Safety and tolerability of zilucoplan in RAISE-XT: A multicenter, open-label extension study in patients with generalized myasthenia gravis

AANEM 2022, Nashville, TN, USA; MGFA Scientific Session; 21 September 2022

Angela Genge[1], Yessar Hussain[2], Henry J. Kaminski[3], M. Isabel Leite[4], Renato Mantegazza[5], Kimiaki Utsugisawa[6], Tuan Vu[7], Melissa Brock[8], Babak Boroojerdi[9], Mark Vanderkelen[10], Guillemette de la Borderie[11], Petra W. Duda[12], James F. Howard Jr.[13], on behalf of the RAISE investigators

[1]Clinical Research Unit, The Montreal Neurological Institute, Montreal, QC, Canada; [2]Department of Neurology, Dell Medical School, The University of Texas at Austin, Austin, TX, USA; [3]Department of Neurology and Rehabilitation Medicine, George Washington University, Washington DC, USA; [4]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK; [5]Neuroimmunology and Neuromuscular Diseases Department, Fondazione Istituto Neurologico, PV, Italy; [6]Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan; [7]Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA; [8]UCB Pharma, Raleigh, NC, USA; [9]UCB Pharma, Monheim, Germany; [10]UCB Pharma, Braine-l'Alleud, Belgium; [11]UCB Pharma, Brussels, Belgium; [12]UCB Pharma, Cambridge, MA, USA; [13]The University of North Carolina at Chapel Hill, Department of Neurology, Chapel Hill, NC, USA

Summary

What we did

- RAISE-XT is an open-label extension study to evaluate the long-term safety, tolerability and efficacy of the complement inhibitor zilucoplan in patients with gMG, who had previously participated in a parent zilucoplan Phase 2 or 3 study
- In this interim analysis, patients had received a median of 253 days of exposure to zilucoplan

What we found

- Zilucoplan had a favorable safety profile with no major safety findings
- MG-ADL score in patients who had received zilucoplan in their parent study continued to improve through to Extension Week 12 (Week E12), 24 weeks from their first dose
- Rapid improvements were observed after Extension Week 1 in patients who received placebo during the parent studies. MG-ADL continued to improve through to Week E12
- Similar effects were observed in QMG, MGC and MG-QoL 15r across both treatment groups

Why it matters

- This 24-week interim analysis of RAISE-XT demonstrated that zilucoplan had a favorable safety profile and was efficacious in the long term
- These data build on the efficacy and safety profile of zilucoplan observed in double-blind Phase 2 and Phase 3 studies

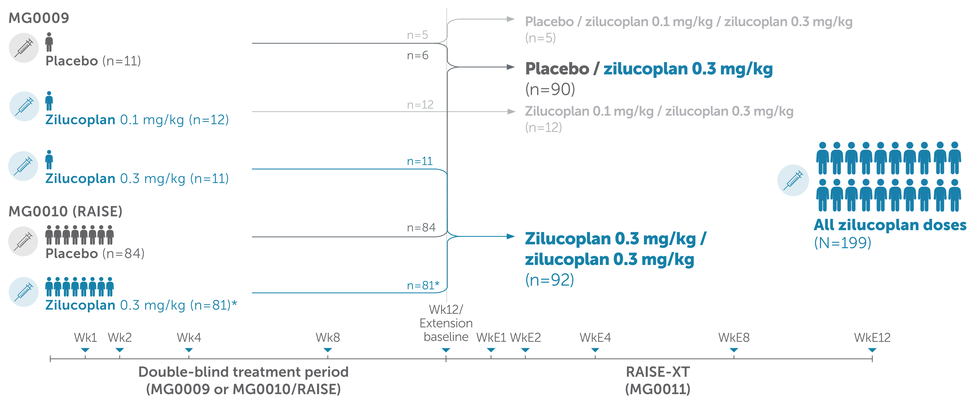
Introduction

- gMG is a heterogeneous, chronic, unpredictable neuromuscular disease characterized by fluctuating fatigable muscle weakness[1]
- Zilucoplan, a macrocyclic peptide that inhibits C5 via a dual mechanism of action,[2] showed favorable safety and efficacy in a Phase 2 study and in RAISE, the pivotal Phase 3 trial[3]
- Collecting long-term clinical data through an open-label extension study contributes to an increased understanding of the safety and efficacy profile of zilucoplan in gMG

