Corticosteroid dose tapering with zilucoplan in patients with generalised myasthenia gravis: 120-week follow-up of RAISE-XT

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Introduction

- Corticosteroids are commonly used to manage the symptoms of MG; however, physicians and patients generally aim to reduce corticosteroid use due to potential systemic side effects and long-term toxicities[1]
- Zilucoplan is a small, 15-amino acid macrocyclic peptide complement C5 inhibitor, approved for the treatment of adults with AChR Ab+ gMG[2]
- This *post hoc* interim analysis evaluated corticosteroid dose changes in patients with gMG during zilucoplan treatment in RAISE-XT (NCT04225871), an ongoing OLE study

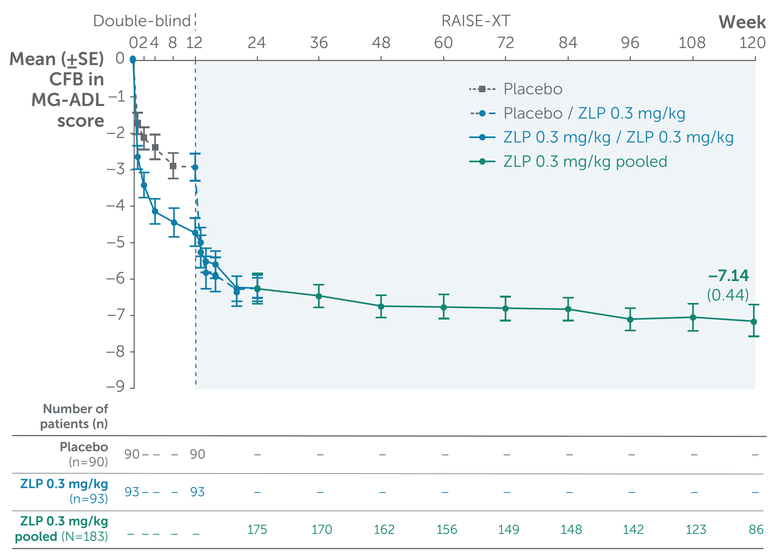
Methods

- In RAISE-XT, adults with gMG who completed a qualifying double-blind study (Phase 2 [NCT03315130]/RAISE [NCT04115293]) administered once-daily subcutaneous zilucoplan 0.3 mg/kg by self-injection
- During the double-blind studies, and the first 12 weeks of RAISE-XT, corticosteroid dose was kept stable; thereafter, dose could be changed at the investigator's discretion
- The proportion of patients who discontinued, reduced or increased their corticosteroid dose* relative to double-blind baseline up to Week 120 (data cut-off: 11 November 2023) was evaluated *post hoc*
  - Discontinuation and reduction in corticosteroid dose were assessed in patients receiving corticosteroids at double-blind baseline
  - Increase in corticosteroid dose was assessed in all patients
- Mean CFB in corticosteroid dose, MG-ADL score and QMG score at Weeks 60 and 120 (Extension Weeks 48 and 108 of RAISE-XT, respectively) were also evaluated
- The prespecifed primary safety endpoint was the incidence of TEAEs
- Prespecified efficacy assessments included change from double-blind baseline to Week 120 in MG-ADL score

Results

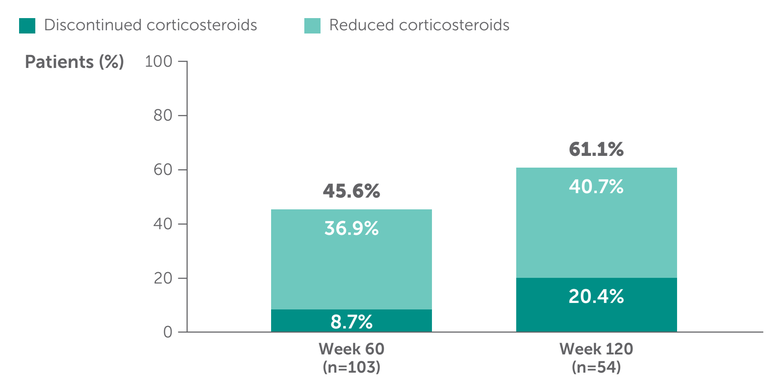
- Overall, 200 patients entered RAISE-XT, of whom 183 received placebo / zilucoplan 0.3 mg/kg or zilucoplan 0.3 mg/kg / 0.3 mg/kg and were included in this analysis (zilucoplan 0.3 mg/kg pooled; **Table 1**)
  - All patients who completed RAISE opted to enroll into RAISE-XT
  - At the time of data cut-off, 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
  - In total, 7.5% (n=15) of patients discontinued due to an AE
- Improvements observed in MG-ADL score from double-blind baseline through Week 24 were sustained through to Week 120 (**Figure 1**)
- Of patients on corticosteroids at double-blind baseline with Week 120 data, 61.1% had reduced or discontinued corticosteroids (**Figure 2**)
  - The mean dose decreased from 23.0 mg/day to 7.5 mg/day, a mean reduction of 15.5 mg/day
- Among all patients with data at Weeks 60 and 120, 4.5% (n=7/156) and 9.3% (n=8/86), respectively, increased corticosteroids relative to double-blind baseline (mean dose increase: 13.2 mg/day and 11.6 mg/day, respectively)
- Mean CFB in MG-ADL score at Weeks 60 and 120 was similar in patients who increased corticosteroids (–5.9 [SD 5.8] and –7.4 [SD 4.6]) and those who reduced or discontinued corticosteroids (**Figure 2**)
- Analysis of patients receiving ≥7.5 mg/day corticosteroids (Cushing threshold)[3,4] at double-blind baseline found that 20.2% and 31.9% had reduced their dose below 7.5 mg/day at Week 60 and Week 120, respectively (**Figure 3**)
- A total of 58.6% (17/29) of patients receiving a corticosteroid dose of >15 mg/day at double-blind baseline reduced their dose to ≤15 mg/day at Week 120 (**Figure 4**)
  - Further, 37.9% (11/29) of patients receiving a corticosteroid dose of >15 mg/day at double-blind baseline reduced their dose to ≤7.5 mg/day at Week 120
- Over a median (range) of 2.2 (0.1–5.6) years' follow-up, TEAEs occurred in 97.0% (194/200) of patients

Figure 1 Mean CFB in MG-ADL score to Week 120



mITT population.

