Long-term safety and efficacy of zilucoplan in myasthenia gravis: Additional interim analyses of RAISE-XT

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Conflicts of interest

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 (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 and UCB Pharma; honoraria from AcademicCME, Alexion AstraZeneca Rare Disease, argenx, Biologix Pharma, CheckRare CME, F. Hoffmann-La Roche, Medscape CME, Merck EMD Serono, NMD Pharma, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, UCB Pharma, Regeneron Pharmaceuticals, Sanofi US, Horizon Therapeutics (now Amgen) and Zai Labs; non-financial support from Alexion AstraZeneca Rare Disease, argenx, UCB Pharma and Toleranzia AB.

Miriam Freimer has served as a paid Consultant for argenx, UCB Pharma and Alexion Pharmaceuticals. She receives research support from the NIH, UCB Pharma, Janssen Pharmaceuticals, Alnylam, Avidity and Fulcrum.

Angela Genge has served as a paid Consultant for Medtronic, Atlantic Research Group, Calico, Apellis, Anexon, 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 RAISE Principal Investigator and has no financial disclosures.

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

Renato Mantegazza has received funding for travel and meeting attendance or advisory board participation from Alexion Pharmaceuticals, argenx, BioMarin, Catalyst, Sanofi, Regeneron Pharmaceuticals, and UCB Pharma.

Marek Smilowski has nothing to disclose.

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

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

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

Babak Boroojerdi, Guillemette de la Borderie, Petra W. Duda and **Mark Vanderkelen** are employees and shareholders of UCB Pharma.

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 the UK association for patients with myasthenia (Myaware) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, Novartis, UCB Pharma and the Guthy-Jackson Charitable Foundation. She serves on scientific or educational advisory boards for UCB Pharma, argenx and Viela Bio (now Horizon Therapeutics).

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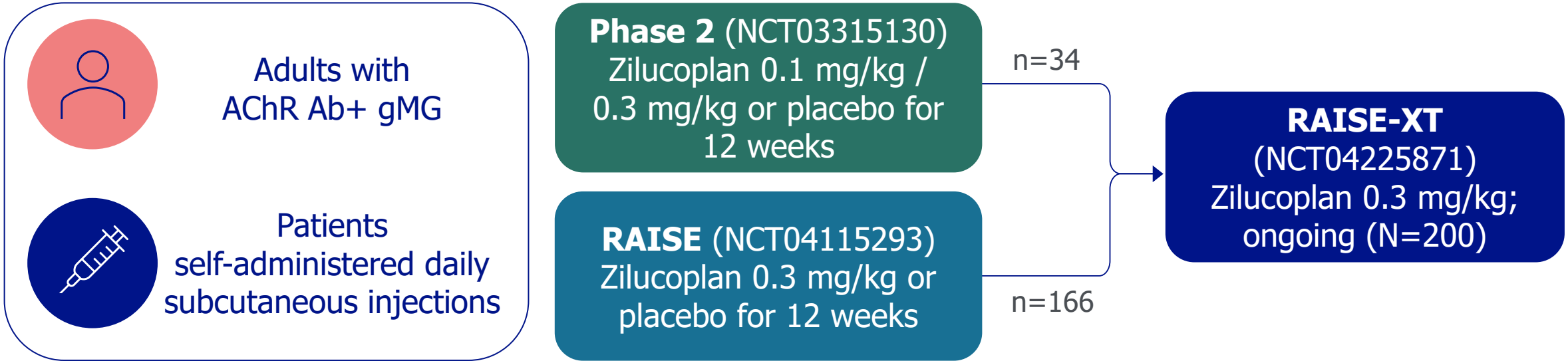
Introduction and study design

- Zilucoplan, a complement C5 inhibitor, showed **significant MG-specific improvements** in patients with AChR Ab+ gMG in the randomized, double-blind, placebo-controlled, Phase 3 RAISE study[1]
- **Long-term data** from RAISE-XT (NCT04225871), an ongoing OLE, will **enhance our understanding** of the **safety and efficacy of zilucoplan** in adults with gMG
- RAISE-XT patients were previously **vaccinated against meningococcus** and received boosters as appropriate

Objective: To evaluate the long-term safety and efficacy of zilucoplan up to 96 weeks of treatment



AChR Ab+, positive for autoantibodies against the acetylcholine receptor; C5, component 5; gMG, generalized myasthenia gravis; MG, myasthenia gravis; OLE, open-label extension.

