AANEM Poster **192**
MGFA Scientific Session Poster **MG40**

Long-term safety and efficacy of zilucoplan in generalized myasthenia gravis: 120-week interim analysis of RAISE-XT

AANEM Annual Meeting & MGFA Scientific Session; Savannah, GA, USA; October 15–18, 2024

James F. Howard Jr.[1], Miriam Freimer[2], Angela Genge[3], Channa Hewamadduma[4,5], Yessar Hussain[6], Angelina Maniaol[7], Renato Mantegazza[8], Kimiaki Utsugisawa[9], Tuan Vu[10], Michael D. Weiss[11], Babak Boroojerdi[12], Petra W. Duda[13], Fiona Grimson[14], Mark Vanderkelen[15] and M. Isabel Leite[16] on behalf of the RAISE-XT study team

[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, Dell Medical School, The University of Texas at Austin, Austin, TX, USA; [7]Department of Neurology, Oslo University Hospital, Oslo, Norway; [8]Department of Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS, Istituto Nazionale Neurologico Carlo Besta, Milan, Italy; [9]Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan; [10]Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA; [11]Department of Neurology, University of Washington Medical Center, Seattle, WA, USA; [12]UCB, Monheim, Germany; [13]UCB, Cambridge, MA, USA; [14]UCB, Slough, UK; [15]UCB, Brussels, Belgium; [16]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Introduction

- Zilucoplan is a small (3.5 kDa), 15-amino acid macrocyclic peptide complement C5 inhibitor with a dual mechanism of action, indicated for the treatment of adult patients with AChR Ab+ gMG[1,2]
- In the randomized, double-blind, placebo-controlled, Phase 3 RAISE study (NCT04115293), zilucoplan treatment resulted in significant and clinically meaningful improvements in MG-specific outcomes in patients with AChR Ab+ gMG[1]
- In the ongoing, OLE study RAISE-XT (NCT04225871), zilucoplan has previously demonstrated sustained efficacy with a favorable safety profile[3]
- Here, we evaluate the long-term safety and efficacy of zilucoplan up to 120 weeks of treatment

Methods

- RAISE-XT is a Phase 3, multicenter, OLE study
- Patients completing qualifying double-blind, placebo-controlled studies (Phase 2 NCT03315130/RAISE) could enter RAISE-XT to self-administer once-daily subcutaneous zilucoplan 0.3 mg/kg
- The primary safety endpoint of RAISE-XT was incidence of TEAEs
- Change from double-blind study baseline to Week 120 in MG-ADL and QMG scores were assessed
- The proportions of patients who achieved MG-ADL response (≥3-point reduction without rescue therapy), QMG response (≥5-point reduction without rescue therapy) and MSE response (MG-ADL score of 0 or 1 without rescue therapy) through to Week 120 were also assessed
- From Week 24, 12 weeks into RAISE-XT, patients who received placebo or zilucoplan 0.3 mg/kg in the qualifying studies were assessed as one pooled treatment group

Results

- In total, 200 patients enrolled in RAISE-XT (**Table 1**)
  - All patients who completed RAISE opted to enroll into RAISE-XT
  - At the time of data cutoff (November 11, 2023), most patients who entered RAISE-XT (73.0%) were still enrolled, with no discontinuations reported by the investigators as being due to lack of efficacy
- At data cutoff, median (range) exposure to zilucoplan was 2.2 (0.11–5.6) years
- The most common TEAEs were COVID-19 and MG worsening (**Table 2**)
- In the qualifying double-blind studies, patients who received zilucoplan 0.3 mg/kg had improvements in MG-ADL and QMG scores vs placebo as early as Week 1 and continued to improve through to Week 24 (**Figure 1**)
- In patients who received placebo in the qualifying studies, rapid improvements in MG-ADL and QMG were observed at the first week after switching to zilucoplan 0.3 mg/kg (Week 13) and continued to improve through to Week 24 (**Figure 1**)
- These improvements in MG-ADL and QMG scores were sustained through to Week 120
- MG-ADL, QMG and MSE responder rates were high and sustained in the pooled zilucoplan 0.3 mg/kg group through to Week 120 (**Figure 2**)

Table 1 Baseline characteristics

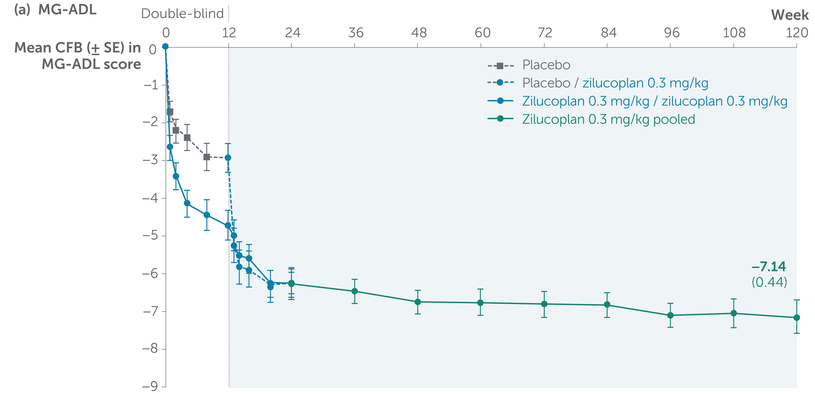
		All zilucoplan (N=200)
	Age, years, mean (SD)	**53.3** (15.0)
	Sex, male, n (%)	**90** (45.0)
MGFA Disease Class, n (%)	IIa/b	**59** (29.5)
	IIIa/b	**129** (64.5)
	IVa/b	**12** (6.0)
Baseline gMG-specific medication, n (%)	MG-ADL score, mean (SD)	**6.3** (4.3)
	QMG score, mean (SD)	**14.0** (5.9)
	Prior thymectomy, n (%)	**96** (48.0)
	Prior MG crisis, n (%)	**62** (31.0)
	Duration of disease, years, mean (SD)	**9.38** (9.73)
	Age at onset, years, mean (SD)	**43.64** (17.94)
	Corticosteroids	**124** (62.0)
	Immunosuppressants	**101** (50.5)
	Cholinesterase inhibitors	**167** (83.5)

Table 2 Overview of TEAEs

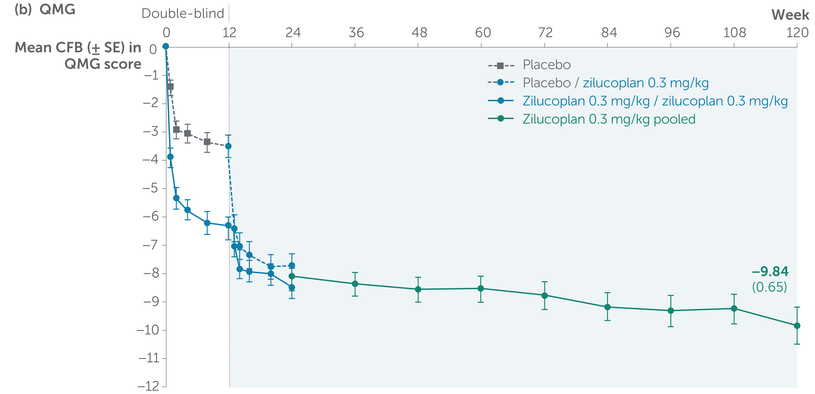
	All zilucoplan (N=200)
Duration of exposure, years, median (range)	**2.2** (0.11–5.6)
Any TEAE, n (%)	**194** (97.0)
COVID-19	**71** (35.5)
MG worsening	**59** (29.5)
Headache	**44** (22.0)
Nasopharyngitis	**42** (21.0)
Arthralgia	**36** (18.0)
Diarrhea	**34** (17.0)
URTI	**34** (17.0)
UTI	**33** (16.5)
Nausea	**32** (16.0)
Fatigue	**31** (15.5)
Serious TEAE, n (%)	**81** (40.5)
Treatment-related serious TEAE,* n (%)	**5** (2.5)
TEAE resulting in permanent withdrawal from IMP,† n (%)	**21** (10.5)
Treatment-related TEAE, n (%)	**73** (36.5)
Severe TEAE, n (%)	**72** (36.0)
TEAEs leading to death,‡ n (%)	**4** (2.0)

*Treatment-related serious TEAEs were one (0.5%) event each of: esophagitis, 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. †Including 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). Most common TEAEs occurring in ≥15% of patients overall are reported only.

Figure 1 Mean CFB in (a) MG-ADL and (b) QMG to Week 120

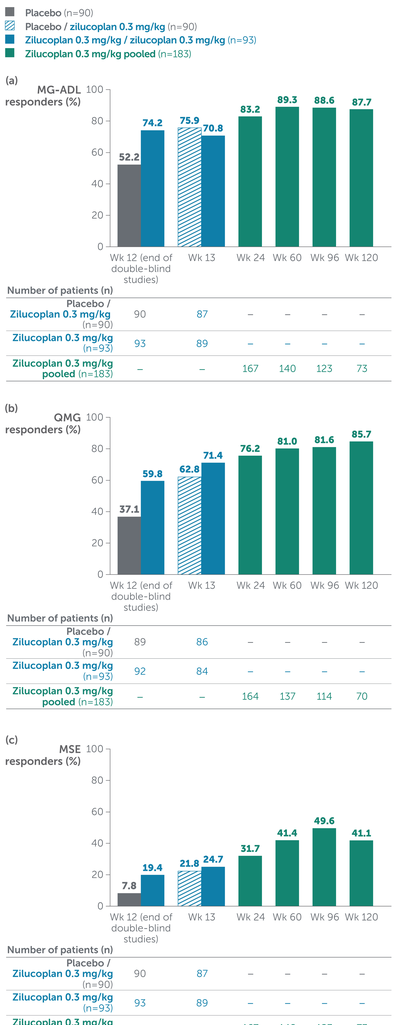


Number of patients (n)											
Placebo (n=90)	90	90	–	–	–	–	–	–	–	–	–
Zilucoplan 0.3 mg/kg (n=93)	93	93	–	–	–	–	–	–	–	–	–
Zilucoplan 0.3 mg/kg pooled (n=183)	–	–	175	170	162	156	149	148	142	123	86



Number of patients (n)											
Placebo (n=90)	90	89	–	–	–	–	–	–	–	–	–
Zilucoplan 0.3 mg/kg (n=93)	93	92	–	–	–	–	–	–	–	–	–
Zilucoplan 0.3 mg/kg pooled (n=183)	–	–	172	169	161	153	149	146	132	119	83

Figure 2 Mean (a) MG-ADL, (b) QMG and (c) MSE responder rates to Week 120



Number of patients (n)						
Placebo / Zilucoplan 0.3 mg/kg (n=90)	90	87	–	–	–	–
Zilucoplan 0.3 mg/kg (n=93)	93	89	–	–	–	–
Zilucoplan 0.3 mg/kg pooled (n=183)	–	–	167	140	123	73

Number of patients (n)						
Placebo / Zilucoplan 0.3 mg/kg (n=90)	89	86	–	–	–	–
Zilucoplan 0.3 mg/kg (n=93)	92	84	–	–	–	–
Zilucoplan 0.3 mg/kg pooled (n=183)	–	–	164	137	114	70

Number of patients (n)						
Placebo / Zilucoplan 0.3 mg/kg (n=90)	90	87	–	–	–	–
Zilucoplan 0.3 mg/kg (n=93)	93	89	–	–	–	–
Zilucoplan 0.3 mg/kg pooled (n=183)	–	–	167	140	123	73

Summary and conclusions

Here we report an interim analysis of RAISE-XT, an ongoing OLE study investigating the safety and efficacy of zilucoplan in patients with AChR Ab+ gMG

Zilucoplan had a favorable safety profile and was well tolerated in the long term

Patients experienced rapid improvements in gMG symptoms from the first week of treatment with zilucoplan, which were sustained through to Week 120

High MG-ADL, QMG and MSE responder rates were sustained through to Week 120 of treatment

Zilucoplan treatment for up to 120 weeks was well tolerated and efficacy was sustained in RAISE-XT, supporting its long-term use in a broad population of patients with AChR Ab+ gMG

Abbreviations: AChR Ab+, acetylcholine autoantibody positive; C5, component 5; CFB, change from baseline; COVID-19, coronavirus disease 2019; gMG, generalized myasthenia gravis; IMP, investigational medicinal product; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MSE, Minimal Symptom Expression; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection; Wk, week.

Acknowledgments: This study was funded by UCB. The authors acknowledge Annabel Dimmock, MBiol, of Ogilvy Health, London, UK, for editorial assistance, which was funded by UCB. The authors thank Veronica Porkess, PhD, of UCB for publication and editorial support. The authors thank the patients and their caregivers, in addition to the investigators and their teams who contributed to this study.

Author disclosures: James F. Howard Jr. has received research support (paid to his institution) from 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, RCORI 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, Tolerantia 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, Annexon Biosciences, Apellis Pharmaceuticals, Atlantic Research Group, Biogen, Calico, Cytokinetics, Eli Lilly, Ionis Pharmaceuticals, Medtronic, Mitsubishi Tanabe Pharma, Orion, Quirkis, 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. 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); and 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, CSLBR 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 performed consulting work for Alexion/AstraZeneca Rare Disease, 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 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.

References: 1. Howard JF Jr, et al. Lancet Neurol. 2023;22(3):395–406. 2. Zilucoplan US Pi. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216834s000lbl.pdf. Accessed July 2024. 3. Howard JF Jr, et al. Long-term safety and efficacy of zilucoplan in myasthenia gravis: additional interim analyses of RAISE-XT [oral presentation]. AAN 2024. 515:002.

Please use this QR code to download a PDF of the poster.