Effect of zilucoplan on myasthenia gravis-specific outcome subdomain scores in RAISE: A Phase 3 study

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Conflicts of interest

Michael D. Weiss has received honoraria for serving on scientific advisory boards for Alexion Pharmaceuticals, Amylyx Pharmaceuticals, argenx, Biogen, Immunovant, Mitsubishi Tanabe Pharma and Ra Pharmaceuticals (now UCB), consulting honoraria from CSL Behring and Cytokinetics, and speaker honoraria from Soleo Health. He also serves as a special government employee for the Food and Drug Administration.

Constantine Farmakidis has received funding for medical advisory board participation from Argenx, J&J and UCB and has served as a paid Consultant for the Muscular Dystrophy Association and UCB.

Miriam Freimer has served as a paid Consultant for Arcellx, argenx and UCB. She receives research support from Abcuro, Alnylam Pharmaceuticals, argenx, Avidity Biosciences, COUR Pharmaceuticals, Dianthus Therapeutics, Fulcrum Therapeutics, Johnson & Johnson Innovative Medicine, the NIH, RemeGen Biosciences and UCB.

Angela Genge has served as a paid Consultant for Alexion Pharmaceuticals, ALS Pharmaceuticals, Amicus Therapeutics, Amylyx Pharmaceuticals, Anelixis Pharmaceuticals, Annexon Biosciences, Apellis Pharmaceuticals, Atlantic Research Group, Biogen, Calico, Cytokinetics, Eli Lilly, Ionis Pharmaceuticals, Medtronic, Mitsubishi Tanabe Pharma, Orion, QurAlis, Ra Pharmaceuticals (now UCB), Roche, Sanofi Genzyme (now Sanofi), UCB and Wave Life Sciences.

Channa Hewamadduma has received funding for consultancy on scientific or educational advisory boards for argenx, Biogen, Lupin, Roche and UCB, and has received an investigator-led research grant from UCB. His study activities were supported by a Sheffield NIHR BRC UK centre grant. He is a trustee of the myasthenia gravis patient organization Myaware.

Yessar Hussain was the RAISE Principal Investigator and has no financial disclosures.

M. Isabel Leite is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from UK associations for patients with myasthenia and with muscular disorders (Myaware and Muscular Dystrophy UK, respectively) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, the Guthy-Jackson Charitable Foundation, Novartis and UCB. She serves on scientific or educational advisory boards for argenx, Horizon Therapeutics (now Amgen) and UCB.

Angelina Maniaol has received payment for travel, meeting attendance, consulting honoraria or advisory board participation from Alexion Pharmaceuticals, argenx, Biogen, CSL Behring, Novartis and UCB.

Kimiaki Utsugisawa has served as a paid Consultant for argenx, Chugai Pharmaceutical, HanAll Biopharma, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Merck, Mitsubishi Tanabe Pharma, UCB and Viela Bio (now Amgen); he has received speaker honoraria from Alexion Pharmaceuticals, argenx, the Japan Blood Products Organization and UCB.

Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, COUR Pharmaceuticals, Dianthus Therapeutics, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron Pharmaceuticals and UCB, and has served as a speaker for Alexion/AstraZeneca Rare Disease, argenx and CSL Behring. He has performed consulting work for Alexion/AstraZeneca Rare Disease, argenx, Dianthus Therapeutics, ImmunAbs and UCB.

Babak Boroojerdi, **Fiona Grimson** and **Natasa Savic** are employees and shareholders of UCB.

James F. Howard Jr. has received research support (paid to his institution) from Ad Scientiam, Alexion/AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention, the Muscular Dystrophy Association, the Myasthenia Gravis Foundation of America, the National Institutes of Health, NMD Pharma, and UCB; has received honoraria/consulting fees from AcademicCME, Alexion/AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.Bio, Hansa Biopharma, Medscape CME, Merck EMD Serono, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, Toleranzia AB and UCB; and has received non-financial support from Alexion/AstraZeneca Rare Disease, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB and UCB.

