Response rates with zilucoplan in generalised myasthenia gravis: 120-week interim analysis of RAISE-XT

James F. Howard Jr.[1], Miriam Freimer[2], Angela Genge[3], Channa Hewamadduma[4,5], Angelina Maniaol[6], Renato Mantegazza[7], Kimiaki Utsugisawa[8], Tuan Vu[9], Michael D. Weiss[10], Babak Boroojerdi[11], Petra W. Duda[12], Fiona Grimson[13], Mark Vanderkelen[14] and M. Isabel Leite[15]

[1]Department of Neurology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, OH, USA; [3]Clinical Research Unit, The Montreal Neurological Institute, Montreal, QC, Canada; [4]Academic Neuroscience Unit, Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK; [5]Sheffield Institute for Translational Neurosciences (SITraN), University of Sheffield, Sheffield, UK; [6]Department of Neurology, Oslo University Hospital, Oslo, Norway; [7]Department of Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS, Istituto Nazionale Neurologico Carlo Besta, Milan, Italy; [8]Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan; [9]Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA; [10]Department of Neurology, University of Washington Medical Center, Seattle, WA, USA; [11]UCB, Monheim, Germany; [12]UCB, Cambridge, MA, USA; [13]UCB, Slough, UK; [14]UCB, Brussels, Belgium; [15]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

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

Miriam Freimer has served as a paid Consultant for Alexion Pharmaceuticals, argenx and UCB. She receives research support from Alnylam Pharmaceuticals, Avidity Biosciences, Fulcrum Therapeutics, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), the NIH and UCB.

Angela Genge has served as a paid Consultant for Alexion Pharmaceuticals, ALS Pharmaceuticals, Amicus Therapeutics, Amylyx Pharmaceuticals, Anelixis Pharmaceuticals, Anexon 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.

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

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.

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); 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 Pharmaceuticals, Amgen, argenx, Cartesian Therapeutics, Dianthus Therapeutics, Immunovant, Johnson & Johnson, Regeneron Pharmaceuticals and UCB, and has served as a speaker for Alexion Pharmaceuticals, argenx, and CSL Behring. He performed consulting work for Alexion Pharmaceuticals, argenx, Dianthus Therapeutics, ImmunAbs and UCB.

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

Babak Boroojerdi, **Petra W. Duda**, **Fiona Grimson** and **Mark Vanderkelen** are employees and shareholders of UCB.

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.

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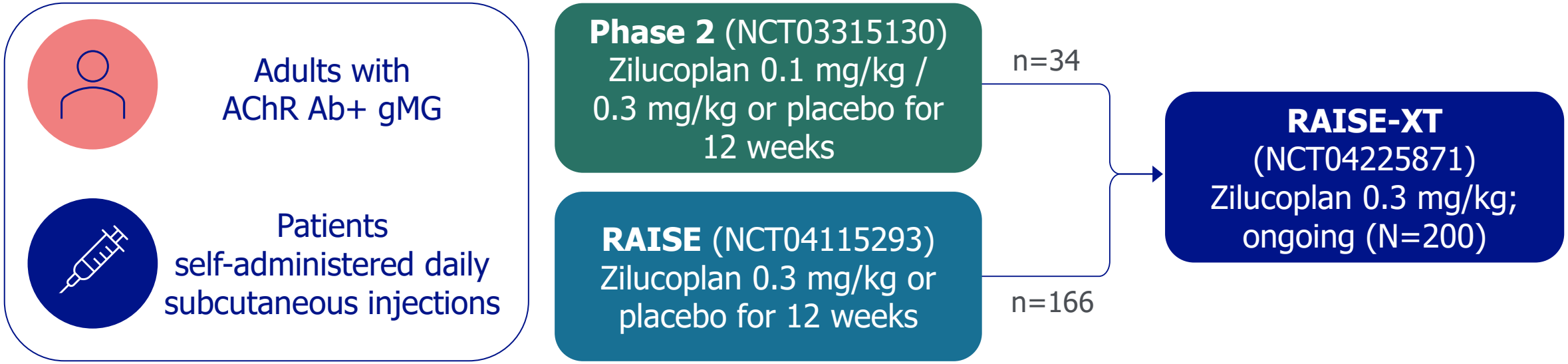
This study was funded by UCB.