1. Howard JF Jr., et al. Lancet Neurol. 2023;22(5):395–406.

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

	All zilucoplan (N=200)
Age, years, mean (SD)	53.3 (15.0)
Sex, male, n (%)	90 (45.0)
MGFA Disease Class, n (%)	
II	59 (29.5)
III	129 (64.5)
IV	12 (6.0)
MG-ADL score, mean (SD)	6.3 (4.3)
QMG score, mean (SD)	14.0 (5.9)

	All zilucoplan (N=200)
Prior thymectomy, n (%)	96 (48.0)
Prior MG crisis, n (%)	62 (31.0)
Thymoma diagnosis, n (%)	48 (24.0)
Duration of disease, years, mean (SD)	9.38 (9.73)
Baseline gMG-specific medication, n (%)	
Corticosteroids	124 (62.0)
Immunosuppressants	101 (50.5)
Cholinesterase inhibitors	167 (83.5)

gMG, generalized myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.

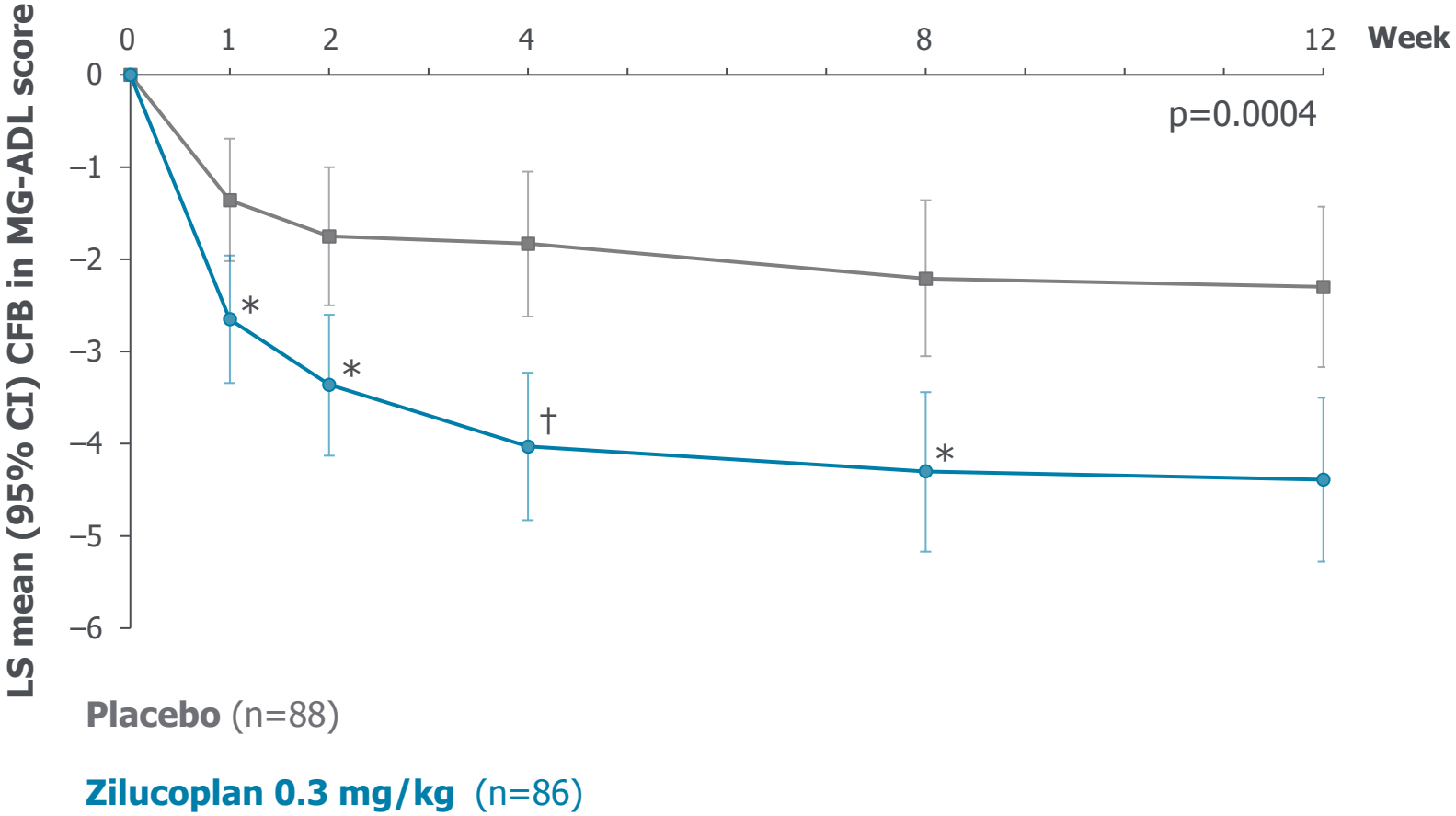
Zilucoplan demonstrated a favorable safety profile and was well tolerated