Statistical analyses were run by UCB.
This study was funded by UCB.
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Introduction and RAISE* study design

- Zilucoplan, a C5 complement inhibitor, showed **rapid** and **clinically meaningful improvement** in **MG-ADL** and **QMG total scores** versus placebo in the randomized, double-blind, placebo-controlled, Phase 3 RAISE study in patients with anti-AChR Ab+ gMG[1]
- gMG is a heterogenous disease, and **patterns of affected muscles may vary between individuals**[2,3]

Objective: Assess the effect of zilucoplan on MG-ADL and QMG subdomain scores in patients with gMG, covering **ocular, bulbar, respiratory** and **limb/axial** muscle groups

Adults with anti-AChR Ab+ gMG

Patients self-administered daily SC injections for 12 weeks

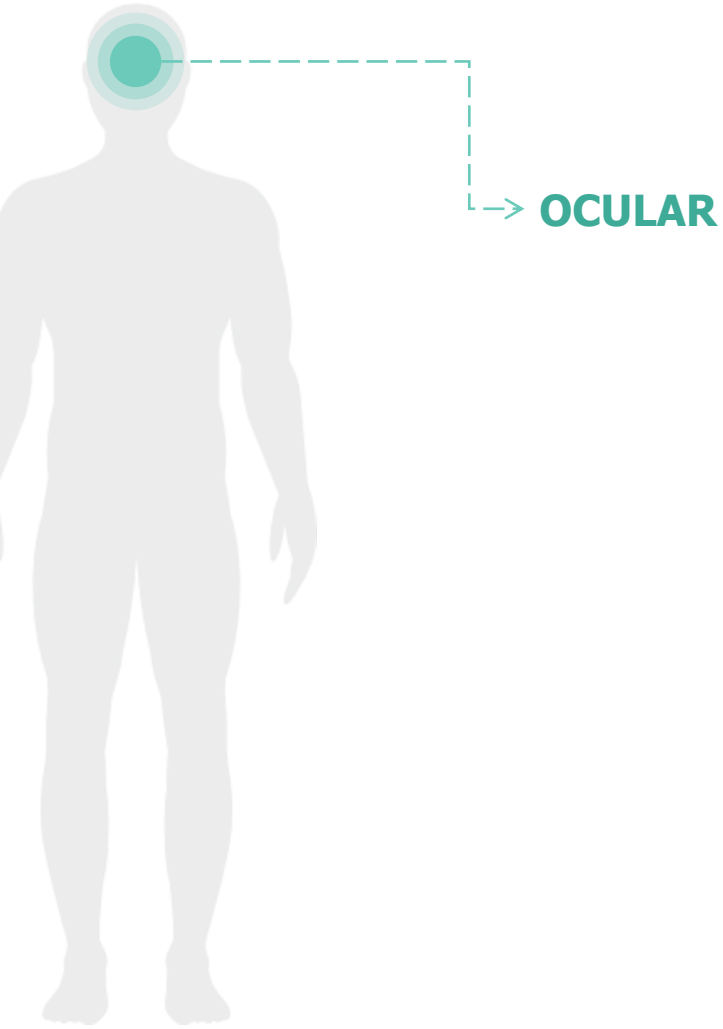
Zilucoplan 0.3 mg/kg
or
placebo

***Post hoc* analyses**

CFB in MG-ADL & QMG subdomain scores at Week 12 in patients with BL subdomain scores ≥1

*NCT04115293.
Anti-AChR Ab+, positive for autoantibodies against the acetylcholine receptor; BL, baseline; C5, component 5; CFB, change from baseline; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous.
1. Howard JF Jr., et al. Lancet Neurol. 2023;22(5):395–406. 2. Gilhus NE, et al. Nat Rev Dis Primers. 2019;5(1):30. 3. Gilhus NE, Verschuuren JJ. Lancet Neurol. 2015:14(10):1023–1036.

MG-ADL and QMG subdomains assessed in RAISE



MG-ADL items[1] Score 0–3 per item	QMG items[2] Score 0–3 per item
• Double vision • Eyelid droop	• Double vision • Ptosis • Facial muscles

MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis.