Methods

- RAISE-XT (NCT04225871) is an ongoing, Phase 3, multicenter, open-label extension study to evaluate the safety and efficacy of zilucoplan in patients with gMG who completed a parent study: Phase 2 (NCT03315130) or Phase 3 (RAISE; NCT04115293) double-blind, randomized, placebo-controlled zilucoplan studies
- The study design is shown in **Figure 1**. A small number of patients received zilucoplan 0.1 mg/kg in Phase 2; the data from these patients are not shown separately here, but are included in the 'All zilucoplan doses' group
- All patients self-administered daily SC injections of zilucoplan 0.3 mg/kg
- Key inclusion criteria included completion of a parent zilucoplan clinical study (Phase 2 or RAISE) and vaccination against *Neisseria meningitidis*
- The primary safety endpoint was incidence of TEAEs. The assessment of TEAEs includes TEAEs from the start of the open-label extension periods of the Phase 2 and Phase 3 studies
- Secondary efficacy endpoints include change from RAISE-XT baseline (post-double-blind period) to RAISE-XT Extension Week 12 (Week E12) in MG-ADL, QMG and MGC scores, and MG-QoL 15r

Figure 1 RAISE-XT study design



*An additional patient from the zilucoplan 0.3 mg/kg treatment group in MG0010 entered RAISE-XT after the cut off date. Data for the greyed-out zilucoplan 0.1 mg/kg treatment groups are not presented separately because, due to the small number of participants in each group, no meaningful conclusions can be made. These patients are included in the 'All zilucoplan doses' group.

Results

Patients

- In total, 199 patients entered the RAISE-XT study
  - 104 of these patients had received zilucoplan in their parent study and continued to receive zilucoplan in RAISE-XT (zilucoplan group)
  - 95 patients had received placebo in their parent study and switched to zilucoplan in RAISE-XT (placebo-switch group)
- At data cut off (18 February 2022), participants had a median (range) duration of exposure of 253.0 days (range 29–1434) during RAISE-XT and the open-label extension portion of the Phase 2 study for participants who continued in RAISE-XT
- Patient demographics are shown in **Table 1**

Safety

- Total exposure to zilucoplan was 228.3 patient exposure years at the time of data cut off
- The overall incidence of TEAEs and treatment-related TEAEs is presented in **Table 2**
- In total, 169 (84.9%) patients experienced a TEAE, and serious TEAEs were experienced by 46 (23.1%) patients (**Table 2**)
- Four (2.0%) treatment-emergent deaths occurred, all in patients with multiple cardiovascular risk factors and none of which considered treatment related: Two (1.0%) deaths were reported as cardiac arrest, one (0.5%) head injury and one (0.5%) in a patient with severe pneumonia 2 days prior to death (**Table 2**)
- The most common TEAEs were headache and worsening of MG, both occurring in 33 (16.6%) patients (**Table 2**)
- Over the duration of the extension study, approximately half (49.2%) of patients experienced infections, which were non-serious in 86% of cases
  - 14 (7.0%) patients had a serious infection, which were mainly COVID-19 pneumonia (n=5, 2.5%) and COVID-19 infection (n=3, 1.5%)
    - No *Neisseria* infections were observed

Efficacy

- For the placebo-switch group, rapid improvement in MG-ADL score was observed at Extension Week 1 (Week E1) and continued through to Week E12 (**Figure 2a**)
- In the zilucoplan group, improvements in MG-ADL score seen during the double-blind parent studies continued to improve further from Week E1 through to Week E12 during zilucoplan treatment in the extension (p=0.0002) (**Figure 2a**)
  - Improvements in MG-ADL score from the end of the double-blind study (Week 12) to Week E12 were also observed for the placebo-switch group (p=0.0075)
- At Week E12, the zilucoplan treatment group achieved an LS mean change in MG-ADL score from double-blind study baseline of
  - 6.30 (95% CI: −7.44, −5.15) (**Figure 2a**)
  - MG-ADL score reduction from baseline for the placebo-switch group, after 12 weeks of zilucoplan, was similar at −6.32 (95% CI: −8.00, −4.65) (**Figure 2a**)
- Similar effects were observed in QMG score across both treatment groups (**Figure 2b**), and in MGC score and MG-QoL 15r (**Figures 2c and 2d**)

