Switching to subcutaneous zilucoplan from IV C5 inhibitors in myasthenia gravis: A Phase 3b study

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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
- 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 analysed
- 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**)
  - Subject's lack of compliance with study procedures
- Subcutaneous zilucoplan was well tolerated, demonstrating a favourable 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

		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 from diagnosis, 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)

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**

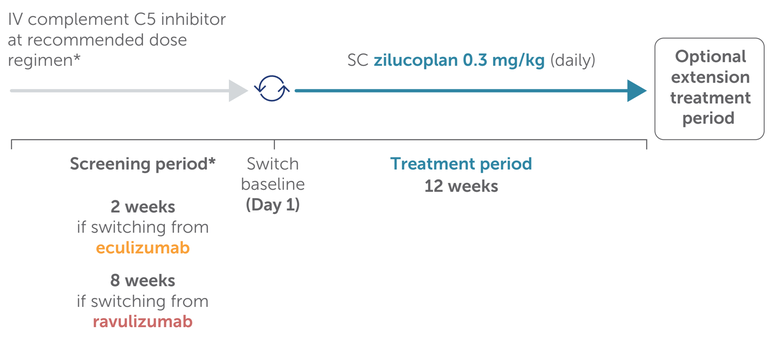
Ravulizumab, other reasons for switching (n=7)
Wearing off, less effective
Experiencing symptoms about 1.5 weeks prior to next infusion
Lack of efficacy
Would like to **try a new treatment** to see if this would **improve MG symptoms**
Would like to **try an alternative** treatment
Recommended by doctor,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

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

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

Figure 1 Study design

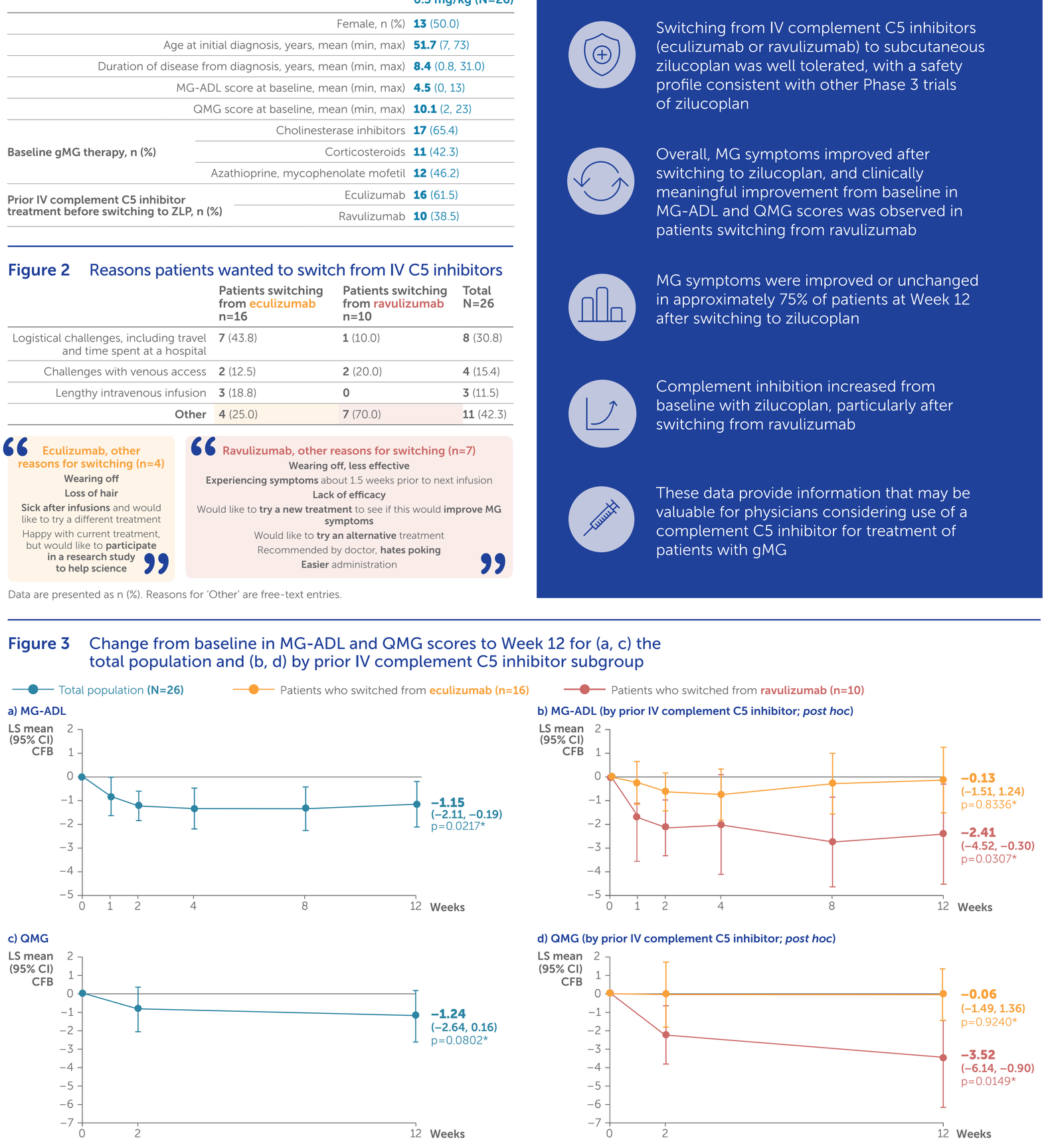


Inclusion criteria
- Adults with AChR Ab+ gMG
- Clinically stable disease†
- Treated with the recommended dose of either
  – IV eculizumab (for ≥3 months) OR
  –IV ravulizumab (for ≥4 months)

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 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



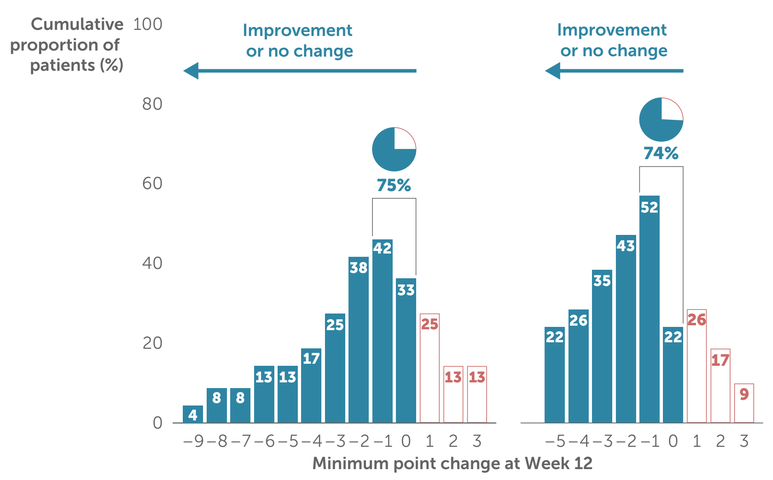
*Nominal p-values are presented.

Table 2 Overview of TEAEs

	Zilucoplan 0.3 mg/kg (N=26)
Any TEAE,* n (%)	**19** (73.1)
Amylase increase	**3** (11.5)
Diarrhoea	**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)

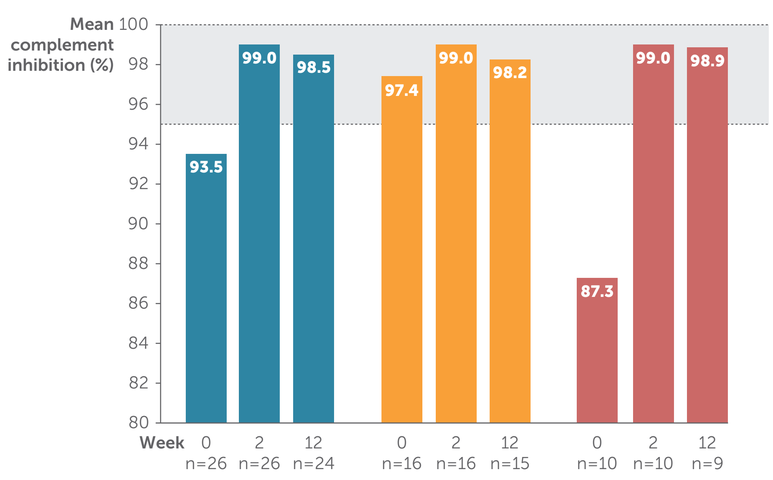
Safety set.
*Specific TEAEs listed are those occurring in ≥5% of patients. †Diverticulitis, not related to zilucoplan. ‡Injection-site pain, injection-site discolouration, pain, anxiety and fatigue (n=1) and reactivation of Epstein-Barr virus (n=1); the TEAEs of injection-site pain and discolouration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

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.

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Abbreviations: AChR Ab+, acetylcholine receptor autoantibody-positive; C5, component 5; CFB, change from baseline; CI, confidence interval; gMG, generalised 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.

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