1. Wolfe GI, et al. Neurology. 1999;52(7):1487–1489. 2. Barohn RJ, et al. Ann N Y Acad Sci. 1998;841:769–772.

MG-ADL and QMG subdomains assessed in RAISE

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BULBAR	• Talking • Chewing • Swallowing	• Swallowing • Speech

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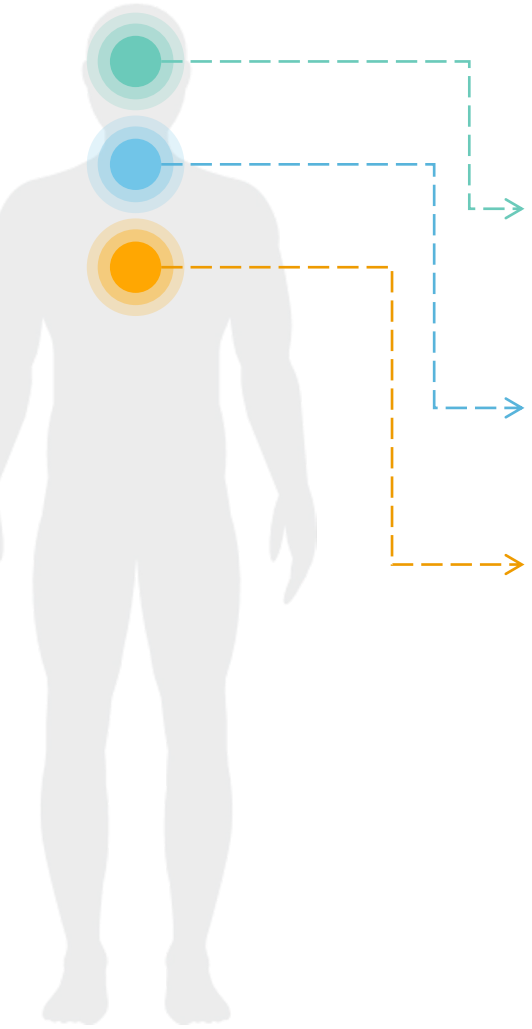

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BULBAR	• Talking • Chewing • Swallowing	• Swallowing • Speech
RESPIRATORY	• Breathing	• Forced vital capacity

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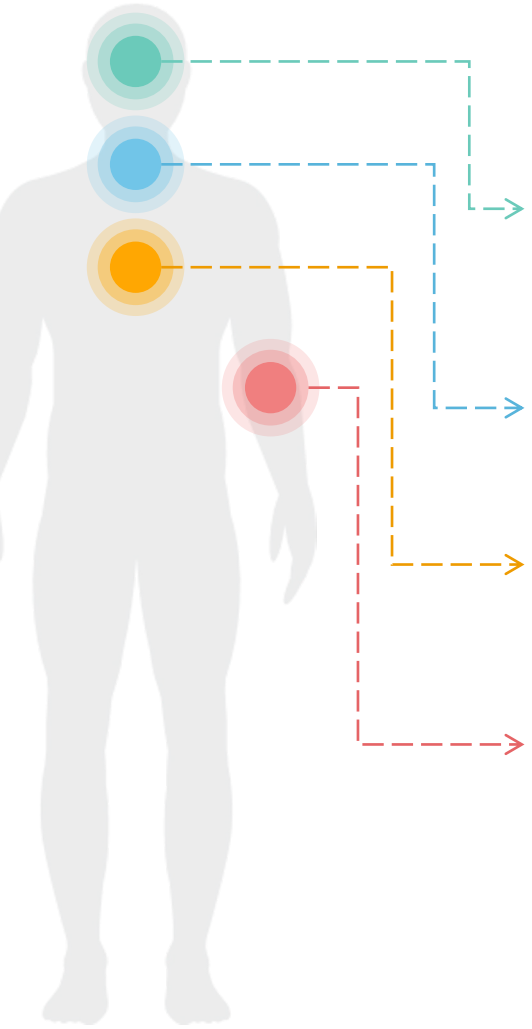

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RESPIRATORY	• Breathing	• Forced vital capacity
LIMB/AXIAL	Impairment of ability to: • Brush teeth or hair • Arise from a chair	• Right/left arm outstretched • Right/left hand grip • Right/left leg outstretched • Head, lifted

