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Quality of life outcomes in RAISE: A double-blind randomized, placebo-controlled study of zilucoplan in gMG

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on behalf of the RAISE investigators

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Zilucoplan is an investigational new product and has not been approved by any authority.

Disclosures

Michael D. Weiss has received honoraria for serving on scientific advisory boards for Alexion, UCB-Ra, argenx, Biogen, Mitsubishi Tanabe Pharma, and Amylyx and speaker honoraria from Soleo Health.

Angela Genge has served as a paid consultant for Medtronic, Atlantic Research Group, Calico, Apellis, Anexon, ALS-Pharma, QurAlis, Orion, Sanofi Genzyme, Ionis, Wave Life Therapies, Anelixis, Roche, Cytokinetics, Mitsubishi Tanabe Pharma, Amylyx, Alexion, UCB Pharma, Ra Pharma, Biogen, Eli Lilly, and Amicus Therapeutics.

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

Henry J. Kaminski is a consultant for Roche, Cabeletta Bio, Lincoln Therapeutics, Takeda, and UCB Pharma; he is CEO and CMO of ARC Biotechnology, LLC based on US Patent 8,961,98. He is Principal Investigator of the Rare Disease Network for Myasthenia Gravis (MGNet) National Institute of Neurological Disorders & Stroke, U54 NS115054 and Targeted Therapy for Myasthenia Gravis. R41 NS110331-01 to ARC Biotechnology.

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 Idec, Novartis, UCB Pharma and the Guthy-Jackson Charitable Foundation. She serves on scientific or educational advisory boards for UCB Pharma, argenx, and Viela/Horizon.

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Kimiaki Utsugisawa has served as a paid consultant for UCB Pharma, argenx, Janssen Pharma, Viela Bio, Chugai Pharma, and Mitsubishi Tanabe Pharma; he has received speaker honoraria from argenx, Alexion Pharmaceuticals and the Japan Blood Products Organization.

Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion, argenx, Ra/UCB Pharma, Harmony/Viela Bio, Janssen/Momenta, Sanofi, Regeneron, and Cartesian Therapeutics; he receives speaking and consulting honoraria from Alexion, UCB, and argenx.

Melissa Brock is an employee and shareholder of UCB Pharma.

Babak Boroojerdi is an employee and shareholder of UCB Pharma.

Mark Vanderkelen is an employee and shareholder of UCB Pharma.

Guillemette de la Borderie is an employee and shareholder of UCB Pharma.

Petra W. Duda is an employee and shareholder of UCB Pharma.

James F. Howard Jr. has received research support (paid to his institution) from Alexion Pharmaceuticals, argenx, BVBA, 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 Alexion Pharmaceuticals, argenx, BVBA, Immunovant Inc., Ra Pharmaceuticals (now UCB Pharma), Regeneron Pharmaceuticals, Sanofi US, and Viela Bio Inc. (now Horizon Therapeutics); and non-financial support from Alexion Pharmaceuticals, argenx, BVBA, Ra Pharmaceuticals (now UCB Pharma) and Toleranzia AB.

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RAISE: A multinational, randomized, double-blind, placebo-controlled Phase 3 study

Single-use pre-filled syringe for self-injection

Screening period
09/2019–09/2021
N=239

4 weeks

Randomisation
N=174 (1:1)

Stratified based on baseline MG-ADL score (≤9 versus ≥10), QMG score (≤17 versus ≥18), and geographical region

Excluded screening failures
n=65

Zilucoplan 0.3 mg/kg
n=86

Placebo
n=88

- Aged ≥18 years
- MGFA Class II–IV gMG
- AChR Ab+
- MG-ADL score of ≥6, QMG score of ≥12
- Vaccinated against *Neisseria meningitidis*
- Stable MG-specific medication

Wk1 Wk2 Wk4 Wk8 Wk12

Treatment period 12 weeks
If rescue therapy is necessary:

Receive **IVIg** or **PLEX treatment**

Extension study (RAISE-XT)

Participants who **permanently discontinued**, had a **safety follow-up visit** 40 days after the last dose of study medication

