID-19 pneumonia	0	1 (1.2)
	Cerebral hemorrhage	1 (1.1)	0

*MG-related TEAE was defined *post-hoc* as any adverse event of 'myasthenia gravis', 'myasthenia gravis crisis', or 'muscular weakness'. 'Myasthenia gravis' (TEAE of MG worsening) occurred in 8 (9.1%) patients in the placebo group and 9 (10.5%) patients in the zilucoplan group. †Includes all deaths. TEAEs leading to discontinuation were cerebral hemorrhage and hyperemesis gravidarum (n=1 [1.1%] patient each) in the placebo group and aphthous ulcer, COVID-19, hepatic enzyme increased, and mouth ulceration (n=1 [1.2%] patient each) in the zilucoplan group.
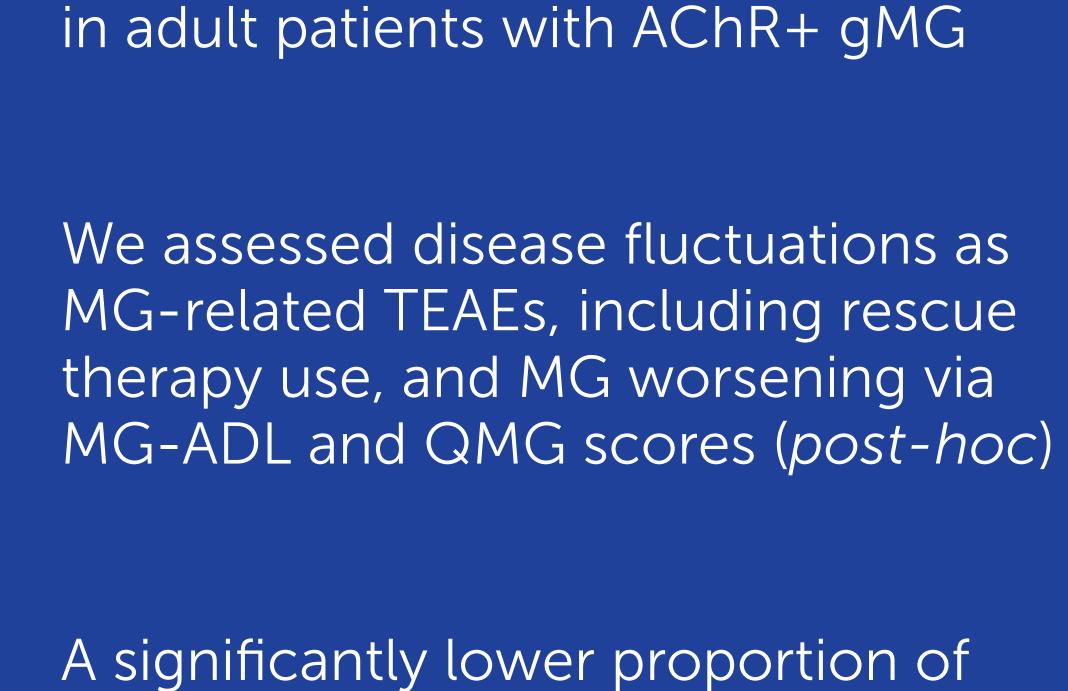
Figure 2   Rescue therapy use in patients who experienced MG-related TEAEs

■ Received rescue therapy at any time during the study
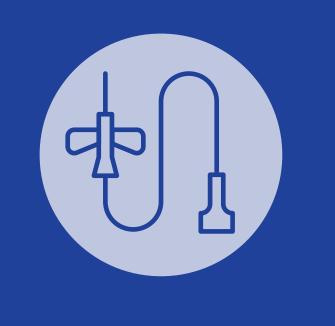■ Did not receive rescue therapy at any time during the study

Summary and conclusions

- RAISE was a randomized, double-blind, placebo-controlled Phase 3 study of zilucoplan, a complement C5 inhibitor, in adult patients with AChR+ gMG

- We assessed disease fluctuations as MG-related TEAEs, including rescue therapy use, and MG worsening via MG-ADL and QMG scores (*post-hoc*)

- A significantly lower proportion of patients receiving zilucoplan experienced MG worsening compared with placebo

- Although a similar proportion of patients reported MG-related TEAEs in the zilucoplan and placebo groups, only 20% of patients who received zilucoplan required rescue therapy compared with 100% of those receiving placebo

- These results demonstrate the efficacy of zilucoplan in decreasing MG worsening and use of rescue therapy in patients with gMG

References: 1. Gilhus NE, Verschuuren J. Lancet Neurol. 2015;14:1023–1036. 2. Howard JF Jr., et al. Ann NY Acad Sci. 2018;1412:113–128. 3. Tang G-Q, et al. Front Immunol. 2023;14:1213920. 4. Howard JF Jr., et al. Lancet Neurol. 2023;22:395–406.

Please scan this QR code to download a PDF of the poster