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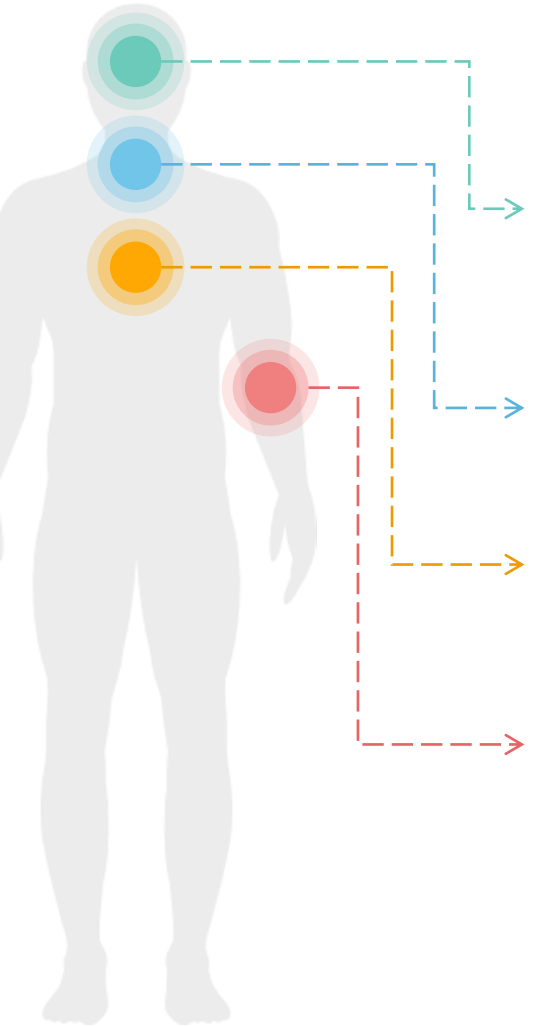

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Post hoc analysis: CFB in MG-ADL and QMG subdomain scores at Week 12
in patients with subdomain scores ≥1 at BL*

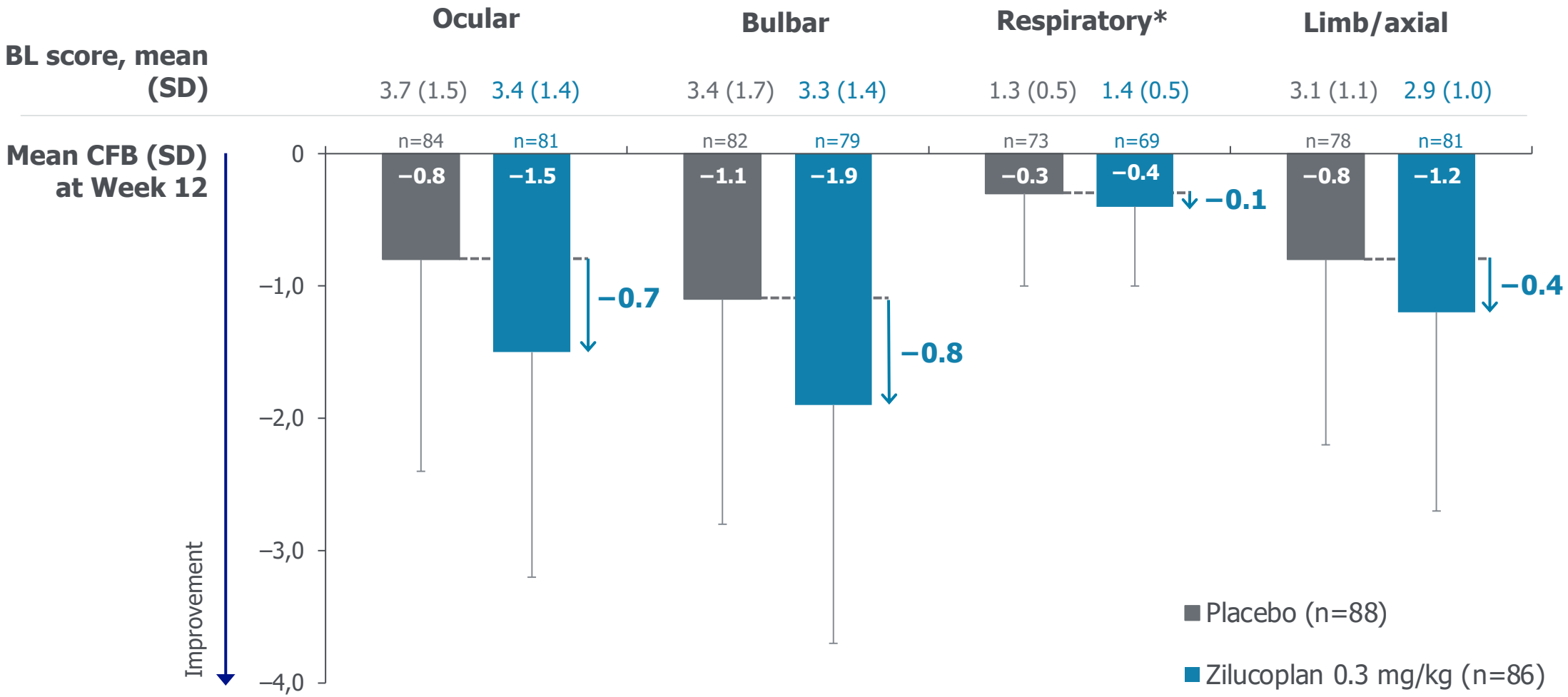
*mITT population, including all randomized patients who received at least one dose of study drug and had at least one post-dosing MG-ADL score.
BL, baseline; CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living; mITT, modified intent-to-treat; QMG, Quantitative Myasthenia Gravis.
1. Wolfe GI, et al. Neurology. 1999;52(7):1487–1489. 2. Barohn RJ, et al. Ann N Y Acad Sci. 1998;841:769–772.