Table 1 Patient demographics

		Placebo/ zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.3 mg/kg/ 0.3 mg/kg (n=92)	All zilucoplan doses (N=199)
Age, years, mean (SD)		53.7 (15.5)	52.9 (14.6)	53.3 (15.0)
Sex, male, n (%)		42 (46.7)	41 (44.6)	90 (45.2)
Weight, kg, mean (SD)		88.6 (26.39)	92.9 (24.05)	91.0 (25.16)
MGFA disease class, n (%)	II (IIa, IIb)	29 (32.2)	25 (27.2)	59 (29.6)
	III (IIIa, IIIb)	57 (63.3)	59 (64.1)	128 (64.3)
	IV (IVa, IVb)	4 (4.4)	8 (8.7)	12 (6.0)
MG-ADL score, mean (SD)		7.7 (4.5)	5.2 (3.9)	6.3 (4.3)
QMG score, mean (SD)		15.6 (6.0)	12.3 (5.0)	13.8 (5.7)
Prior thymectomy, n (%)		38 (42.0)	45 (48.9)	88 (44.2)
Duration of disease, years, mean (SD)		9.25 (10.45)	9.05 (8.95)	9.25 (9.56)
Age at onset, years, mean (SD)		44.03 (18.70)	43.75 (17.45)	43.79 (17.86)
Treatment refractory,* n (%)		42 (50.0)	42 (51.9)	84 (50.9)

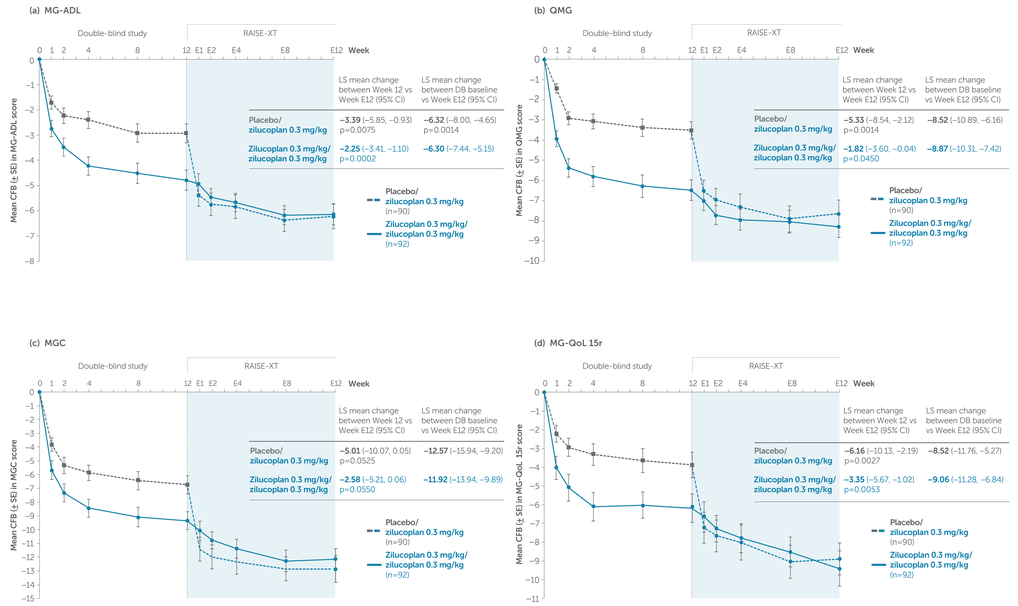
mITT population.
*A participant is considered 'treatment refractory' if they have had treatment for at least 1 year with two or more of the following therapies: Prednisone, azathioprine, mycophenolate, cyclosporin, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids; OR history of treatment with at least one of the above therapies for 1 year or more and required chronic PLEX, IVIg or SCIg at least every 3 months for the 12 months prior to enrollment.

