Early and sustained response over time with zilucoplan in generalised myasthenia gravis: 120-week *post hoc* analysis of RAISE-XT

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Introduction

- Zilucoplan, a macrocyclic peptide complement C5 inhibitor, has shown clinically meaningful and sustained improvements in MG-specific outcomes in patients with anti-AChR Ab+ gMG up to 12 weeks in RAISE (Phase 3; NCT04115293), and up to 120 weeks in the ongoing RAISE-XT study (Phase 3 OLE; NCT04225871)[1,2]
- After one week of treatment with zilucoplan, 43.0% (n=40/93) of patients were MG-ADL responders and 33.3% (n=31/93) were QMG responders[3]
  - At Week 12 of RAISE, significantly more patients in the zilucoplan group were responders compared with placebo[1]
- This *post hoc* analysis assessed the durability of response up to Week 120 of zilucoplan treatment in Week 1 MG-ADL and QMG responders and non-responders

Methods

- In the ongoing RAISE-XT study, adults with anti-AChR Ab+ gMG who completed the RAISE or Phase 2 (NCT03315130) double-blind studies self-administered once-daily subcutaneous zilucoplan 0.3 mg/kg[2,4]
  - The primary outcome of RAISE-XT was incidence of TEAEs[4]
- Early responders were defined as patients who experienced improvement in symptoms without rescue therapy at Week 1 of the double-blind studies:
  - MG-ADL responder: ≥3-point improvement from baseline
  - QMG responder: ≥5-point improvement from baseline
- The percentage of follow-up time patients spent in response was calculated up to Week 120 for Week 1 responders and Week 1 non-responders (interim data cut: 11 November 2023)
  - The responder status for each patient was calculated daily by imputing the data based on the status at the last visit

Results

- Overall, 93 patients were randomised to zilucoplan 0.3 mg/kg in the double-blind studies and entered RAISE-XT
- Baseline characteristics for MG-ADL responders are presented in **Table 1**
- MG-ADL and QMG response rates at Week 1 were sustained at ≥80.0% up to Week 120 (**Figures 1a and 2a**)
  - Over 120 weeks, MG-ADL and QMG Week 1 responders remained in response for a median (range) of 98.9% (5.8–99.2) and 99.0% (2.5–99.2) of their time in the study, respectively (**Figures 1b and 2b**)
- The proportions of MG-ADL and QMG Week 1 non-responders who responded later increased up to Week 12, and were sustained at ≥57.1% from Week 13 up to Week 120 (**Figures 1c and 2c**)
  - Over 120 weeks, MG-ADL and QMG Week 1 non-responders were in response for a median (range) of 84.6% (0.0–98.3) and 66.7% (0.0–98.9) of their time in the study, respectively (**Figures 1d and 2d**)
- In RAISE-XT, TEAEs occurred in 97.0% (194/200) of patients
  - Overall, 40.5% (81/200) of patients experienced a serious TEAE, of whom 2.5% (5/200) experienced a serious treatment-related TEAE

