Early responders with zilucoplan: An interim analysis of RAISE-XT in patients with generalized myasthenia gravis

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MGFA Scientific Session 2023
Phoenix, AZ, USA; November 01, 2023

Conflicts of interest

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.

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).

Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion Pharmaceuticals, argenx, Ra Pharmaceuticals (now UCB Pharma), Viela Bio (now Horizon Therapeutics), Momenta (now Johnson and Johnson), Regeneron Pharmaceuticals, Immunovant and Cartesian Therapeutics, and has received speaking and/or consulting honoraria from Alexion Pharmaceuticals, argenx, Dianthus and UCB Pharma.

Raphaelle Beau Lejdstrom, Babak Boroojerdi, Fiona Grimson, Pauline Payen and **Natasa Savic** are employees and shareholders of UCB Pharma.

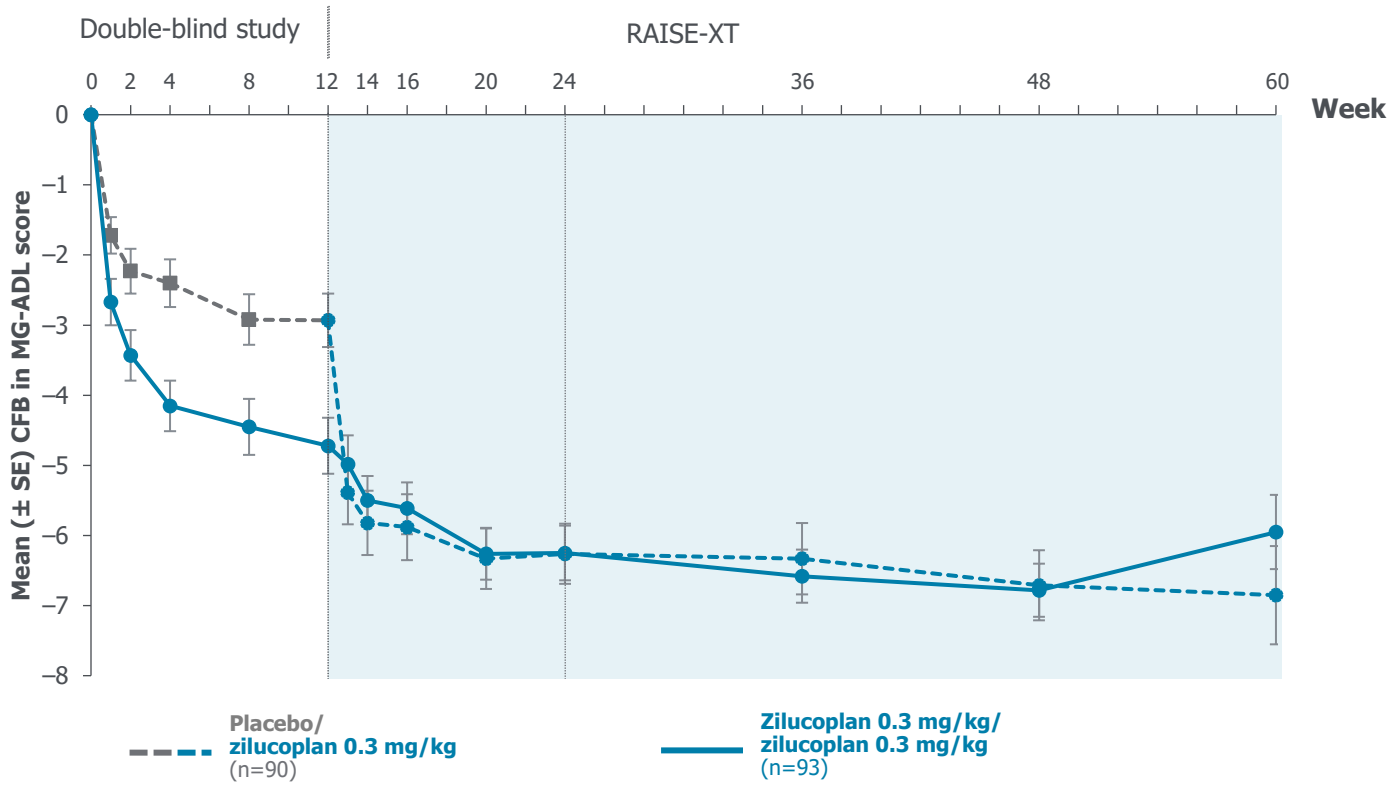
James F. Howard Jr. has received research support (paid to his institution) from Alexion Pharmaceuticals, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention (Atlanta, GA, USA), the Myasthenia Gravis Foundation of America, the Muscular Dystrophy Association, the National Institutes 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, Viela Bio (now Horizon Therapeutics) and Zai Labs; and non-financial support from Alexion Pharmaceuticals, argenx, Ra Pharmaceuticals (now UCB Pharma) and Toleranzia AB.