Zilucoplan and placebo were administered as a once-daily SC injection. Patients were enrolled from East Asia, Europe and North America. AChR Ab+, acetylcholine receptor autoantibody positive; CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous; TEAE, treatment-emergent adverse event; Wk, Week.
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Patient demographics and baseline characteristics

Patient demographics and baseline disease characteristics were balanced between treatment arms

	Placebo (n=88)	**Zilucoplan 0.3 mg/kg** (n=86)
Age, years, mean (SD)	53.3 (15.7)	52.6 (14.6)
Sex, male, n (%)	41 (46.6)	34 (39.5)
MG-ADL score, mean (SD)	10.9 (3.4)	10.3 (2.5)
MG-QoL 15r score, mean (SD)	18.9 (6.8)	18.6 (6.6)
Neuro-QoL Fatigue score, mean (SD)	29.7 (6.9)	29.4 (7.4)
WPAI score*, mean (SD)	56.3 (24.2)	54.3 (28.3)
EQ-5D-5L VAS, mean (SD)	52.9 (19.6)	57.4 (18.1)

mITT population. mITT population includes all randomized participants who received at least one dose of study drug and had at least one post-dosing MG-ADL score.
*Proportion of overall work impairment due to problem expressed as a percentage.
MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MG-QoL 15r, Myasthenia Gravis Quality of Life 15-item revised scale; mITT, modified intention-to-treat; Neuro-QoL, Quality of Life in Neurological Disorder; SD, standard deviation; VAS, visual analog scale; WPAI, Work Productivity and Activity Impairment.
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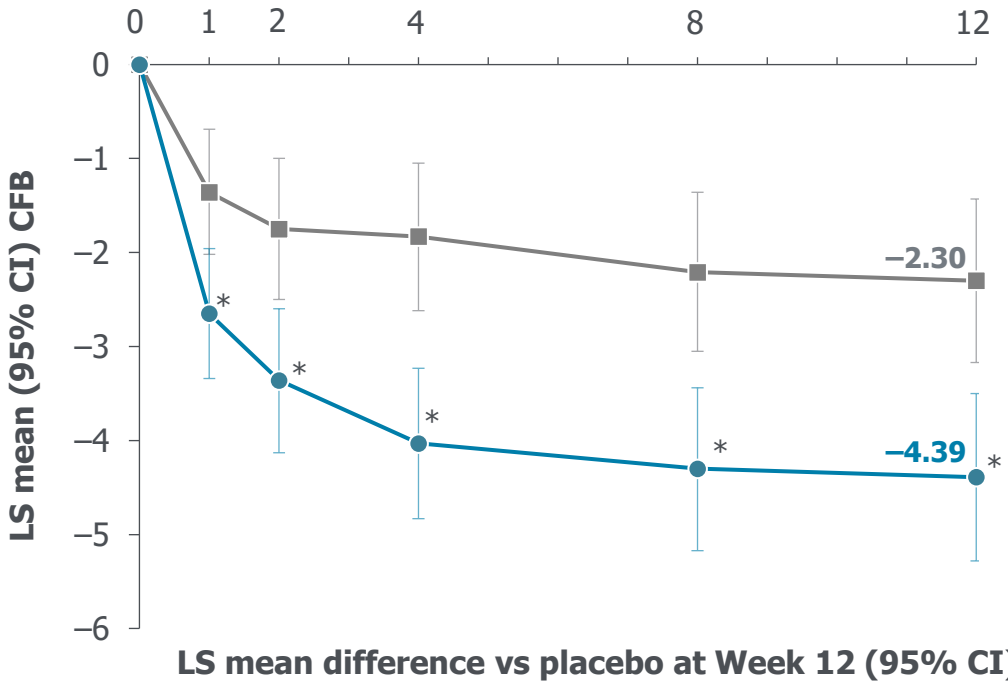
Statistically significant CFB in MG-ADL and MG-QoL 15r scores at Week 12

The effect of zilucoplan on MG-QoL 15r was consistent with the primary endpoint

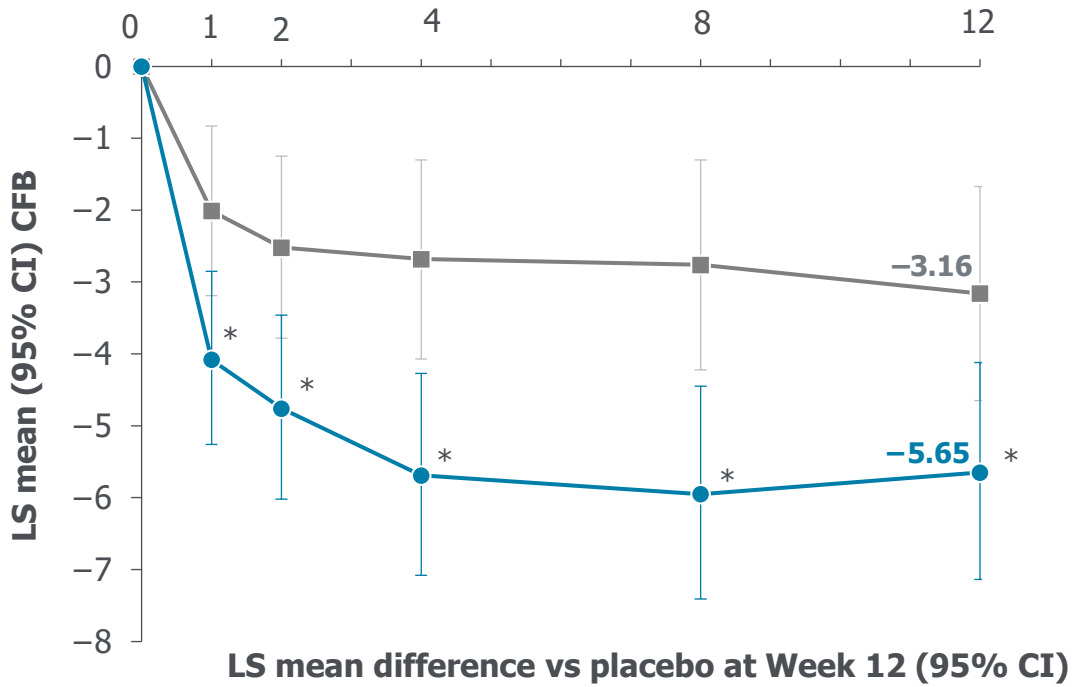
MG-ADL (primary endpoint)



LS mean difference vs placebo at Week 12 (95% CI)

−2.09 (−3.24, −0.95); p<0.001

MG-QoL 15r



LS mean difference vs placebo at Week 12 (95% CI)

−2.49 (−4.45, −0.54); p=0.0128

Placebo (n=88)

Zilucoplan 0.3 mg/kg (n=86)

*p<0.05 vs placebo.
mITT population. mITT population includes all randomized subjects who received at least one dose of study drug and had at least one post-dosing MG-ADL score. Treatment group differences were assessed using a MMRM analysis of ANCOVA, where treatment failures (rescue therapy, death or myasthenic crisis) were imputed with baseline or the last available value, whichever was worse. A fixed sequential testing procedure was applied for multiplicity of the continuous secondary endpoints with the following order: QMG, MGC, MG-QoL 15r (Family 1).
ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; MGC, Myasthenia Gravis Composite; MMRM, mixed model repeated measures.
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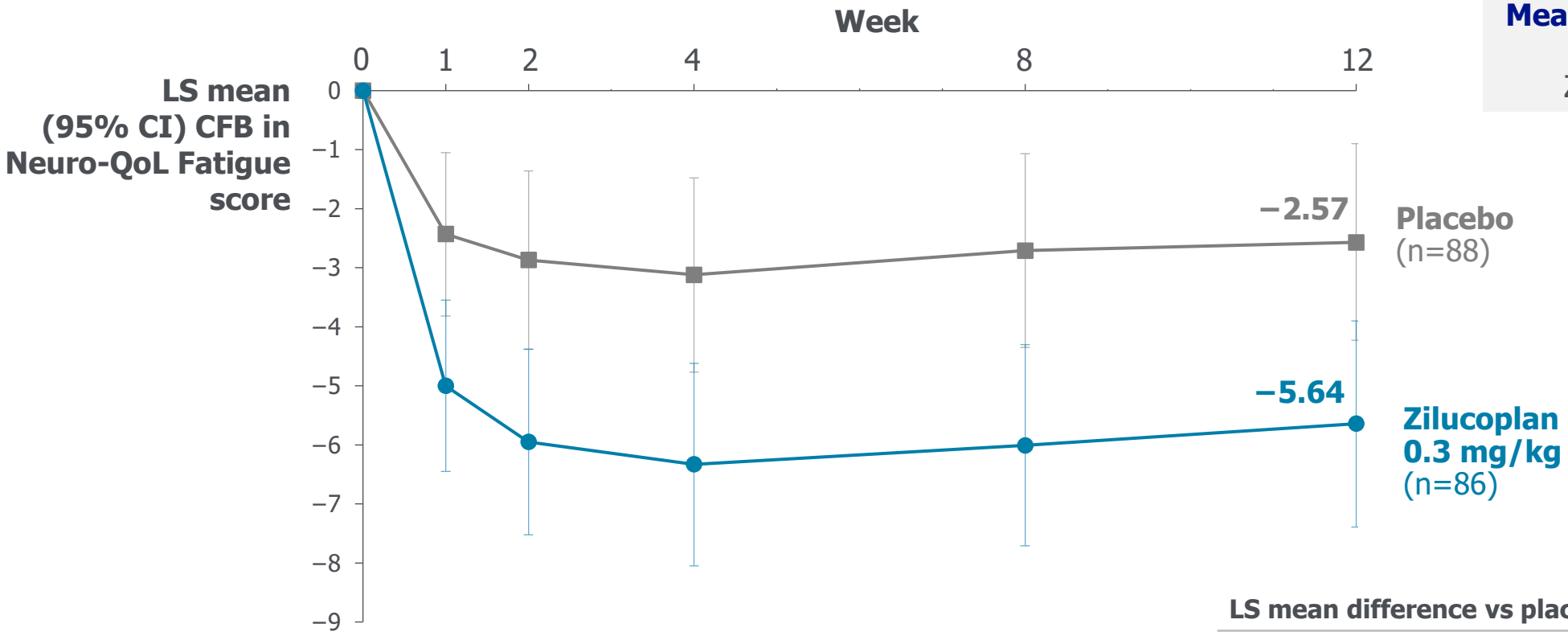
Improvements from baseline in Neuro-QoL Fatigue at Week 12

- Consistently greater improvement in fatigue with zilucoplan vs placebo (Neuro-QoL short form fatigue scale)
- Differentiation started at Week 1, increased through Week 4 and was maintained up to Week 12



Mean baseline values (SD)
Placebo: 29.7 (6.9)
Zilucoplan: 29.4 (7.4)

LS mean difference vs placebo at Week 12 (95% CI)

−3.06 (−5.27, −0.85); p=0.0069*

mITT population. mITT population includes all randomized subjects who received at least one dose of study drug and had at least one post-dosing MG-ADL score. Statistics by visit are descriptive. *Nominal p value; endpoint was not pre-specified in multiplicity testing.
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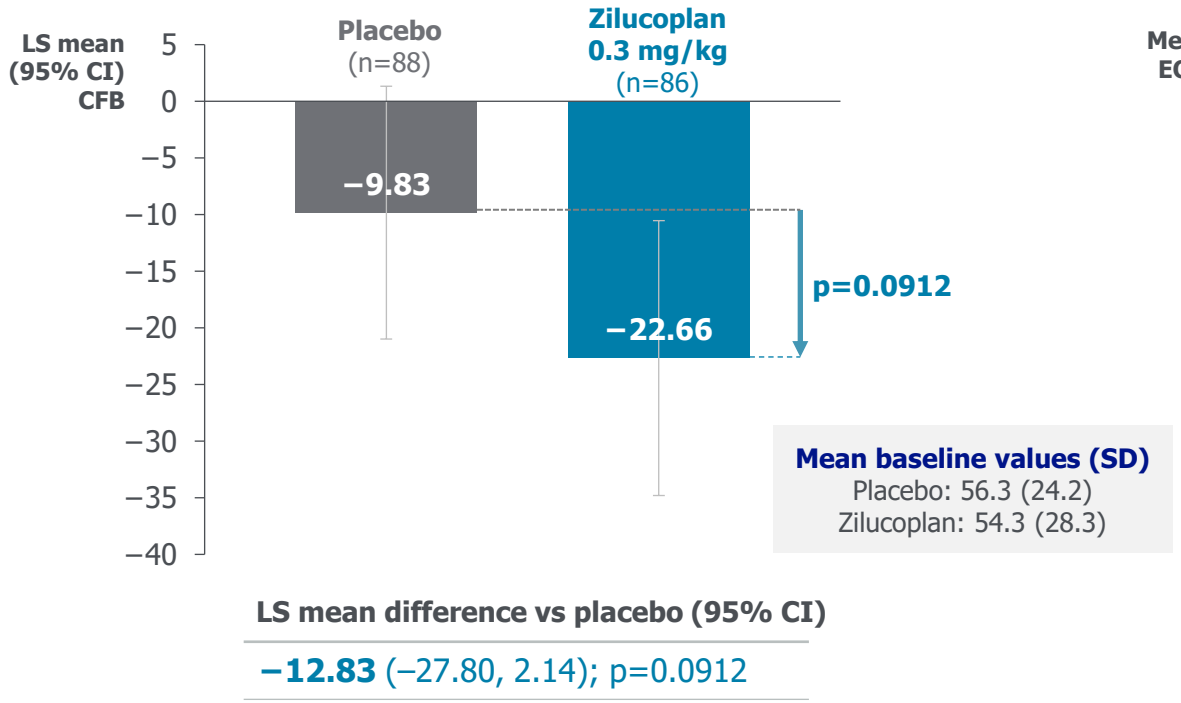
Improvements from baseline in work productivity and EQ-5D-5L VAS scores

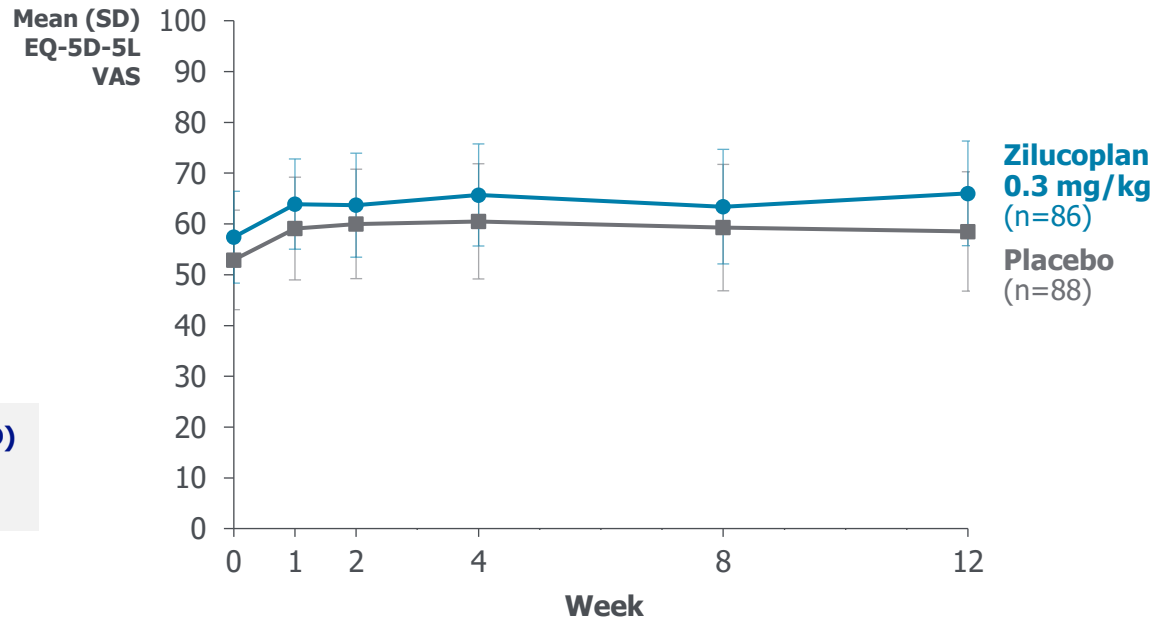
Work productivity

- Work productivity improved by 12.83 percentage points by Week 12 for zilucoplan vs placebo (WPAI:SHP "proportion of overall work impairment due to problem" questionnaire)



EQ-5D-5L VAS

- Greater mean increases from baseline in EQ-5D-5L VAS score with zilucoplan vs placebo were observed from Week 1 and maintained through Week 12 (8.97 vs 5.81, respectively)



mITT population. mITT population includes all randomized subjects who received at least one dose of study drug and had at least one post-dosing MG-ADL score.
BL, baseline; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.
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Overview of TEAEs

- The most common TEAEs were injection-site reactions (26.7% zilucoplan vs 14.8% placebo); all were non-serious, and mild in severity, except for one instance of injection-site pain of moderate severity in the zilucoplan group
- No patients discontinued due to an injection-site reaction

	Placebo (n=88) n (%)	**Zilucoplan 0.3 mg/kg** (n=86) n (%)
Any TEAE	62 (70.5)	66 (76.7)
Serious TEAE	13 (14.8)	11 (12.8)
TEAE resulting in permanent withdrawal from IMP*	2 (2.3)	4 (4.7)
Treatment-related TEAE	22 (25.0)	28 (32.6)
Severe TEAE	11 (12.5)	10 (11.6)
Death	1 (1.1)	1 (1.2)
COVID-19	0	1 (1.2)
Cerebral hemorrhage	1 (1.1)	0

Zilucoplan:

- Aphthous ulcer
- Mouth ulceration
- Hepatic enzyme increase
- COVID-19 (causing death, not treatment-related)

Placebo:

- Hyperemesis gravidarum
- Cerebral hemorrhage (causing death, not treatment-related)

Safety set. *Includes deaths.
Severe TEAEs: zilucoplan (24 events in 10 patients): anemia, leukopenia, upper abdominal pain, aphthous ulcer, mouth ulceration, odynophagia, COVID-19, COVID-19 pneumonia, esophageal candidiasis, oral candidiasis, pneumonia, sepsis, tonsilitis, lipase increase, amylase increase, weight decrease, muscle spasm, (worsening of) myasthenia gravis (4 events in 3 patients), dyspnea, pulmonary embolism, deep vein thrombosis; placebo (14 events in 11 patients): vomiting, COVID-19, COVID-19 pneumonia (2 events in 2 patients), tooth infection, muscular weakness, (worsening of) myasthenia gravis (5 events in 3 patients), cerebral hemorrhage, cerebrovascular accident, hyperemesis gravidarum.
COVID-19, coronavirus disease 2019; IMP, investigational medicinal product.
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Conclusions

- Zilucoplan **clinically meaningfully and highly statistically significantly improved MG-ADL at Week 12** versus placebo in patients with AChR+ gMG, meeting its primary endpoint
- Zilucoplan **improved QoL outcomes vs placebo**:
  - Zilucoplan **statistically significantly improved MG-QoL 15r at Week 12** versus placebo
  - Zilucoplan-treated patients reported consistently greater improvement in **fatigue** compared to placebo-treated patients
  - Greater improvements from baseline in **WPAI score** were observed with zilucoplan versus placebo, suggesting an increase in participation and productivity at work for zilucoplan-treated patients
  - Consistently greater mean increases from baseline in **EQ-5D-5L VAS score** were observed in the zilucoplan group compared with the placebo treatment group
- Zilucoplan had a **favorable safety profile** with no major safety findings and **good tolerability**, confirming the results of the Phase 2 study
- All patients in the zilucoplan arm who completed the 12-week treatment period have entered the ongoing RAISE-XT extension study (NCT04225871)

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