Introduction and study design

- Zilucoplan, a macrocyclic peptide complement C5 inhibitor, showed **significant** and **clinically meaningful improvements** in patients with AChR Ab+ gMG in the randomised, 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

Objective: To assess efficacy endpoints, including **MG-ADL**, **QMG** and **MSE response rates**, up to 120 weeks of treatment



Data cut-off: 11 November 2023.
AChR Ab+, positive for autoantibodies against the acetylcholine receptor; C5, component 5; gMG, generalised myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MSE, minimal symptom expression; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis.
1. Howard JF Jr., et al. Lancet Neurol. 2023;22(5):395–406.

RAISE-XT: Baseline characteristics

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

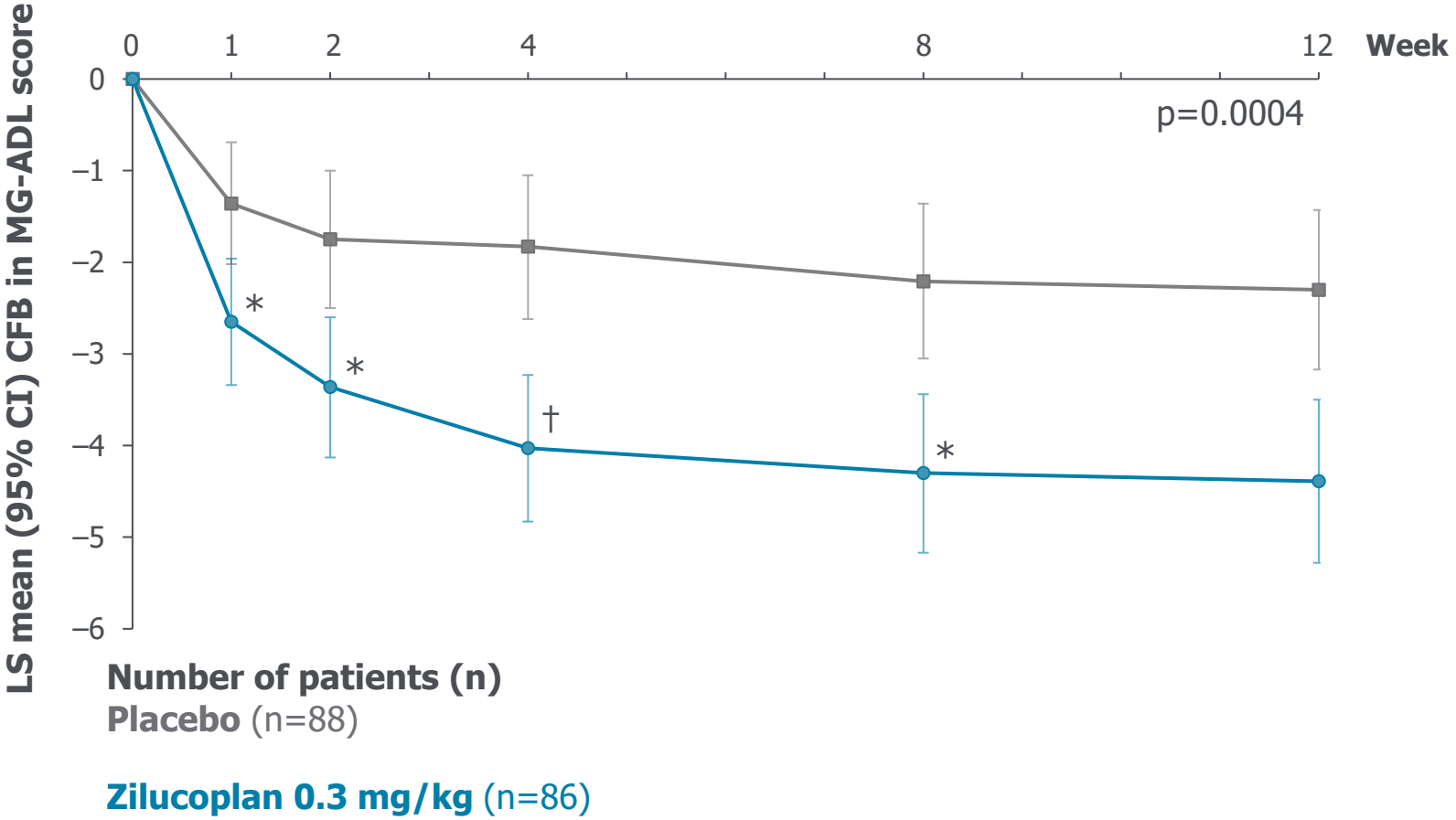
	All zilucoplan (N=200)
Age, years, mean (SD)	53.3 (15.0)
Sex, male, n (%)	90 (45.0)
MGFA Disease Class, n (%)	
IIa/b	59 (29.5)
IIIa/b	129 (64.5)
IVa/b	12 (6.0)
MG-ADL score, mean (SD)	6.3 (4.3)
QMG score, mean (SD)	14.0 (5.9)