Statistical analyses were run by UCB Pharma.
This study was funded by UCB Pharma.

Introduction

- Zilucoplan, a complement C5 inhibitor, showed significant MG-specific improvements in patients with AChR Ab+ gMG in Phase 2 and Phase 3 RCTs[1,2]
- Interim analyses of RAISE-XT (NCT04225871), an ongoing OLE, demonstrated that zilucoplan was efficacious and well tolerated in the long term[3]
- Further long-term data from RAISE-XT will enhance our understanding of the safety and efficacy of zilucoplan in patients with gMG

Change from baseline in MG-ADL score[3]



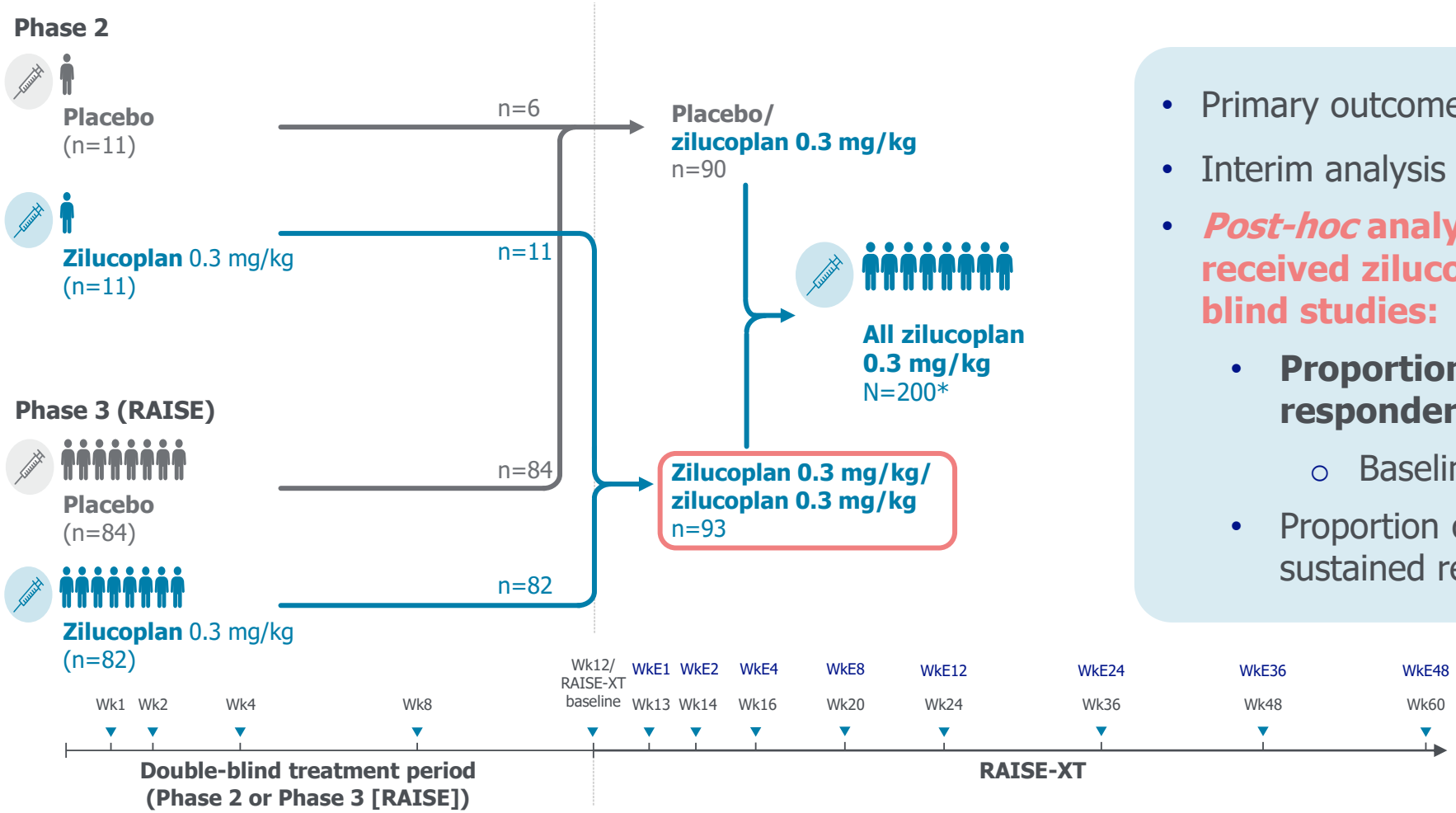
Objective: To assess long-term outcomes and baseline characteristics of MG-ADL and QMG responders at Week 1

AChR Ab+, positive for autoantibodies against the acetylcholine receptor; C5, component 5; gMG, generalized myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; NMJ, neuromuscular junction; QMG, OLE; open-label extension; Quantitative Myasthenia Gravis; RCT, randomized controlled trial; SE, standard error.

1. Howard JF, Jr., et al. JAMA Neurol. 2020;77(5):582–592; 2. Howard JF, Jr., et al. Lancet Neurol. 2023;22(5):395–406;
3. Leite MI, et al. Long-term safety, efficacy and self-injection satisfaction with zilucoplan in myasthenia gravis: an interim analysis of RAISE-XT [poster]. EAN 2023. Poster EPO-219.

Methods

Adults with gMG who completed the zilucoplan Phase 2 or Phase 3 (RAISE) study could opt to enroll in RAISE-XT

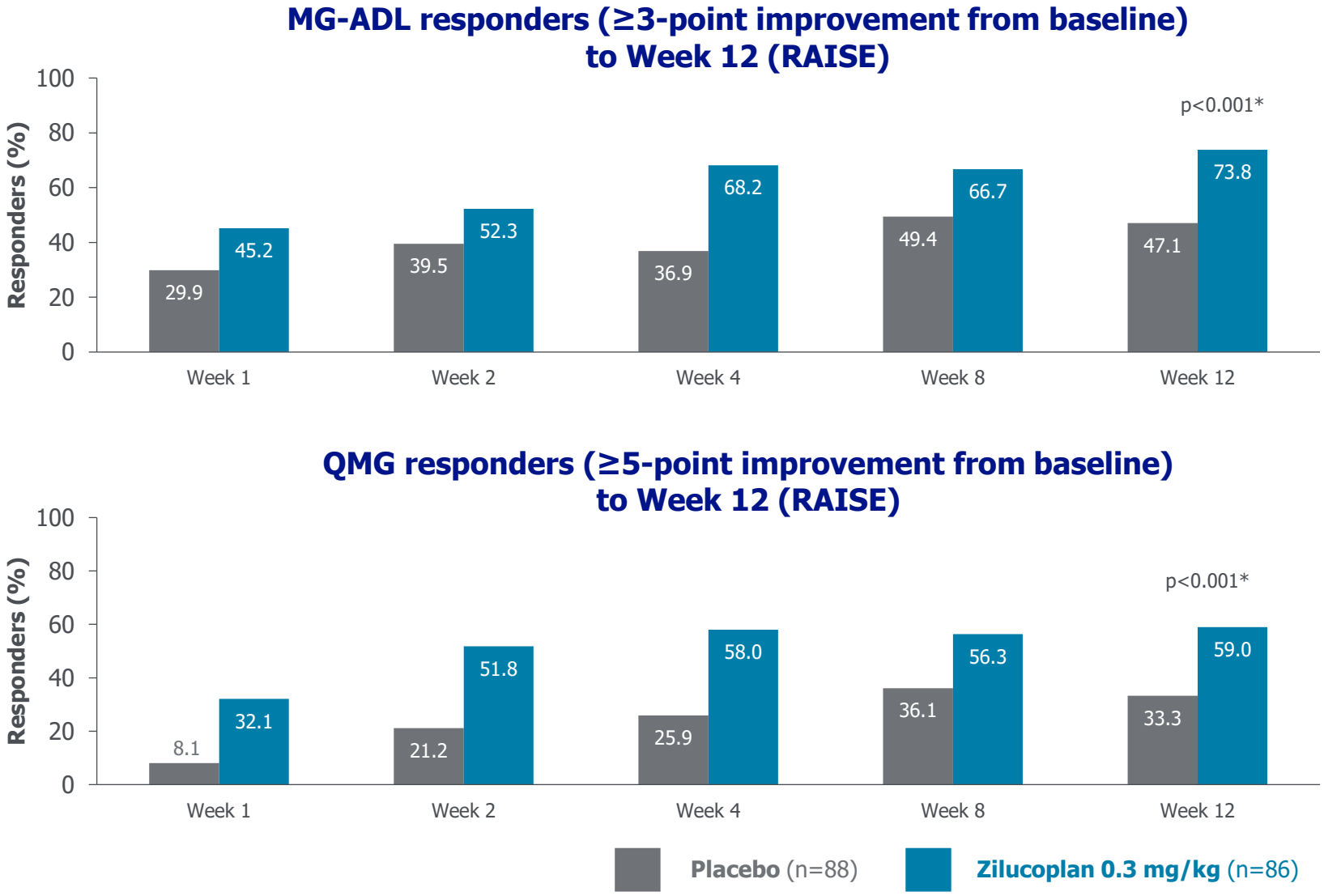


- Primary outcome: incidence of TEAEs
- Interim analysis cut-off: September 08, 2022
- ***Post-hoc* analysis of patients who received zilucoplan 0.3 mg/kg in double-blind studies:**
  - **Proportion of MG-ADL and/or QMG responders† at Week 1**
    - Baseline characteristics
  - Proportion of responders† at Week 1 who sustained response up to Week 60

*Phase 2 and its extension study also included patients who received zilucoplan 0.1 mg/kg (placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg [n=5] and zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg [n=12]. These patients are not included in this efficacy analysis because, due to the small number of participants in each group, no meaningful conclusions can be drawn; however, these patients are included in the 'all zilucoplan' group and assessed for safety.
†Response defined as ≥3.0-point reduction for MG-ADL or ≥5.0-point reduction for QMG, without rescue therapy.
E, extension; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis; TEAE, treatment-emergent adverse event; Wk, Week.

MG-ADL and QMG responder rates to Week 12 in RAISE

- At **Week 12**, significantly more patients in the zilucoplan group were responders compared with placebo
- **Median time to response** was significantly faster with zilucoplan than placebo:
  - **MG-ADL: 15.0** days (95% CI: 9, 18) vs 29.0 days (95% CI: 15, 57); p=0.0012
  - **QMG: 16.0** days (95% CI: 15, 29) vs 86.0 days (95% CI: 57, NA); p<0.001



*p value calculated based on the Chi-squared statistic, serving as exploratory analysis.
CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living; NA, not available; QMG, Quantitative Myasthenia Gravis.