RAISE included a broad, mild-to-severe gMG population

		Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
Age, years, mean (SD)		53.3 (15.7)	52.6 (14.6)
Sex, female, n (%)		47 (53.4)	52 (60.5)
White, n (%)		62 (70.5)	66 (76.7)
MGFA Disease Class, n (%)	IIa/IIb	27 (30.7)	22 (25.6)
	IIIa/IIIb	57 (64.8)	60 (69.8)
	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)
Duration of disease from diagnosis, years, mean (SD)		9.0 (10.4)	9.3 (9.5)
Prior MG crisis, n (%)		29 (33.0)	28 (32.6)
Thymoma diagnosis, n (%)		18 (20.5)	21 (24.4)
Previous thymectomy, n (%)		37 (42.0)	45 (52.3)
Prior corticosteroids,* n (%)		74 (84.1)	77 (89.5)
Prior NSISTs,* n (%)		54 (61.4)	49 (57.0)

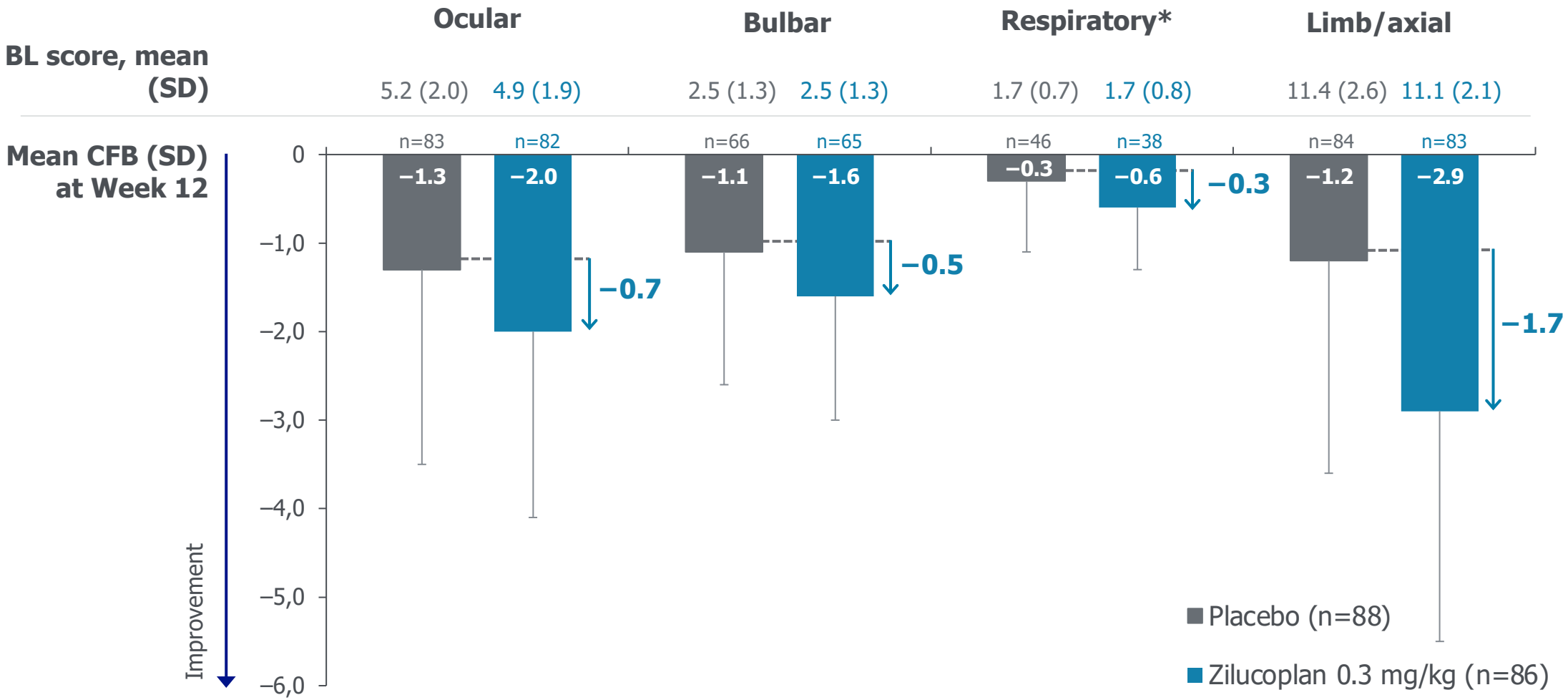
mITT population, unless otherwise stated. *Safety set, including all randomized patients who received at least one dose of either placebo or zilucoplan.
gMG, generalized myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; mITT, modified intent-to-treat; NSIST, non-steroidal immunosuppressant therapy; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.