Table 2 Overview of TEAEs

	Placebo/ zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.3 mg/kg/ 0.3 mg/kg (n=92)	All zilucoplan doses (N=199)
Any TEAE, n (%)	76 (84.4)	76 (82.6)	169 (84.9)
Headache	12 (13.3)	15 (16.3)	33 (16.6)
Myasthenia gravis	16 (17.8)	11 (12.0)	33 (16.6)
COVID-19	11 (12.2)	13 (14.1)	27 (13.6)
Nausea	12 (13.3)	10 (10.9)	25 (12.6)
Nasopharyngitis	10 (11.1)	9 (9.8)	25 (12.6)
Diarrhea	6 (6.7)	13 (14.1)	23 (11.6)
Arthralgia	6 (6.7)	9 (9.8)	20 (10.1)
Serious TEAE, n (%)	14 (15.6)	25 (27.2)	46 (23.1)
TEAE resulting in permanent withdrawal from IMP, n (%)	8 (8.9)	6 (6.5)	14 (7.0)
Treatment-related TEAE, n (%)	23 (25.6)	23 (25.0)	51 (25.6)
Severe TEAE, n (%)	13 (14.4)	18 (19.6)	39 (19.6)
Deaths, n (%)	1 (1.1)	3 (3.3)	4 (2.0)

Safety set.

Figure 2 Change from baseline to Week E12 in (a) MG-ADL, (b) QMG, (c) MGC and (d) MG-QoL 15r scores



mITT population. Separate repeated measures model for each treatment group comparing the change from baseline at Week 12 to Week E12, where baseline is from the double-blind study.

Conclusions

- In this interim analysis of RAISE-XT, zilucoplan demonstrated a favorable long-term safety profile over 24 weeks with no major safety findings, and good tolerability, as well as improvements in signs and symptoms of disease activity
- Longer exposure to zilucoplan did not lead to higher rates of TEAEs overall vs the placebo-switch group
- In participants who received zilucoplan 0.3 mg/kg treatment during the parent studies, MG-ADL, QMG, MGC and MG-QoL 15r scores continued to improve further through to Week E12
- In participants who received placebo during the parent studies, rapid improvements were observed as early as 1 week after switching to zilucoplan, and continued through to Week E12
- RAISE-XT is ongoing and additional long-term safety and efficacy data will be assessed

Abbreviations: CFB, change from baseline; CI, confidence interval; C5, complement component 5; DB, double blind; gMG, generalized myasthenia gravis; IMP, investigational medicinal product; IVIg, intravenous immunoglobulin; LS, least squares; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QoL 15r, Myasthenia Gravis Quality of Life 15-item revised scale; mITT, modified intention-to-treat; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event.

Acknowledgments: This study was funded by UCB Pharma. The authors acknowledge Rachel Price and Natasha Michaeloff of Ogilvy Health, London, UK, for editorial assistance, which was funded by UCB Pharma. The authors acknowledge Veronica Porkess, UCB Pharma, Slough, UK, for publication coordination. The authors thank the patients and their caregivers, in addition to the investigators and their teams who contributed to this study.

Author disclosures: This study was funded by UCB Pharma. 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. He has received 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 (Myawake) 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. Renato Mantegazza has received funding for travel and meeting attendance or advisory board participation from Alexion, Argenx, Biomarin, Catalyst, Sanofi, Regeneron, and UCB Pharma. 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/AstraZeneca Rare Disease, Argenx, Ra/UCB Pharma, Horizon/Viela Bio, Janssen/Momenta, Sanofi, Regeneron, and Cartesian Therapeutics; he receives speaking and consulting honoraria from Alexion, UCB Pharma, 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 Telerania AB.

References: 1. Cutter G, et al. Cross-sectional analysis of the myasthenia gravis patient registry: Disability and treatment. Muscle Nerve. 2019;60:707–715. 2. Howard JF, et al. Exp Opin Investig Drug. 2021;30:483–493. 3. Leite MI, et al. Zilucoplan in myasthenia gravis: Safety and tolerability results from the Phase 3 randomised RAISE study [poster]. ICNMD 2022. ePoster 03.04.03.

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