Summary and conclusions

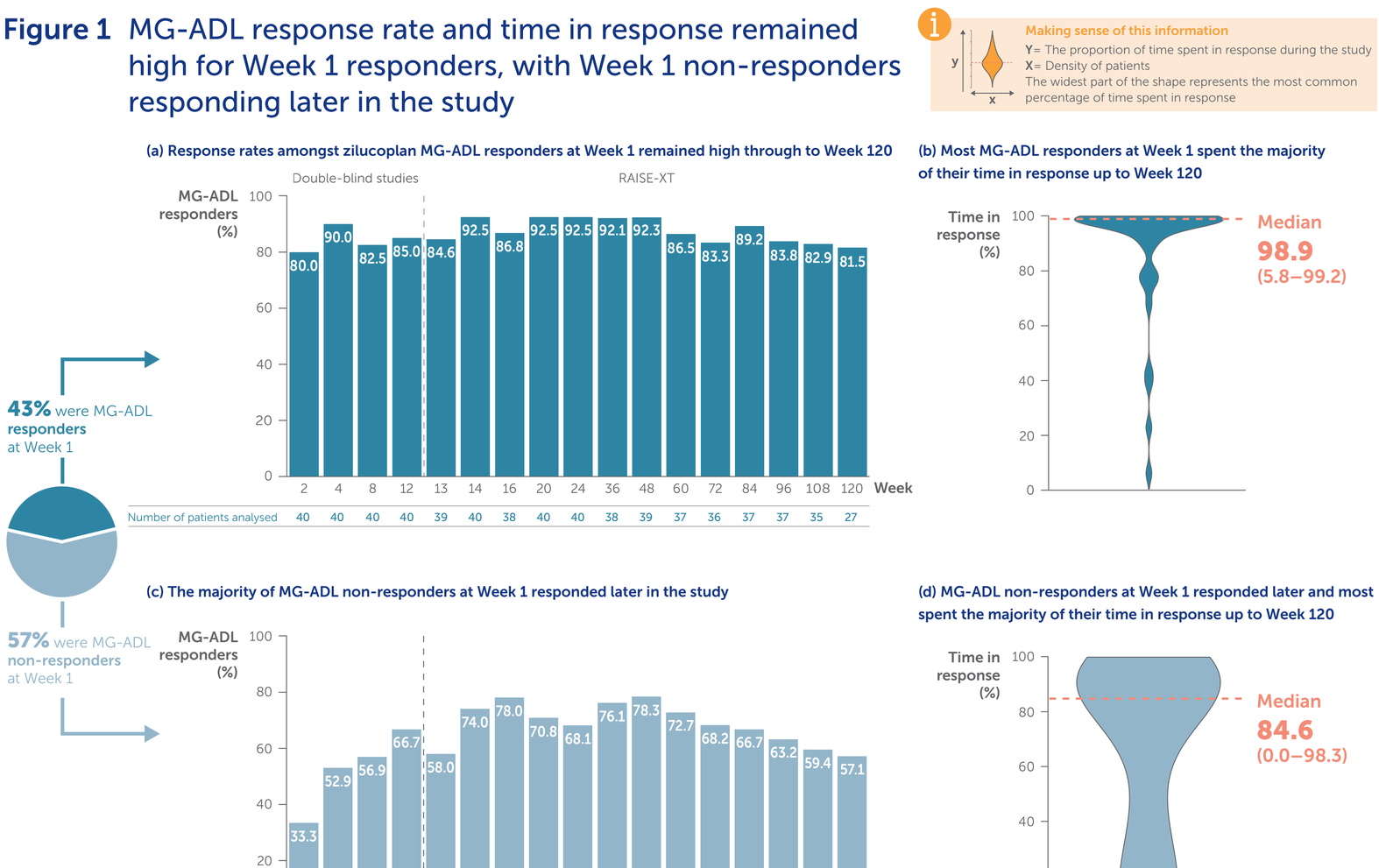
This *post hoc* analysis of RAISE-XT assessed the durability of response up to Week 120 of treatment in MG-ADL and QMG early (Week 1) responders and non-responders to zilucoplan treatment

The time in response of the early MG-ADL and QMG responders remained high (99%) up to Week 120 of zilucoplan treatment

The majority of Week 1 non-responders responded later in the study with continued use of zilucoplan and spent over two-thirds of their time in response through to Week 120