	All zilucoplan N=200
Duration of zilucoplan exposure, years, median (range)	1.8 (0.11–5.1)
Any TEAE, n (%)	191 (95.5)
Serious TEAE, n (%)	71 (35.5)
TEAE resulting in permanent withdrawal from IMP,† n (%)	19 (9.5)
Treatment-related TEAE, n (%)	70 (35.0)
Severe TEAE, n (%)	64 (32.0)
TEAEs leading to death,‡ n (%)	4 (2.0)

Most common TEAEs	**All zilucoplan** N=200
COVID-19, n (%)	64 (32.0)
Myasthenia gravis, n (%)	58 (29.0)
Headache, n (%)	40 (20.0)
Nasopharyngitis, n (%)	39 (19.5)
Diarrhea, n (%)	33 (16.5)
Nausea, n (%)	32 (16.0)
Arthralgia, n (%)	32 (16.0)
URTI, n (%)	32 (16.0)
Fatigue, n (%)	30 (15.0)

†Includes all deaths. ‡No deaths were considered treatment related. TEAEs leading to death included cardiac arrest (n=2) and accidental head injury (n=1) in the zilucoplan 0.3 mg/kg / 0.3 mg/kg group, and death from an unknown cause (n=1) in the placebo / zilucoplan 0.3 mg/kg group. Most common TEAEs occurring in ≥15% of patients overall are reported only. Data cutoff: May 11, 2023.
COVID-19, coronavirus disease 2019; IMP, investigational medicinal product; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

RAISE: Rapid and clinically meaningful improvements in MG-ADL score



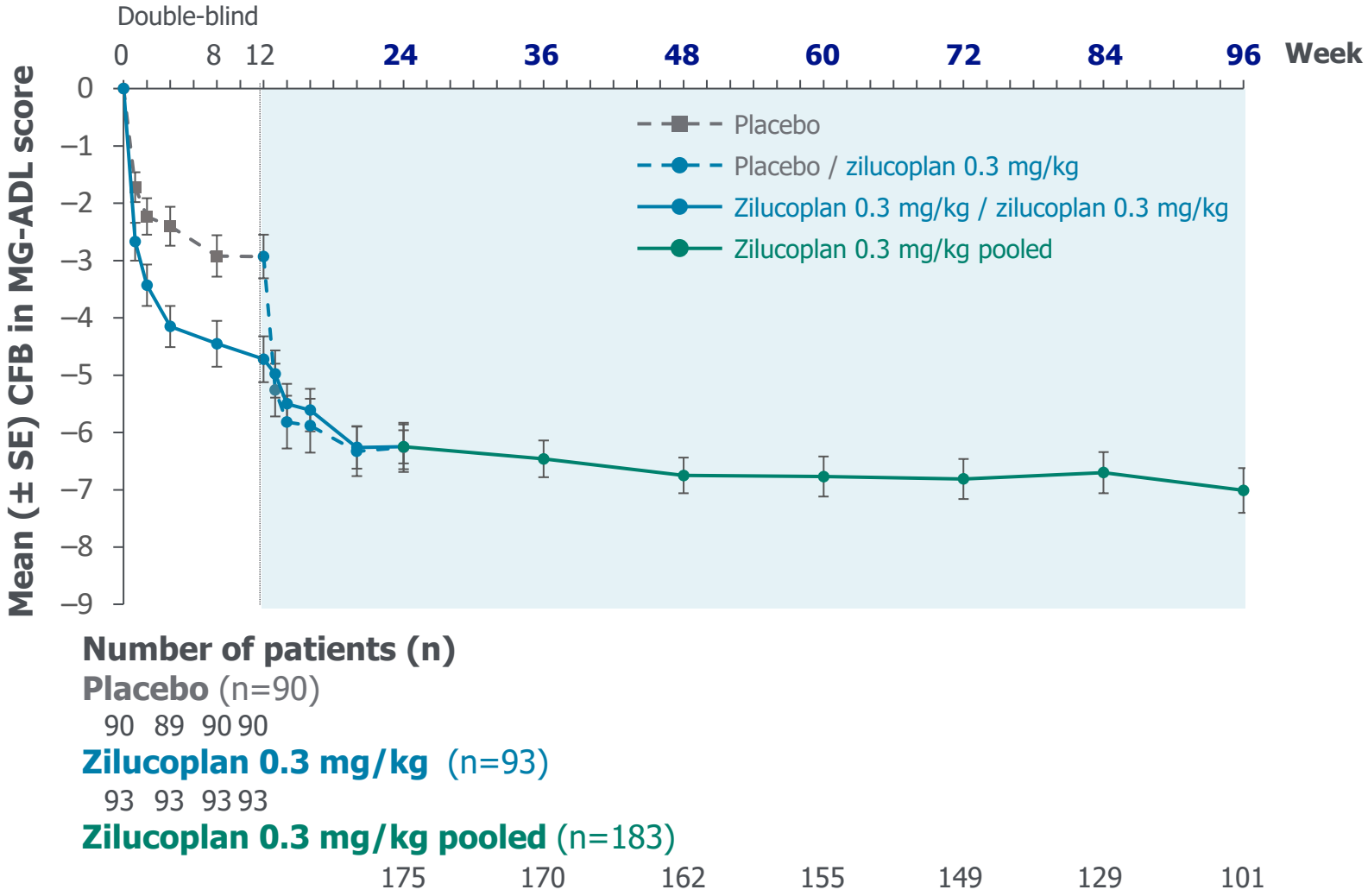
Mean CFB in MG-ADL score:

- **Rapid effect at Week 1** with **clinically meaningful improvement‡ at Week 12** for those receiving zilucoplan[1]

*p<0.01 vs placebo (*post hoc*, not multiplicity controlled). †p<0.001 vs placebo (*post hoc*, not multiplicity controlled). ‡≥2-point change in MG-ADL score indicates a clinically meaningful improvement. CFB, change from baseline in qualifying double-blind study; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living; LS, least squares.

1. Howard JF Jr., et al. Lancet Neurol. 2023;22(5):395–406.

RAISE-XT: Improvements in MG-ADL score were sustained through to Week 96



Mean CFB in MG-ADL score:

- **Increased rapidly at Week 1** in those who switched from placebo to zilucoplan
- **Continued to improve through to Week 24 and was sustained through to Week 96** for pooled zilucoplan 0.3 mg/kg patients

Similar patterns over time were observed for:

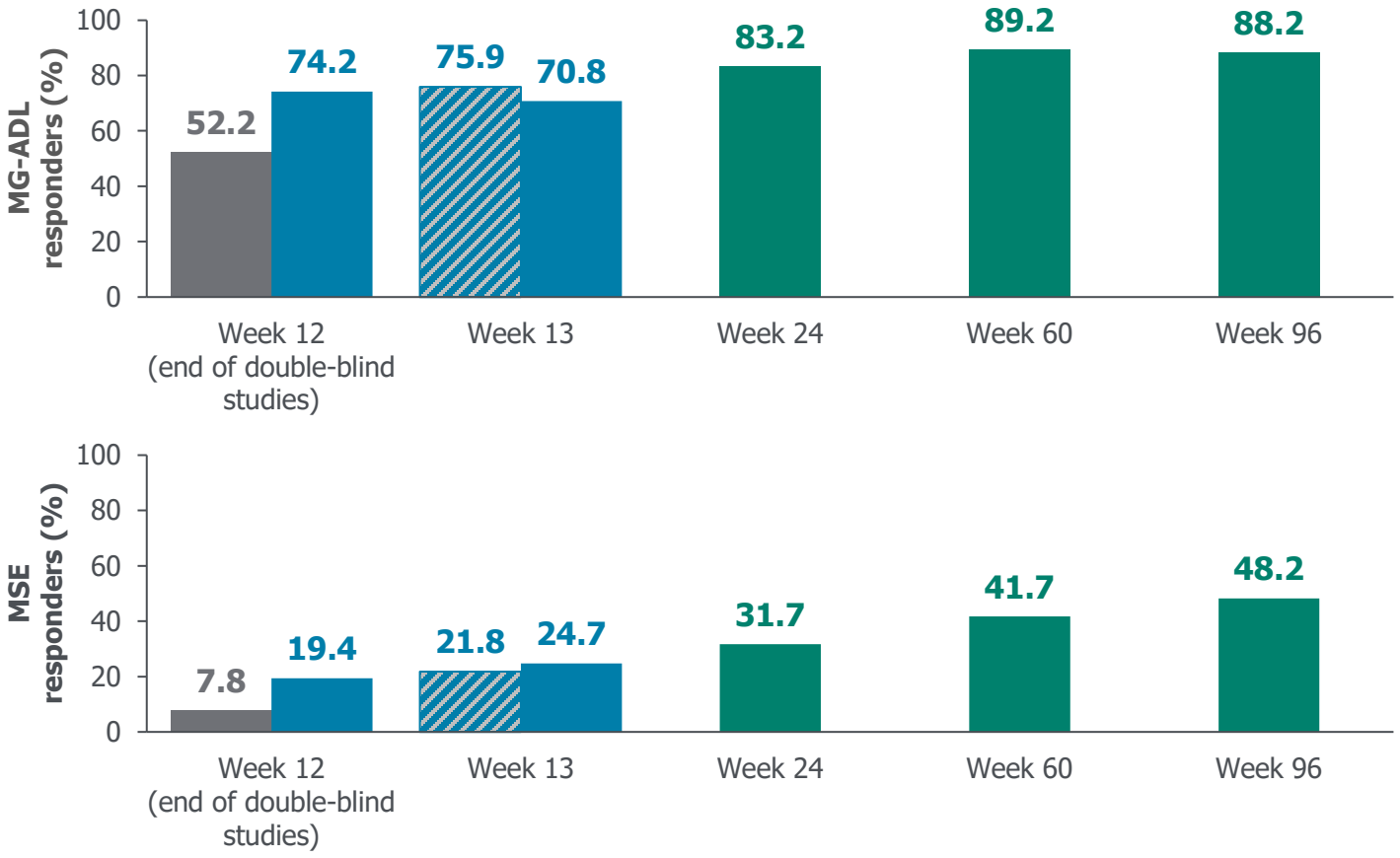
- **QMG score**
- **MGC score**
- **MG-QoL 15r score**
- **Neuro-QoL fatigue score**

Data cutoff: May 11, 2023.
CFB, change from baseline in qualifying double-blind study; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MG-QoL 15r, Myasthenia Gravis Quality of Life 15-item revised; Neuro-QoL, Quality of Life in Neurological Disorders; QMG, Quantitative Myasthenia Gravis; SE, standard error.