MG-ADL scores improved at Week 12 across all subdomains in patients with subdomain BL scores ≥1



mITT population. Data shown for patients with MG-ADL subdomain score ≥1 at BL for the relevant subdomain. Error bars denote SD.
*Patients had mild respiratory symptoms at baseline; mean (SD) MG-ADL respiratory subdomain scores at baseline were 1.1 (0.6) for placebo and 1.1 (0.7) for zilucoplan in the overall population.
BL, baseline; CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living; mITT, modified intent-to-treat; SD, standard deviation.

QMG scores improved at Week 12 across all subdomains in patients with subdomain BL scores ≥1



mITT population. Data shown for patients with QMG subdomain ≥1 at BL for the relevant subdomain. Error bars denote SD.
*Patients had mild respiratory symptoms at baseline; mean (SD) QMG respiratory subdomain scores at baseline were 0.9 (1.0) for placebo and 0.8 (1.0) for zilucoplan in the overall population.
BL, baseline; CFB, change from baseline; mITT, modified intent-to-treat; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.

Zilucoplan demonstrated a favorable safety profile and was well tolerated

	Placebo (N=88)	**Zilucoplan 0.3 mg/kg** (N=86)
Any TEAE, n (%)	62 (70.5)	66 (76.7)
Serious TEAEs, n (%)	13 (14.8)	11 (12.8)
TEAEs resulting in permanent withdrawal from study drug,* n (%)	2 (2.3)	4 (4.7)
Treatment-related TEAEs, n (%)	22 (25.0)	28 (32.6)
Severe TEAEs, n (%)	11 (12.5)	10 (11.6)
TEAEs leading to death,† n (%)	1 (1.1)	1 (1.2)

Safety set.
*Includes all deaths. †One patient died in each group; neither death was considered related to the study drug.
TEAE, treatment-emergent adverse event.
Howard JF Jr., et al. Lancet Neurol. 2023;22(5):395–406.

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Most common TEAEs,‡ n (%)	Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
Headache	14 (15.9)	13 (15.1)
MG worsening	8 (9.1)	9 (10.5)
Injection-site bruising	8 (9.1)	14 (16.3)
Diarrhea	2 (2.3)	9 (10.5)

Safety set.
*Includes all deaths. †One patient died in each group; neither death was considered related to the study drug. ‡Most common TEAEs listed are those occurring in ≥10% of patients in either treatment group.
MG, myasthenia gravis; TEAE, treatment-emergent adverse event.
Howard JF Jr., et al. Lancet Neurol. 2023;22(5):395–406.

Summary and conclusions

gMG may affect a range of muscle groups depending on the individual, and treatments may affect these muscle groups differently

In these *post hoc* analyses of the RAISE study, zilucoplan treatment led to improvements from baseline and relative to placebo across all subdomain scores in MG-ADL and QMG

Zilucoplan demonstrated a favorable safety profile and was well tolerated

These data support zilucoplan as a treatment option for patients with gMG across a broad range of symptom patterns

gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis.