Corticosteroid dose tapering in patients with generalized myasthenia gravis on zilucoplan: Interim analysis of RAISE-XT

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Introduction

- In the randomized, double-blind, placebo-controlled, 12-week, Phase 3 RAISE study (NCT04115293), the macrocyclic peptide complement C5 inhibitor zilucoplan significantly improved MG-specific outcomes in patients with AChR Ab+ gMG, with a favorable safety profile[1]
- Patients and physicians generally aim to reduce corticosteroid use where possible due to safety risks associated with long-term use[2]
- Per protocol, corticosteroid dose was kept stable in the Phase 2 study (NCT03315130), the RAISE study and during the first 12 weeks of the ongoing OLE study, RAISE-XT (NCT04225871)[1,3]
- After the first 12 weeks of zilucoplan treatment in RAISE-XT, corticosteroid dose could be changed at the investigator's discretion
  - Here we evaluate changes in corticosteroid dose during RAISE-XT

Methods

- RAISE-XT enrolled adult patients who completed either the Phase 2 or the RAISE study where they received either zilucoplan or placebo
  - In RAISE-XT, patients self-administered SC zilucoplan 0.3 mg/kg daily
  - The primary endpoint was the incidence of TEAEs
- In this *post hoc* analysis, we assessed the proportion of patients who discontinued, reduced or increased their corticosteroid dose relative to the double-blind study baseline up to Week 120 (interim data cut-off date: November 11, 2023)
  - Only patients receiving a corticosteroid at baseline were included in the analysis of patients who discontinued or reduced corticosteroids
  - Patients who increased or started corticosteroids were evaluated as a proportion of the overall population
  - Mean CFB in corticosteroid dose and MG-ADL score at Week 60 and Week 120 (Extension Weeks 48 and 108 of RAISE-XT, respectively) were evaluated for each category

Results

- Overall, 200 patients entered RAISE-XT (**Table 1**)
- At Week 120, of patients who were on corticosteroids at baseline and had data available, 33/54 (61.1%) had reduced the dose or discontinued corticosteroids (mean dose reduction: 15.5 mg) (**Figures 1 and 2**)
- Overall, 7/156 (4.5%) patients at Week 60 and 8/86 (9.3%) patients at Week 120 increased or started corticosteroids relative to double-blind baseline, with a mean dose increase of 13.2 mg and 11.6 mg, respectively
- Mean CFB in MG-ADL score was –6.6 (SD 3.6) in patients who discontinued or reduced their corticosteroid dose at Week 120 (**Figure 1**)
- Mean CFB in MG-ADL score was similar in patients who increased or started corticosteroids: –5.9 (SD 5.8) and –7.4 (SD 4.6) at Week 60 and Week 120, respectively
- In the RAISE-XT overall population, TEAEs occurred in 194/200 (97.0%) patients
  - The most frequently reported TEAEs were COVID-19 (71 [35.5%] patients) and MG (59 [29.5%] patients)
  - 81/200 (40.5%) patients experienced a serious TEAE
- There was no meaningful difference in infection rates between patients who reduced their corticosteroid dose and those who did not (**Table 2**)

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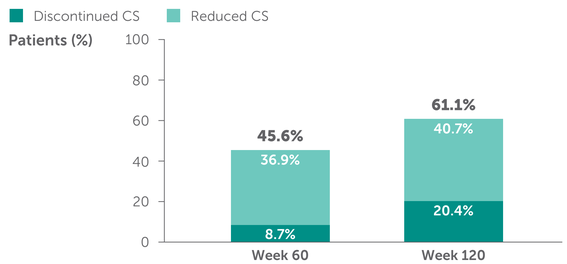
Table 1 Demographics and baseline disease characteristics

		Zilucoplan 0.3 mg/kg N=200
	Age, years, mean (SD)	**53.3** (15.0)
	Sex, male, %	**45.0**
MGFA Disease Class	II, %	**29.5**
	III, %	**64.5**
	IV, %	**6.0**
	MG-ADL score, mean (SD)	**6.3** (4.3)
	QMG score, mean (SD)	**14.0** (5.9)
	Prior thymectomy, %	**48.0**
	Prior MG crisis, %	**31.0**
	Duration of disease, years, mean (SD)	**9.4** (9.7)
	Age at disease onset, years, mean (SD)	**43.6** (17.9)
Prior gMG-specific medication	Corticosteroids, %	**88.5**
	Immunosuppressants, %	**73.5**
	Cholinesterase inhibitors, %	**97.0**

Figure 1 Proportions of patients in RAISE-XT who discontinued or reduced their corticosteroid dose*



	Week 60 (n=103)	Week 120 (n=54)
n (%)	**47** (45.6)	**33** (61.1)
Mean (SD) CFB in MG-ADL score	**–6.3** (4.9)	**–6.6** (3.6)

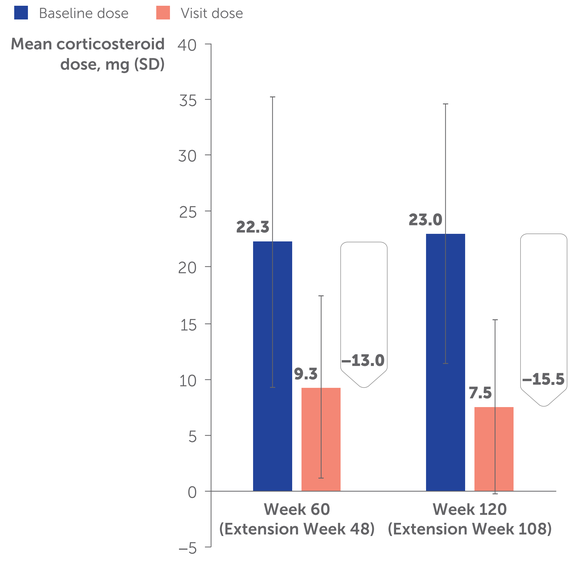
Corticosteroid dose remained stable prior to Week 24 (i.e., Extension Week 12 of RAISE-XT).
*Analyzed in patients with >0 mg corticosteroid dose at baseline in the double-blind study.

Table 2 Infection rates for corticosteroid dose cohorts

	Time period before first CS dose reduction n=75	Time period after first CS dose reduction n=75	No CS dose reduction n=125
Patients with infections, n	41	52	87
Event rate, infections/PYAR	1.12	1.18	0.99

mITT population.

Figure 2 Corticosteroid dose change in patients who discontinued or reduced their corticosteroid dose*



The daily corticosteroid dose was defined as the total prednisone-equivalent daily dose, summed across multiple corticosteroids taken. Corticosteroid dose remained stable prior to Week 24 (i.e., Extension Week 12 of RAISE-XT). n=103 at Week 60 and n=54 at Week 120.
*Analyzed in patients with >0 mg corticosteroid dose at baseline in the double-blind study.

Summary and conclusions

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

More than 60% of patients had reduced their dose or discontinued corticosteroids at Week 120 of zilucoplan treatment

Mean reductions from baseline in MG-ADL up to Week 120 were similar in patients who discontinued, decreased or increased their corticosteroid dose

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

Abbreviations: Ab+, autoantibody positive; AChR, acetylcholine receptor; C5, component 5; CFB, change from baseline; CS, corticosteroid; gMG, generalized 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; PYAR, person year at risk; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous; SD, standard deviation; TEAE, treatment-emergent adverse event.

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