	All zilucoplan (N=200)
Prior thymectomy, n (%)	96 (48.0)
Prior MG crisis, n (%)	62 (31.0)
Age at disease onset, years, mean SD	43.6 (17.9)
Duration of disease,* years, mean (SD)	9.4 (9.7)
Baseline gMG-specific medication, n (%)	
Corticosteroids	124 (62.0)
Immunosuppressants	101 (50.5)
Cholinesterase inhibitors	167 (83.5)

*From date of diagnosis.

gMG, generalised 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.

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



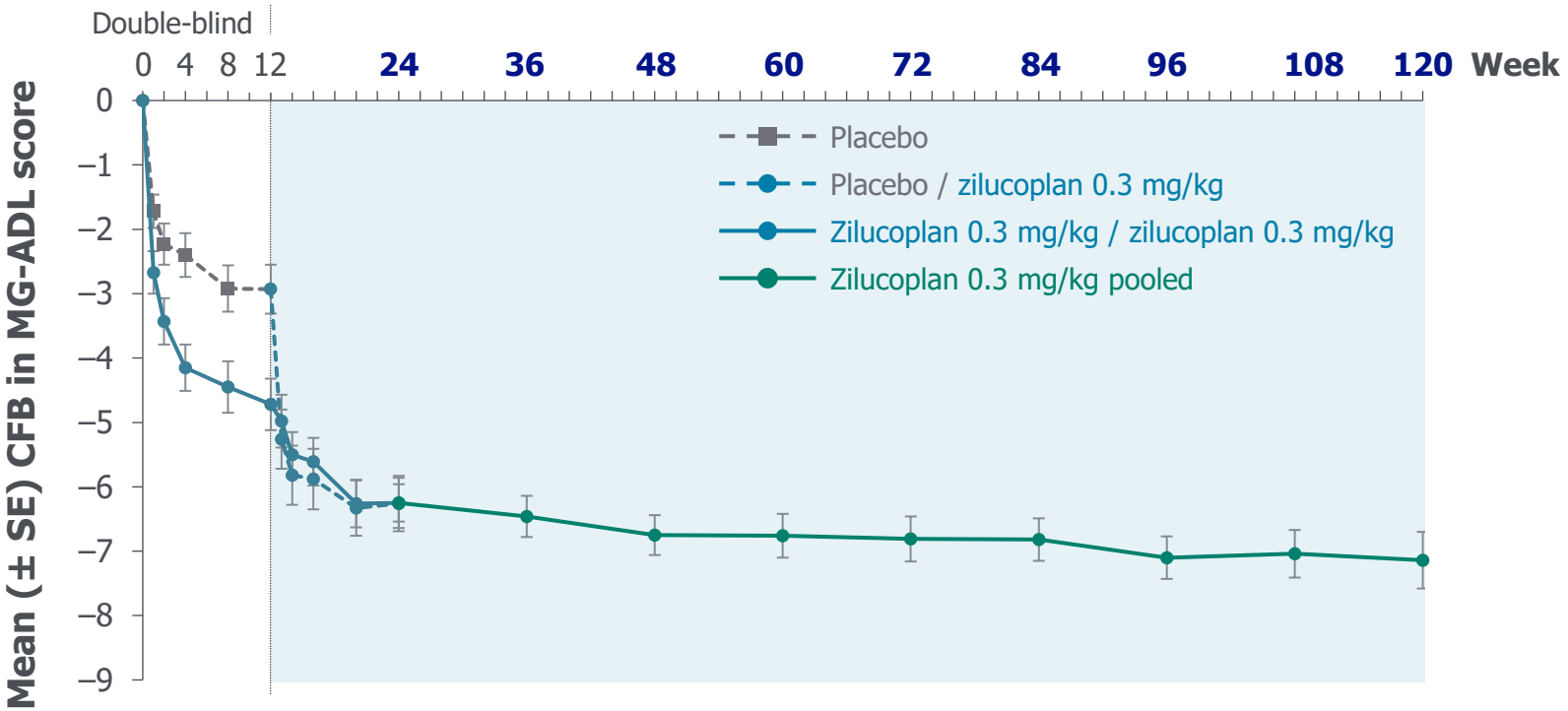
Mean CFB in MG-ADL score:

- **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; 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 120



Number of patients (n)

Placebo (n=90)

90 90

Zilucoplan 0.3 mg/kg (n=93)

93 93

Zilucoplan 0.3 mg/kg pooled (n=183)

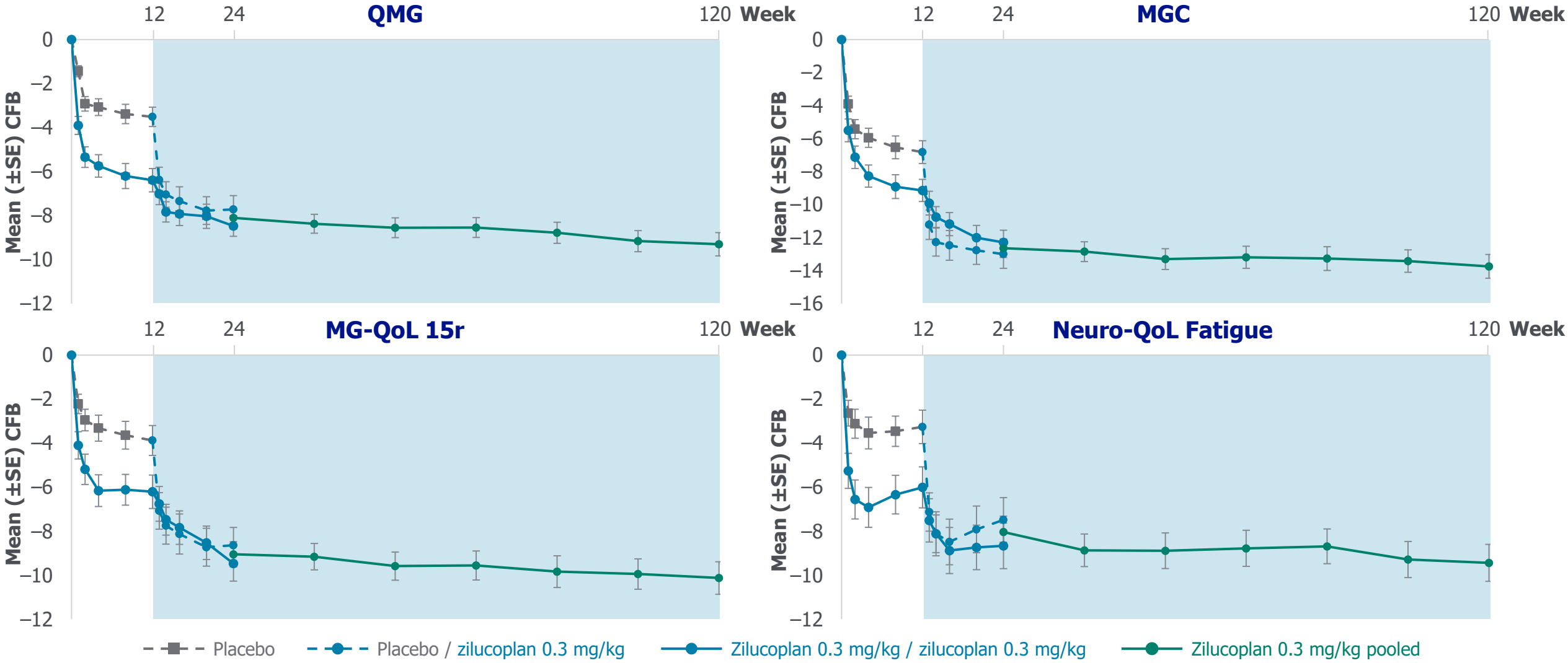
175 170 162 156 149 148 142 123 86

Mean CFB in MG-ADL score:

- **Increased rapidly one week** after **switching** from placebo to zilucoplan 0.3 mg/kg
- **Continued to improve through to Week 24** and was **sustained through to Week 120** for pooled zilucoplan 0.3 mg/kg patients

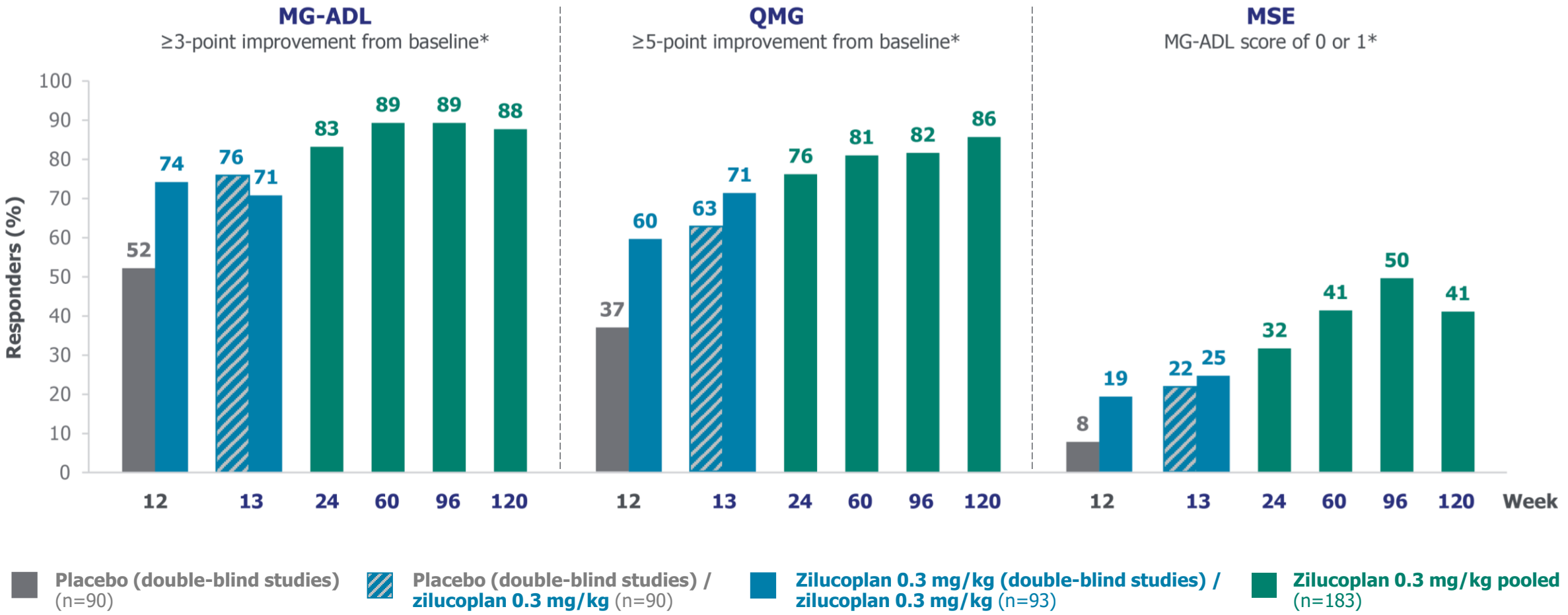
Data cut-off: 11 November 2023.
CFB, change from baseline of qualifying double-blind study; MG-ADL, Myasthenia Gravis Activities of Daily Living; SE, standard error.

Sustained improvements were also observed for other endpoints



Data cut-off: 11 November 2023.
CFB, change from baseline of qualifying double-blind study; 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.

Overall rates of MG-ADL, QMG and MSE responders were high and were sustained through to Week 120



Data cut-off: 11 November 2023.
*Without rescue therapy.
MG-ADL, Myasthenia Gravis Activities of Daily Living; MSE, minimal symptom expression, QMG, Quantitative Myasthenia Gravis.

Most TEAEs were mild or moderate in severity

	All zilucoplan N=200
Duration of exposure, years, median (range)	2.2 (0.1–5.6)
Any TEAE, n (%)	194 (97.0)
Treatment-related TEAE, n (%)	73 (36.5)
Serious TEAE, n (%)	81 (40.5)
Treatment-related serious TEAE,* n (%)	5 (2.5)
Severe TEAE, n (%)	72 (36.0)
TEAE resulting in permanent withdrawal from IMP,† n (%)	21 (10.5)
TEAEs leading to death,‡ n (%)	4 (2.0)

Most common TEAEs	All zilucoplan N=200
COVID-19, n (%)	71 (35.5)
MG worsening, n (%)	59 (29.5)
Headache, n (%)	44 (22.0)
Nasopharyngitis, n (%)	42 (21.0)
Arthralgia, n (%)	36 (18.0)
Diarrhoea, n (%)	34 (17.0)
URTI, n (%)	34 (17.0)
UTI, n (%)	33 (16.5)
Nausea, n (%)	32 (16.0)
Fatigue, n (%)	31 (15.5)

Data cut-off: 11 November 2023. Most common TEAEs occurring in ≥15% of patients overall are reported only.
*Treatment-related serious TEAEs were one (0.5%) event each of: oesophagitis, injection-site infection (occurring on the right inner thigh, which is not a recommended injection site), colonic abscess and cellulitis in one patient each and headache and photophobia in the same patient. †Includes all deaths. ‡No deaths were considered treatment related. TEAEs leading to death included cardiac arrest (n=2), accidental head injury (n=1) and death from an unknown cause (n=1).
COVID-19, coronavirus disease 2019; IMP, investigational medicinal product; MG, myasthenia gravis; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Conclusions

- Patients experienced rapid improvement of symptoms, as early as 1 week after zilucoplan treatment, which were sustained through to Week 120
- Improvements were consistent across MG-ADL, QMG, MGC, MG-QoL 15r and Neuro-QoL Fatigue scores
- High MG-ADL, QMG and MSE responder rates were sustained through to Week 120 of treatment
- Zilucoplan had a favourable safety profile and was well tolerated in the long term

MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MG-QoL 15r, Myasthenia Gravis Quality of Life 15-item revised; MSE, minimal symptom expression; Neuro-QoL, Quality of Life in Neurological Disorders; QMG, Quantitative Myasthenia Gravis.