MG-ADL responder rates were sustained and MSE responder rates improved through to Week 96

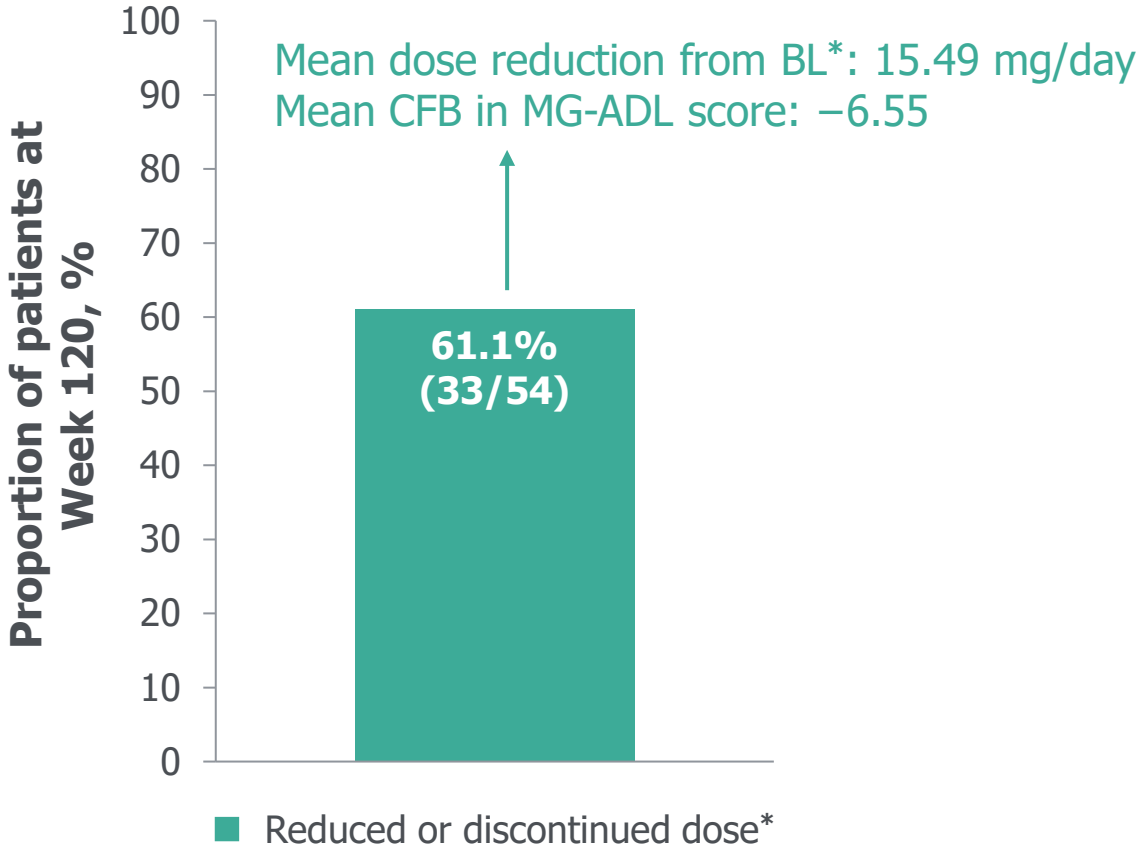
- **MG-ADL responder rates** (≥3-point improvement from baseline*) were high and sustained through to Week 96

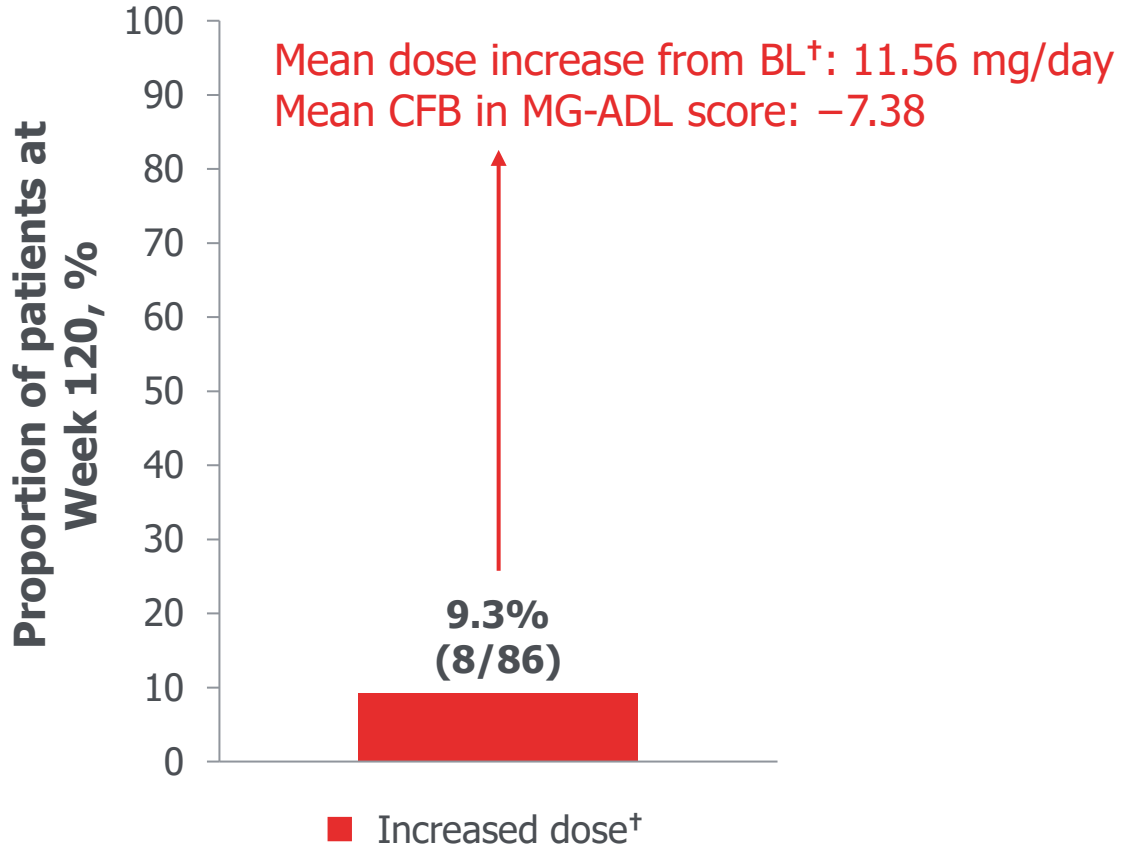
- **MSE responder rates** (MG-ADL score of 0 or 1) increased rapidly and continued to improve through to Week 96



*In participants who have not received rescue medication. Data cutoff: May 11, 2023.
MG-ADL, Myasthenia Gravis Activities of Daily Living; MSE, minimal symptom expression.

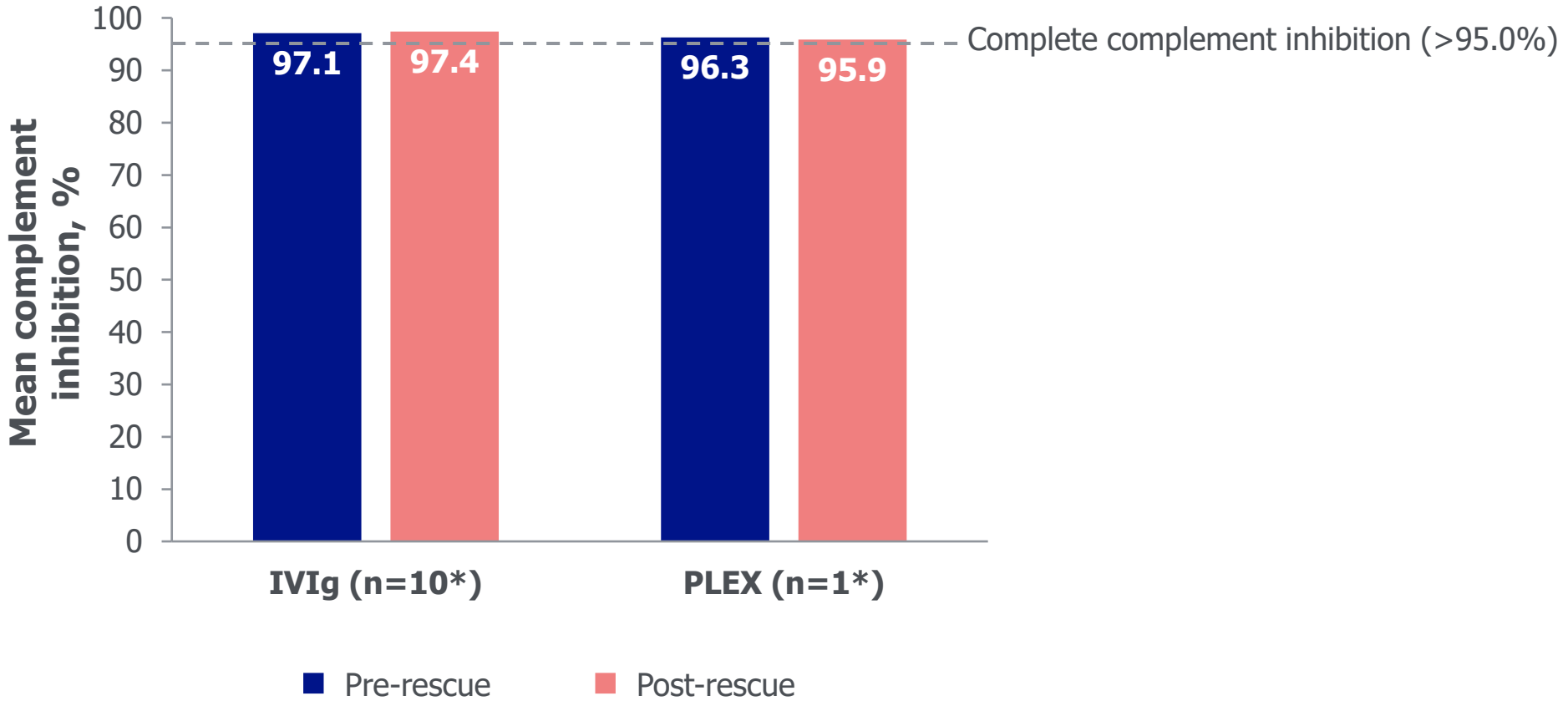
61% of patients reduced or discontinued corticosteroid dose during zilucoplan treatment with maintained efficacy





*Among patients receiving corticosteroid treatment at double-blind BL (N=54). †Among all patients (N=86).
Data cutoff: November 11, 2023. BL, baseline; CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living.

Complete complement inhibition was maintained during concomitant use of zilucoplan with IVIg and PLEX



*Events with available data. Complement activity was measured by sRBC lysis assay, with post-administration measurement taken up to 1 day after rescue treatment.
Data cutoff: September 8, 2022. IVIg, intravenous immunoglobulin; PLEX, plasma exchange; sRBC, sheep red blood cell.

Conclusions

- Zilucoplan had a favorable safety profile and was well tolerated in the long term
- There was a rapid improvement of symptoms, which was sustained through to Week 96
- In the majority of patients, reduction in dose or discontinuation of concomitant corticosteroids was possible with maintained efficacy while receiving zilucoplan
- Complete complement inhibition was maintained after rescue therapy (IVIg or PLEX) during zilucoplan treatment, confirming that zilucoplan can be used concomitantly with IVIg or PLEX without the need for supplemental dosing

IVIg, intravenous immunoglobulin; PLEX, plasma exchange.