Long-term outcomes of Week 1 MG-ADL and QMG responders

Of patients randomized to zilucoplan 0.3 mg/kg in the double-blind studies (n=93):

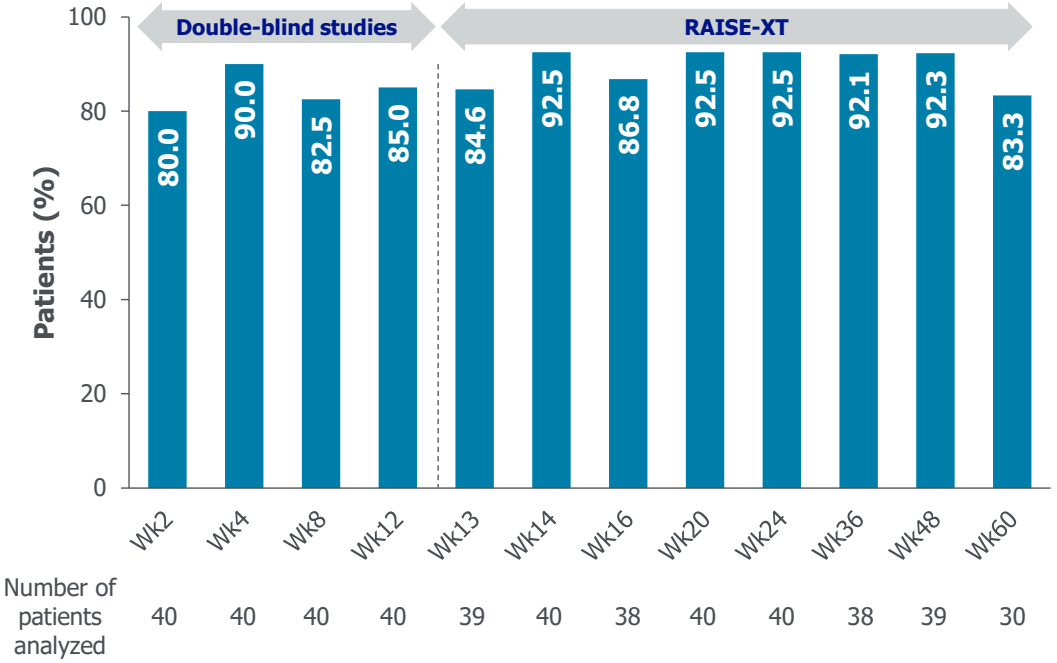
MG-ADL: 43.0% responders at Week 1

- Week 1 responders had **≥80.0%** response rates up to Week 60
- Remained in response for **88.1%** of study

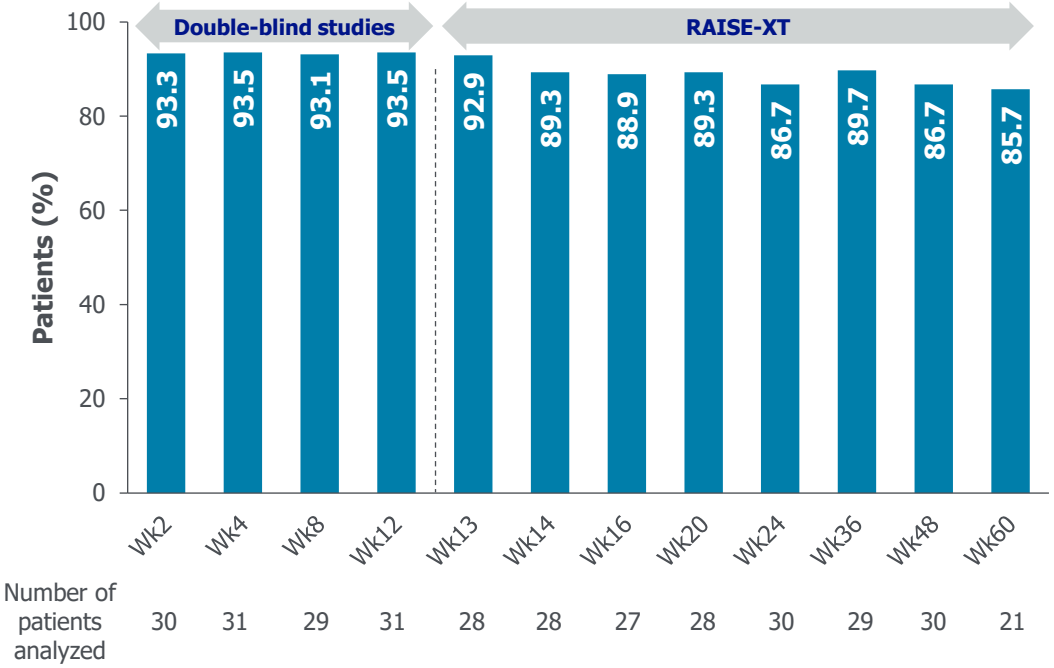
QMG: 33.3% responders at Week 1

- Week 1 responders had ≥**85.7%** response rates up to Week 60
- Remained in response for **88.8%** of study