Figure 2 Proportion of patients who reduced or discontinued corticosteroids



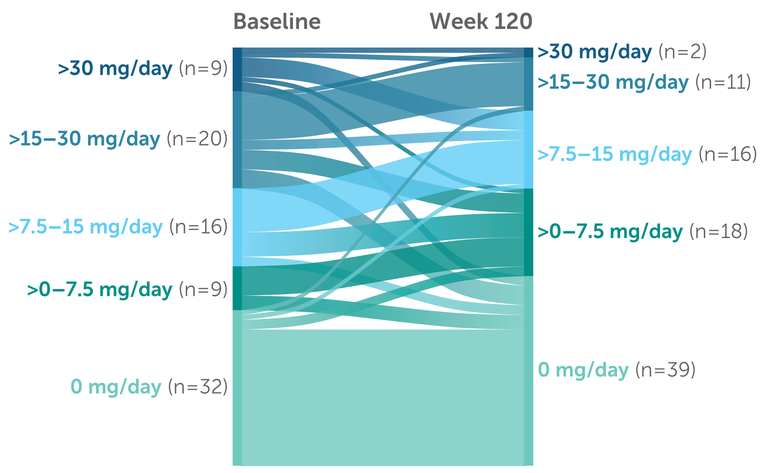
	Week 60 (n=103)	Week 120 (n=54)
Mean (SD) CFB in MG-ADL score	**–6.3** (4.9)	**–6.6** (3.6)
Mean (SD) CFB in QMG score	**–8.8** (6.4)	**–9.8** (6.5)

mITT population. Data for patients with >0 mg/day corticosteroid dose at double-blind baseline.

Figure 3 Time to crossing the Cushing threshold in patients with a corticosteroid dose ≥7.5 mg/day at double-blind baseline

mITT population. The Cushing threshold is defined as the individual steroid dose, which, if exceeded over a prolonged period, leads to Cushing's syndrome. It is generally considered as a prednisone-equivalent daily dose of 7.5 mg.[3,4] Time to Cushing threshold was defined as the earliest date of corticosteroid dose <7.5 mg/day during the OLE minus the date of double-blind baseline plus 1 divided by 7. Patients who did not cross the Cushing threshold were censored at the date of withdrawal/study completion or the date of their last visit.

Figure 4 Change in daily corticosteroid dose from double-blind baseline to Week 120



mITT population. Only patients with observations at both timepoints are included.

Table 1 Demographics and baseline disease characteristics

		ZLP 0.3 mg/kg pooled (N=183)
	Age, years, mean (SD)	**53.3** (15.0)
	Sex, male, n (%)	**83** (45.4)
MGFA Disease Class, n (%)	IIa/b	**54** (29.5)
	IIIa/b	**117** (63.9)
	IVa/b	**12** (6.6)
	MG-ADL score, mean (SD)	**6.4** (4.4)
	QMG score, mean (SD)	**14.1** (5.9)
	Prior thymectomy, n (%)	**88** (48.1)
	Prior MG crisis, n (%)	**59** (32.2)
	Duration of disease*, years, mean (SD)	**9.4** (9.9)
Baseline gMG-specific therapies, n (%)	Cholinesterase inhibitor	**149** (81.4)
	Corticosteroids†	**112** (61.2)
	IST‡	**92** (50.3)

mITT population. *From diagnosis. †Corticosteroids comprised prednisone, prednisolone and methylprednisolone. ‡ISTs comprised azathioprine, mycophenolate mofetil, ciclosporin, methotrexate and tacrolimus.

Summary and conclusions

This *post hoc* analysis investigated changes in concomitant corticosteroid dose among patients receiving zilucoplan in the RAISE-XT OLE study

More than 60% of patients had reduced or discontinued corticosteroids at Week 120 of zilucoplan treatment, with a mean dose reduction of 15.5 mg/day, while experiencing sustained efficacy

Overall, 32% of patients treated with a corticosteroid dose above the Cushing threshold (7.5 mg/day) at baseline were able to reduce their dose below 7.5 mg/day at Week 120 of zilucoplan treatment

Sustained efficacy for up to 120 weeks with zilucoplan treatment allowed for tapering or discontinuation of concomitant corticosteroids, which could be beneficial for managing the safety risks associated with long-term corticosteroid use

Footnote: *The total prednisone-equivalent daily dose was calculated by converting the daily dose for each corticosteroid into a prednisone-equivalent dose using prespecified conversions and summing across each corticosteroid taken.

Abbreviations: AChR Ab+, positive for autoantibodies against the acetylcholine receptor; AE, adverse event; C5, component 5; CFB, change from baseline; gMG, generalised myasthenia gravis; IST, immunosuppressive therapy; 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; SE, standard error; TEAE, treatment-emergent adverse event; ZLP, zilucoplan.

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