# 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

# Introduction

- MG is an autoimmune disease characterized by fluctuating muscle weakness and fatigue<sup>1</sup>
- Complement-mediated architectural destruction of the NMJ by pathogenic autoantibodies is a major mechanism involved in gMG pathology<sup>2</sup>
- 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<sup>3,4</sup>
- 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<sup>4</sup>
- 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<sup>4</sup>
- 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  $\geq$ 3-point or  $\geq$ 5-point increase from baseline in MG-ADL or QMG scores in the mITT population at any point during the study, respectively, 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)

Ta	ble	1	Ba

M	GFA	Disease	Clas
n	(%)		

	Du

MG medi	cation at
baseline,	<b>n (%)</b> †

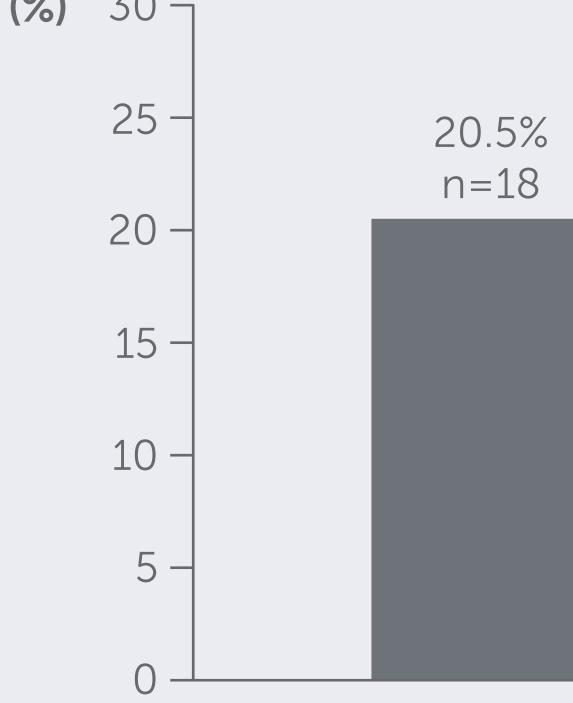
mITT population unless otherwise stated. mITT population includes all randomized participants who received at least one dose of study drug and have at least one post-dosing MG-ADL score. \*A participant is considered 'treatment refractory' if they have had treatment for  $\geq 1$  year with  $\geq 2$  of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporin, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids; OR history of treatment with  $\geq 1$  of the above therapies for  $\geq 1$  year and required chronic PLEX, IVIg or SCIg at least every 3 months for the 12 months prior to enrollment. <sup>†</sup>Safety set. Includes all participants who received at least one dose of study drug, with participants analyzed based on the actual study treatment received.

### aseline demographic and disease characteristics

		Disselas	7:1
		Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)
	Age, years, mean (SD)	<b>53.3</b> (15.7)	<b>52.6</b> (14.6)
	Sex, male, n (%)	<b>41</b> (46.6)	<b>34</b> (39.5)
	II (IIa, IIb)	<b>27</b> (30.7)	<b>22</b> (25.6)
ISS,	III (IIIa, IIIb)	<b>57</b> (64.8)	60 (69.8)
	IV (IVa, IVb)	4 (4.5)	4 (4.7)
	MG-ADL score, mean (SD)	<b>10.9</b> (3.4)	<b>10.3</b> (2.5)
	QMG score, mean (SD)	<b>19.4</b> (4.5)	<b>18.7</b> (3.6)
	Prior thymectomy, n (%)	<b>37</b> (42.0)	<b>45</b> (52.3)
uration	of disease, years, mean (SD)	<b>9.0</b> (10.4)	<b>9.3</b> (9.5)
	Treatment refractory, n (%)*	<b>44</b> (50.0)	<b>44</b> (51.2)
Dia	gnosed with thymoma, n (%)	<b>18</b> (20.5)	<b>20</b> (23.3)
	Cholinesterase inhibitor	<b>73</b> (83.0)	74 (86.0)
	Corticosteroids	<b>51</b> (58.0)	<b>59</b> (68.6)
	Azathioprine, MMF	<b>35</b> (39.8)	<b>29</b> (33.7)
	Cyclosporin, methotrexate,	<b>15</b> (17.0)	<b>12</b> (14.0)
	tacrolimus		

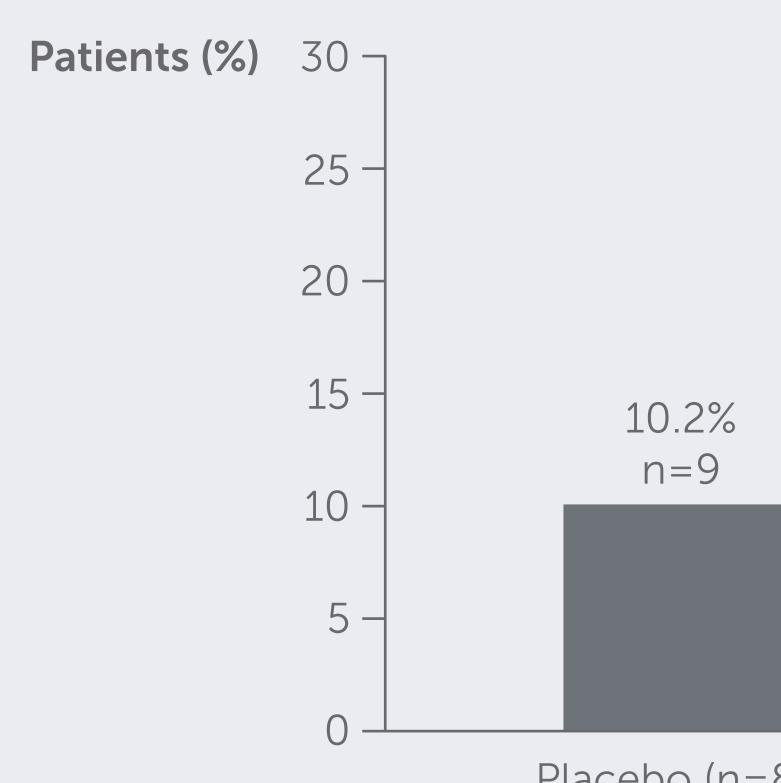
# MG worsening at any time during the study Figure 1 **>3-point increase in MG-ADL Patients (%)** 30 ¬ 20.5%

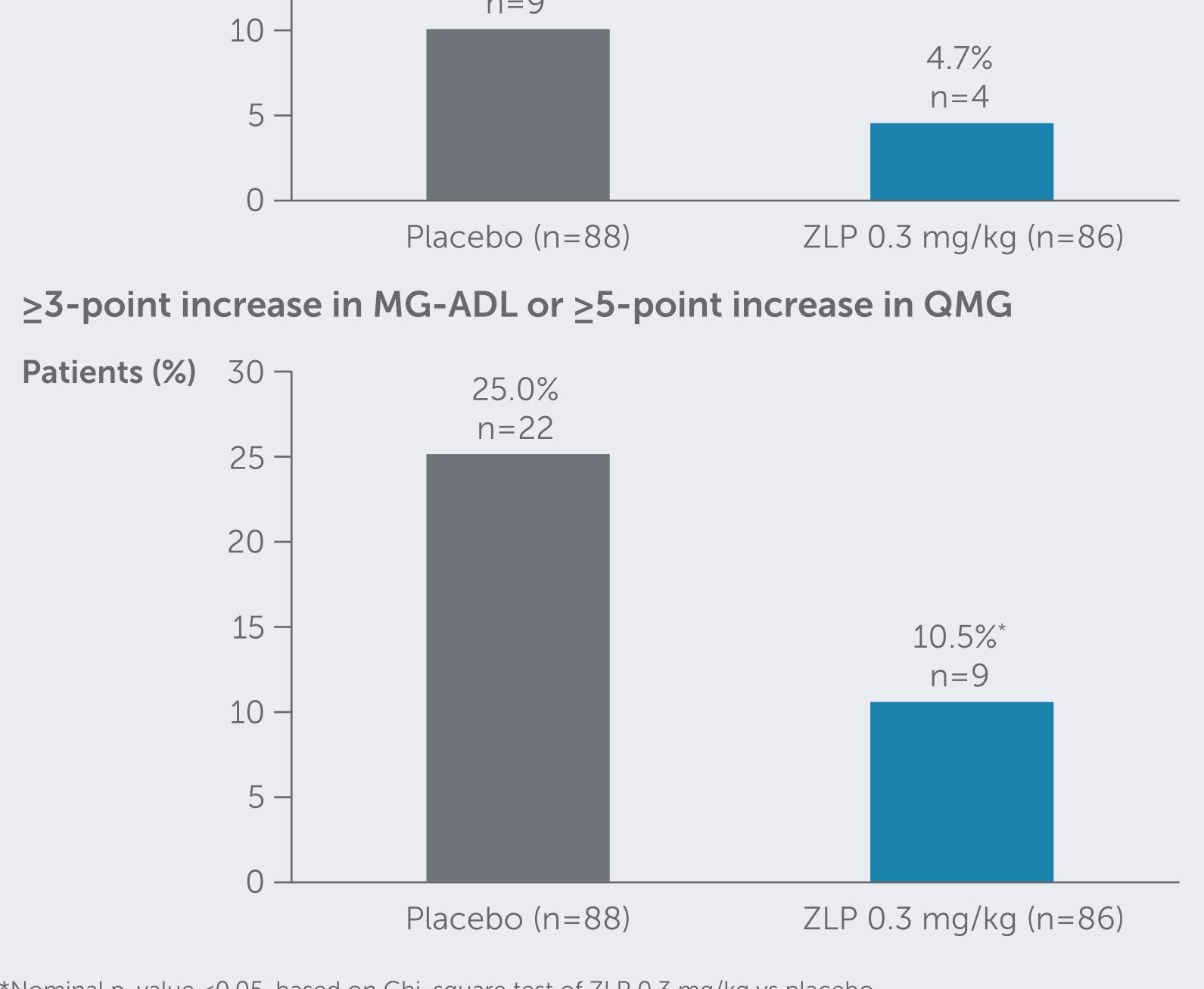




Placebo (n=88)

>5-point increase in QMG

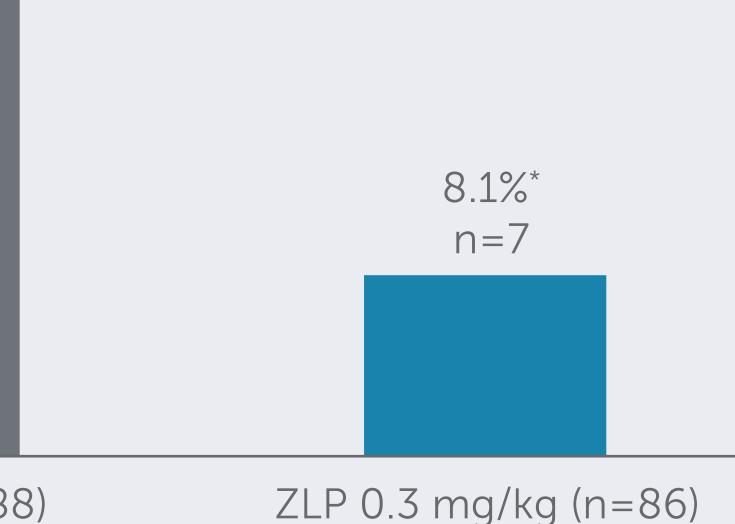




\*Nominal p-value < 0.05, based on Chi-square test of ZLP 0.3 mg/kg vs placebo.

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

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



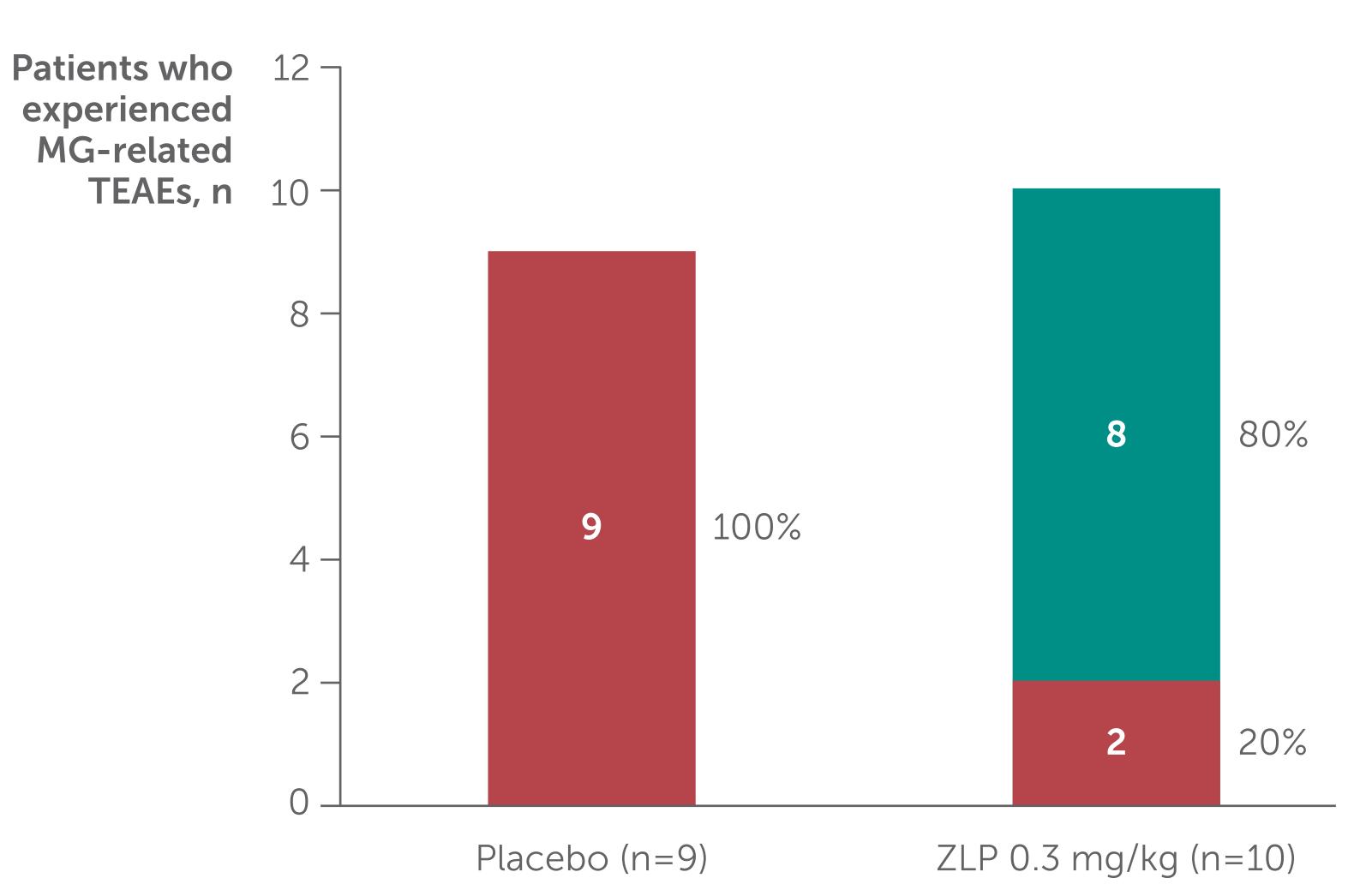
### **Overview of TEAEs** Table 2

		Placebo (n=88) n (%)
Any TEAE		<b>62</b> (70.5)
Injection-site bruising		<b>8</b> (9.1)
Headache		<b>14</b> (15.9)
MG-related TEAE*		9 (10.2)
Diarrhea		<b>2</b> (2.3)
Serious TEAE		<b>13</b> (14.8)
<b>TEAE resulting in permanent</b>	withdrawal from IMP <sup>†</sup>	<b>2</b> (2.3)
<b>Treatment-related TEAE</b>		<b>22</b> (25.0)
Severe TEAE		<b>11</b> (12.5)
	Total	<b>1</b> (1.1)
Deaths	COVID-19/ COVID-19 pneumonia	0
	Cerebral hemorrhage	<b>1</b> (1.1)

\*MG-related TEAE was defined *post-hoc* as any adverse event of '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. <sup>†</sup>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

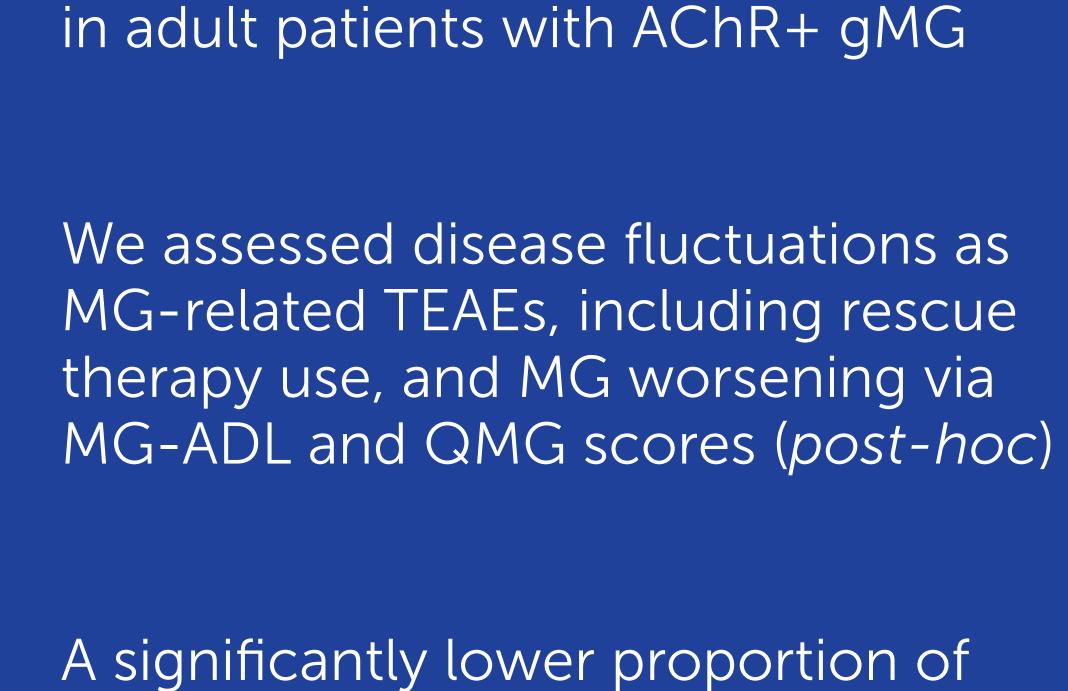
### Rescue therapy use in patients who experienced **MG-related TEAEs**



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

# Summary and conclusions





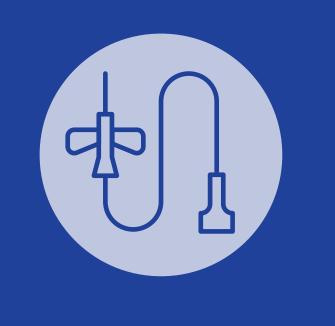
RAISE was a randomized, double-blind,

zilucoplan, a complement C5 inhibitor,

placebo-controlled Phase 3 study 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



RAISE

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

breviations: AChR+, acetylcholine receptor autoantibody-positive; C5(b), complement component 5(b); CFB, change from baseline; COVID-19, coronavirus disease 2019; (g)MG, (generalized) myasthenia gravis; IMP, investigational medicinal product; IVIg, intravenous immunoglobulin; MAC, membrane attack complex; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; mITT, modified intention to treat; MMF, mycophenolate mofetil; NMJ, euromuscular junction; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SCIg, subcutaneous immunoglobulin; SD, standard deviation; TEAE, treatmentemergent adverse event; ZLP, zilucoplan.

Acknowledgments: This study was funded by UCB Pharma. The authors acknowledge David Onoja and Rachel Price, PhD, of Ogilvy Health, London, UK, for editorial support in the form of writing, drafting tables and figures, collating author comments, and editorial assistance, which was funded by UCB Pharma. The authors acknowledge Veronica Porkess, PhD, of UCB Pharma, Slough, UK, for publication coordination. The authors thank the patients and their caregivers, in addition to the investigators and their teams who contributed to this study.

Author disclosures: Angela Genge has served as a paid Consultant for Medtronic, Atlantic Research Group, Calico, Apellis, Annexon, ALS Pharmaceuticals, QurAlis, Orion, Sanofi Genzyme, Ionis, Wave Life Therapies, Anelixis, Roche, Cytokinetics, Mitsubishi Tanabe Pharma, Amylyx, Alexion Pharmaceuticals, UCB Pharma, Ra Pharmaceuticals (now UCB Pharma), Biogen, Eli Lilly, and Amicus Therapeutics. Channa Hewamadduma has received funding for consultancy on scientific or educational advisory boards for UCB Pharma, argenx, Lupin, Roche and Biogen. His study activities were supported by a Sheffield NIHR BRC UK centre grant. Yessar Hussain was the Principal Site Investigator in the RAISE study and has no financial disclosures. Raphaëlle Beau Lejdstrom, Babak Boroojerdi, Fiona Grimson and Natasa Savic are employees and

shareholders of UCB Pharma. James F. Howard Jr. has received research support (paid to his institution) from Alexion Pharmaceuticals, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention (Atlanta, GA, USA), the Myasthenia Gravis Foundation of America, the Muscular Dystrophy Association, the National Institutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases), PCORI, Ra Pharmaceuticals (now UCB Pharma), and Takeda Pharmaceuticals; honoraria from AcademicCME, Alexion Pharmaceuticals, argenx, Biologix Pharma, F. Hoffmann-La Roche, Immunovant, Merck EMD Serono, NMD Pharma, Novartis, PeerView CME, Ra Pharmaceuticals (now UCB Pharma), Regeneron Pharmaceuticals, Sanofi US, Viela Bio (now Horizon Therapeutics) and Zai Lab; and non-financial support from Alexion Pharmaceuticals, argenx, Ra Pharmaceuticals (now UCB Pharma), and Toleranzia AB.



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 use this QR code to download a PDF of the poster.