MG-ADL response rate amongst zilucoplan
MG-ADL responders at Week 1



QMG response rate amongst zilucoplan
QMG responders at Week 1



MG-ADL, Myasthenia Gravis Activities of Daily Living; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis; Wk, Week.

Demographics and baseline disease characteristics of responders at Week 1 versus the overall population

There were no relevant differences between responders at Week 1 compared with the overall population of patients in the zilucoplan group

		Zilucoplan 0.3 mg/kg	
		Responders at Week 1 n=40	**Overall population** n=93
	Age, years, mean (SD)	49.6 (15.7)	52.9 (14.5)
	Sex, male, %	40.0	44.1
MGFA Disease Class	II, %	25.0	26.9
	III, %	60.0	64.5
	IV, %	15.0	8.6
	MG-ADL score, mean (SD)	10.2 (2.6)	9.9 (2.6)
	QMG score, mean (SD)	20.2 (3.9)	18.8 (3.9)
	Prior thymectomy, %	55.0	52.7
	Prior MG crisis, %	30.0*	32.3*
	Duration of disease, years, mean (SD)	8.5 (8.3)	9.4 (9.4)
	Age at onset, years, mean (SD)	41.3 (18.6)	43.4 (17.6)
Prior gMG medications	Corticosteroids, %	92.5	91.4
	Immunosuppressants, %	77.5	68.8
	Cholinesterase inhibitors, %	100.0	97.8

*Missing data for one patient.
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.

Overview of TEAEs in RAISE-XT

Zilucoplan demonstrated a favorable safety profile and was well tolerated; no new safety concerns were identified compared with parent studies

	All zilucoplan N=200
Any TEAE, n (%)	188 (94.0)
Myasthenia gravis, n (%)	52 (26.0)
COVID-19, n (%)	49 (24.5)
Headache, n (%)	35 (17.5)
Diarrhea, n (%)	30 (15.0)
Nasopharyngitis, n (%)	30 (15.0)
Serious TEAE,* n (%)	64 (32.0)
Serious, treatment-related TEAE, n (%)	2 (1.0)
TEAE resulting in permanent withdrawal from IMP,† n (%)	17 (8.5)
Treatment-related TEAE, n (%)	67 (33.5)
Severe TEAE, n (%)	57 (28.5)
TEAEs leading to deaths,‡ n (%)	4 (2.0)

*The most common serious TEAEs were myasthenia gravis worsening (n=15, 8%) and COVID-19 pneumonia (n=4, 2%). Treatment-related serious TEAEs were: one event of esophagitis; and one event of injection site infection (occurring on the right inner thigh, which is not a recommended injection site). †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.
COVID-19, coronavirus disease 2019; IMP, investigational medicinal product; TEAE, treatment-emergent adverse event.

Conclusions

- MG-ADL and QMG responders at Week 1 remained responders for almost 90% of the time up to Week 60 of zilucoplan treatment
- In Week 1 responders, response rates were at least 80% for MG-ADL and 85% for QMG throughout the double-blind and OLE phases of the study, up to Week 60
- There were no meaningful differences in the baseline disease characteristics of MG-ADL and QMG responders at Week 1 compared with the overall population of patients in the zilucoplan group
- Zilucoplan had a favorable safety profile and was well tolerated in the long term
- These data demonstrate that responders at Week 1 sustained their response over long-term zilucoplan treatment

AChR Ab+, positive for autoantibodies against the acetylcholine receptor; gMG, generalized myasthenia gravis;
MG-ADL, Myasthenia Gravis Activities of Daily Living; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis.