Switching to subcutaneous zilucoplan from IV complement component 5 inhibitors in myasthenia gravis: A Phase 3b study

MGFA Scientific Session 2024; Savannah, GA, USA; October 15, 2024

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Introduction

- Zilucoplan, a macrocyclic peptide complement C5 inhibitor, is self-administered as a subcutaneous injection, which offers an alternative to IV infusion of antibody-based complement C5 inhibitors, eculizumab and ravulizumab, at the hospital
- Phase 3 studies of zilucoplan in gMG have shown that daily injection results in complete complement inhibition, and sustained efficacy for up to 120 weeks (see Howard, *et al.* AANEM 2024 poster #192)[1–3]
- We aimed to evaluate the safety, tolerability and efficacy of subcutaneous zilucoplan in adults with AChR Ab+ gMG who switched from IV complement C5 inhibitors to subcutaneous zilucoplan

Methods

- MG0017 (NCT05514873) is a Phase 3b, open-label, single-arm study with a 12-week treatment period throughout which patients self-administered daily subcutaneous zilucoplan 0.3 mg/kg (**Figure 1**)
- Eligible patients had clinically stable disease on an IV complement C5 inhibitor and were willing to switch to zilucoplan
- Incidence of TEAEs (primary endpoint) and change from baseline in MG-ADL and QMG scores (assessed by mixed models for repeated measures) were analyzed
- Complement inhibition was measured by the sheep red blood cell lysis assay with >95% inhibition defined as complete[4]

Results

- In total, 26 patients enrolled and received zilucoplan (**Table 1**)
  - 16 patients switched from eculizumab and 10 from ravulizumab
  - Reasons for wanting to switch included logistical challenges, challenges with venous access, lengthy infusion times and perceptions of diminishing efficacy (**Figure 2**)
- Of these, 23 patients completed the treatment period and 3 discontinued due to:
  - TEAEs (n=2; **Table 2**)
  - Patient's lack of compliance with study procedures (n=1)
- Subcutaneous zilucoplan was well tolerated, demonstrating a favorable safety profile (**Table 2**)
- MG-ADL and QMG scores improved after switching to zilucoplan (**Figure 3a, 3c**)
  - Clinically meaningful and nominally significant improvements were observed in MG-ADL and QMG scores in patients who switched from ravulizumab (**Figure 3b, 3d**)
- MG symptoms were improved or unchanged in approximately 75% of patients at Week 12 after switching to zilucoplan (**Figure 4a, 4b**)
- Complement inhibition at Week 12 increased with zilucoplan treatment, particularly after switching from ravulizumab (**Figure 5**)

Table 1 Demographics and baseline disease characteristics

		Zilucoplan 0.3 mg/kg (N=26)
Female, n (%)		**13** (50.0)
Age at initial diagnosis, years, mean (min, max)		**51.7** (7, 73)
Duration of disease, years, mean (min, max)		**8.4** (0.8, 31.0)
MG-ADL score at baseline, mean (min, max)		**4.5** (0, 13)
QMG score at baseline, mean (min, max)		**10.1** (2, 23)
Baseline gMG therapy, n (%)	Cholinesterase inhibitors	**17** (65.4)
	Corticosteroids	**11** (42.3)
	Azathioprine, mycophenolate mofetil	**12** (46.2)
Prior IV complement C5 inhibitor treatment before switching to ZLP, n (%)	Eculizumab	**16** (61.5)
	Ravulizumab	**10** (38.5)

These data were previously presented at the 36th Annual Meeting for the Japanese Society for Neuroimmunology in Toyama, Japan; October 3–5, 2024.

Figure 1 Study design

Inclusion criteria
- Adults with AChR Ab+ gMG
- Clinically stable disease†
- Treated with the recommended dose of either
  – IV eculizumab (for ≥3 months) OR
  – IV ravulizumab (for ≥4 months)

Endpoints included
- Incidence of TEAEs (primary endpoint)
- CFB in MG-ADL and QMG scores at Week 12 (secondary endpoints)
- Pharmacodynamics (complement inhibition by sheep RBC lysis assay; other endpoint)

*The last dose of IV complement C5 inhibitor administration could not occur beyond the screening visit (Day –14, ±3 days) for patients receiving eculizumab, or Day –56 (±3 days) for patients receiving ravulizumab, to ensure approximately 2 weeks' or 8 weeks' interval, respectively, before the first SC zilucoplan administration. †Per investigator's judgment, with ≤2-point change in MG-ADL score at baseline compared with screening visit.

Figure 2 Reasons patients wanted to switch from IV C5 inhibitors

	Patients switching from eculizumab n=16	Patients switching from ravulizumab n=10	Total N=26
Logistical challenges, including travel and time spent at a hospital	**7** (43.8)	**1** (10.0)	**8** (30.8)
Challenges with venous access	**2** (12.5)	**2** (20.0)	**4** (15.4)
Lengthy intravenous infusion	**3** (18.8)	**0**	**3** (11.5)
Other	**4** (25.0)	**7** (70.0)	**11** (42.3)

Eculizumab, other reasons for switching (n=4)
- **Wearing off**
- **Loss of hair**
- **Sick after infusions** and would like to try a different treatment
- Happy with current treatment, but would like to **participate in a research study to help science**

Ravulizumab, other reasons for switching (n=7)
- **Wearing off, less effective**
- **Experiencing symptoms** about 1.5 weeks prior to next infusion
- **Lack of efficacy**
- Would like to **try a new treatment** to see if this would **improve MG symptoms**
- Would like to **try an alternative** treatment
- Recommended by doctor, **hates poking**
- **Easier** administration

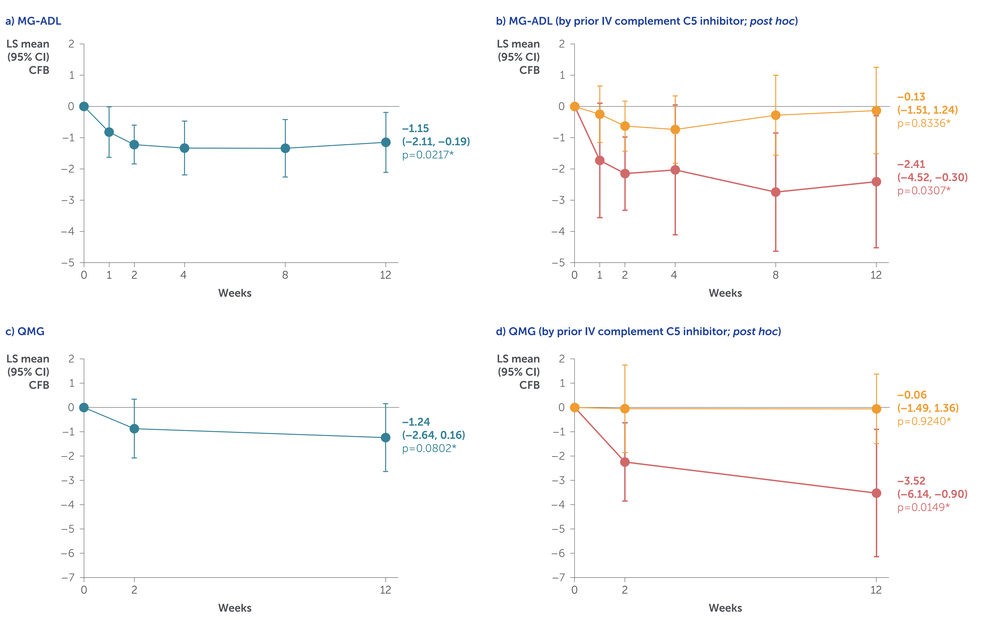
Data are presented as n (%). Reasons for 'Other' are free-text entries.

Table 2 Overview of TEAEs

	Zilucoplan 0.3 mg/kg (N=26)
Any TEAE,* n (%)	**19** (73.1)
Amylase increase	**3** (11.5)
Diarrhea	**2** (7.7)
Injection-site pain	**2** (7.7)
Lipase increase	**2** (7.7)
Nausea	**2** (7.7)
Pain	**2** (7.7)
Sinusitis	**2** (7.7)
Serious TEAE,† n (%)	**1** (3.8)
Treatment-related TEAE, n (%)	**6** (23.1)
TEAE resulting in permanent withdrawal from IMP, n (%)‡	**2** (7.7)
Severe TEAE, n (%)	**2** (7.7)

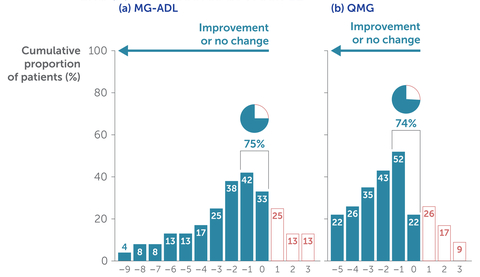
Safety set.
*Specific TEAEs listed are those occurring in ≥5% of patients. †Diverticulitis, not related to zilucoplan. ‡Injection-site pain, injection-site discoloration, pain, anxiety and fatigue (n=1) and reactivation of Epstein-Barr virus (n=1); the TEAEs of injection-site pain and discoloration that resulted in permanent withdrawal were deemed treatment-related by the investigator.

Figure 3 Change from baseline in MG-ADL and QMG scores to Week 12 for (a, c) the total population and (b, d) by prior IV complement C5 inhibitor subgroup



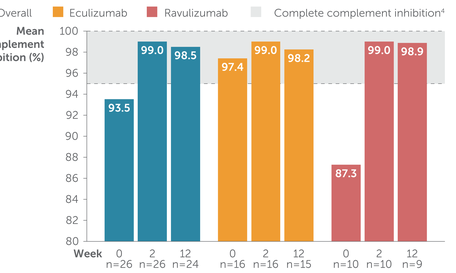
*Nominal p-values are presented.

Figure 4 Minimum point change from baseline in (a) MG-ADL and (b) QMG scores at Week 12



Pie chart percentages represent the proportion of patients who saw no change (x = 0) or who improved by ≥1 point (x = –1).

Figure 5 Complement inhibition following switching to zilucoplan



One patient who withdrew early is not included in Week 12 as blood sample was taken 16 days after the last zilucoplan dose.
Complement activity was measured using the sheep red blood cell assay.

Summary and conclusions

- Switching from IV complement C5 inhibitors (eculizumab or ravulizumab) to subcutaneous zilucoplan was well tolerated, with a safety profile consistent with other Phase 3 trials of zilucoplan
- Overall, MG symptoms improved after switching to zilucoplan, and clinically meaningful improvement from baseline in MG-ADL and QMG scores was observed in patients switching from ravulizumab
- MG symptoms were improved or unchanged in approximately 75% of patients at Week 12 after switching to zilucoplan
- Complement inhibition increased from baseline with zilucoplan, particularly after switching from ravulizumab
- These data provide information that may be valuable for physicians considering use of a complement C5 inhibitor for treatment of patients with gMG

Abbreviations: AChR Ab+, acetylcholine receptor autoantibody-positive; CS, component 5; CFB, change from baseline; CI, confidence interval; gMG, generalized myasthenia gravis; IMP, investigational medicinal product; IV, intravenous; LS, least squares; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis; RBC, red blood cell; SC, subcutaneous; TEAE, treatment-emergent adverse event; ZLP, zilucoplan.

Acknowledgments: This study was funded by UCB. The authors acknowledge Julia Stevens, PhD, 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: 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. Urvi Desai has served on advisory boards for argenx, Alnylam Pharmaceuticals, Biogen, Catalyst, CSL Behring, Fulcrum Therapeutics, Sarepta, Takeda Pharmaceuticals and UCB. She has served on speaker bureaus for Alexion Pharmaceuticals, Alnylam Pharmaceuticals, argenx and CSL Behring. Her institution has received research support from Mitsubishi Tanabe Pharma. Raghav Govindarajan has served on advisory boards for argenx, Janssen Pharmaceuticals, Roche and UCB and participated in speaker bureaus for Alexion Pharmaceuticals, argenx and UCB. Min Kang receives research support from UCSF and has served on advisory boards for UCB. Shaida Khan has served as a paid Consultant for UCB and has served on advisory boards for argenx and UCB. She receives research support from the Fichtenbaum Charitable Trust. Bhupendra Khatri has received personal compensation from Alexion Pharmaceuticals, argenx, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Novartis, Sanofi Genzyme (now Sanofi), Terumo BCT, TG Therapeutics and UCB. Todd Levine has nothing to disclose. Samir Macwan has received personal compensation for serving as a Consultant for Alexion Pharmaceuticals, argenx, Kabafusion and UCB. He has received personal compensation for serving on a speakers' bureau for Abbvie, Alexion Pharmaceuticals, argenx and Grifols. The institution of Dr. Macwan has received research support from Alexion Pharmaceuticals and Dysimmune Diseases Foundation. Perry B. Shieh has nothing to disclose. Michael D. Weiss has received honoraria for serving on scientific advisory boards for Alexion Pharmaceuticals, Amylyx Pharmaceuticals, argenx, Biogen, Immunovant, Mitsubishi Tanabe Pharma and Ra Pharmaceuticals (now UCB), 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 is an employee and shareholder of UCB. Eumorphia Maria Delicha is an employee of UCB. Brittany Harvey is an employee and shareholder of UCB. Andreea Lavrov is an employee and shareholder of UCB. Puneet Singh is an employee of UCB and shareholder of UCB and GSK. James F. Howard Jr. has received research support (paid to his institution) from Alexion AstraZeneca Rare Disease, argenx, Caelestan 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, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, F. Hoffmann-La Roche, Medscape CME, Merck EMD Serono, NMD Pharma, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, Platform9 CME, Regeneron Pharmaceuticals, Sanofi US, UCB, and Zai Labs; and has received non-financial support from Alexion AstraZeneca Rare Disease, argenx, Biohaven Ltd, Tolerantia AB and UCB.

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