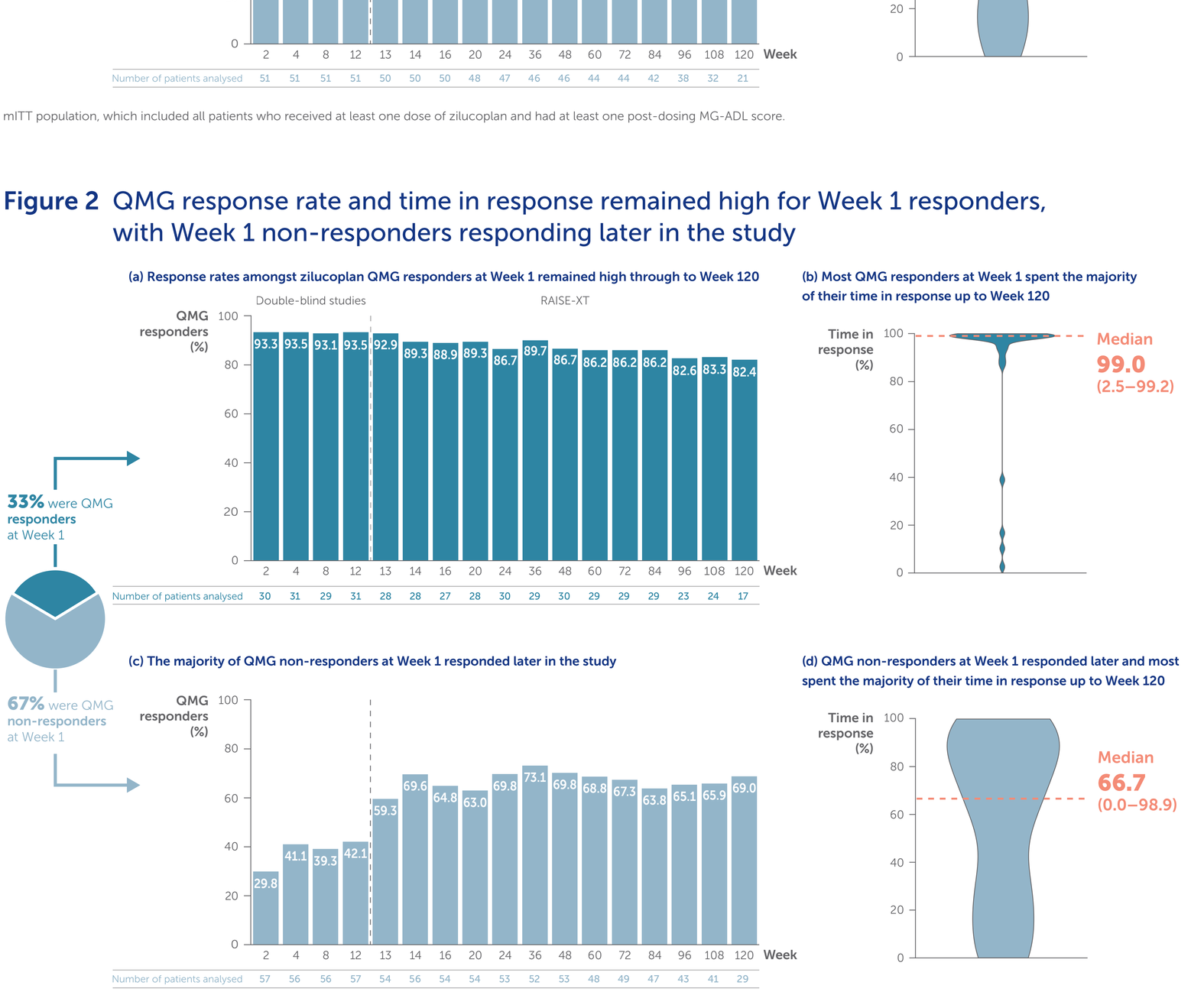
These data demonstrate rapid and sustained efficacy with long-term zilucoplan treatment

Figure 1 MG-ADL response rate and time in response remained high for Week 1 responders, with Week 1 non-responders responding later in the study



mITT population, which included all patients who received at least one dose of zilucoplan and had at least one post-dosing MG-ADL score.

Figure 2 QMG response rate and time in response remained high for Week 1 responders, with Week 1 non-responders responding later in the study



mITT population.

Table 1 There were no relevant differences in patient demographics and baseline disease characteristics between Week 1 MG-ADL responders and the overall population in the zilucoplan group

		Zilucoplan 0.3 mg/kg	
		MG-ADL responders at Week 1 n=40	Overall population n=93
	Age, years, mean (SD)	**49.6** (15.7)	**52.9** (14.5)
	Sex, male, %	**40.0**	**44.1**
MGFA Disease Class	IIa/b, %	**25.0**	**26.9**
	IIIa/b, %	**60.0**	**64.5**
	IVa/b, %	**15.0**	**8.6**
	MG-ADL score, mean (SD)	**10.2** (2.6)	**9.9** (2.6)
	QMG score, mean (SD)	**20.2** (3.9)	**18.8** (3.9)
	Prior thymectomy, %	**55.0**	**52.7**
	Prior MG crisis, %	**30.0***	**32.3***
	Duration of disease,† years, mean (SD)	**8.5** (8.3)	**9.4** (9.4)
	Age at onset, years, mean (SD)	**41.3** (18.6)	**43.4** (17.6)
Prior gMG medications	Corticosteroids, %	**92.5**	**91.4**
	Immunosuppressants, %	**77.5**	**68.8**
	Cholinesterase inhibitors, %	**100.0**	**97.8**

mITT population. 'MG-ADL responders' are patients who had an MG-ADL total score improvement of ≥3 points from baseline at Week 1. Similar results were observed for QMG responders at Week 1.
*Missing data for one patient. †From diagnosis.

Abbreviations: Anti-AChR Ab+, positive for antibodies against the acetylcholine receptor; C5, component 5; gMG, generalised myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; mITT, modified intention to treat; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis; SD, standard deviation; TEAE, treatment-emergent adverse event.

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