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Concomitant use of zilucoplan with intravenous immunoglobulin or plasma exchange during RAISE and RAISE-XT

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Introduction

- Patients with MG may experience symptom exacerbations that require rescue therapy with IVIg or PLEX[1]
  - After rescue therapy, those receiving treatment with monoclonal antibody complement C5 inhibitors require supplemental dosing[2,3]
- Zilucoplan is a small, 15-amino acid macrocyclic peptide complement C5 inhibitor approved for the treatment of adults with AChR Ab+ gMG[4]
- Here, we evaluate the impact of rescue therapy (IVIg or PLEX) on zilucoplan concentration and complement inhibition in patients enrolled in the Phase 3 RAISE (NCT04115293) and RAISE-XT (NCT04225871) studies

Methods

- The Phase 3 RAISE study was a double-blind, placebo-controlled study of zilucoplan in which patients aged 18–74 years with MGFA Disease Class II–IV AChR Ab+ gMG, an MG-ADL score ≥6 and a QMG score ≥12 were randomized 1:1 to once-daily subcutaneous zilucoplan 0.3 mg/kg or placebo for 12 weeks
- Patients completing RAISE (or the qualifying Phase 2 study [NCT03315130]) could enter the ongoing RAISE-XT OLE study (data cutoff: September 8, 2022) to receive once-daily zilucoplan 0.3 mg/kg
- The primary safety endpoint of RAISE-XT was the incidence of TEAEs
- During the Phase 2 study, RAISE, and RAISE-XT, patients could receive concomitant IVIg or PLEX treatment as rescue therapy if, per the investigator's judgment, escalation of gMG therapy became necessary
- PK and PD analyses were carried out *post hoc* for patients with ≥1 week of exposure to zilucoplan 0.3 mg/kg across RAISE and RAISE-XT
  - No patients receiving zilucoplan 0.3 mg/kg in the Phase 2 study received rescue therapy
- When rescue therapy was administered, zilucoplan dosing was held until after administration of rescue therapy and PK/PD sampling
  - Zilucoplan plasma concentration was measured pre- and post-rescue therapy by liquid chromatography-tandem mass spectrometry on the day of rescue and compared to the estimated zilucoplan plasma concentration of 4.45 mg/L at which patients were expected to achieve complete complement inhibition (>95%)[5]
  - Complement activity was measured pre- and post-rescue by sRBC lysis assay
- Blood samples for PK and PD analyses were taken within 1 hour prior to administration of rescue therapy; samples for PK analysis were also taken within 1 hour after administration of rescue, with the post-rescue measurement for PD analysis taken up to 1 day after rescue
- Only rescue events with both a pre- and post-rescue zilucoplan concentration or sRBC lysis measurement were included in the PK or PD analyses, respectively
- All analyses were descriptive

Results

Patients

- A broad gMG population with mild-to-severe disease as per MGFA disease classification was enrolled across RAISE and RAISE-XT
- Median (range) exposure to zilucoplan in RAISE-XT was 1.2 (0.11–4.45) years
- Among patients with ≥1 week of exposure to zilucoplan 0.3 mg/kg across RAISE and RAISE-XT (N=200), 21 (10.5%) patients received IVIg and 10 (5.0%) patients received PLEX rescue therapy, including one patient who received both IVIg and PLEX
- Across these 30 patients, there were a total of 60 IVIg and 22 PLEX rescue events from which the PK and PD cohorts were defined based on the availability of pre- and post-rescue data:
  - PK cohort: n=17 and n=3 rescue events, respectively
  - PD cohort: n=10 and n=1 rescue event(s), respectively

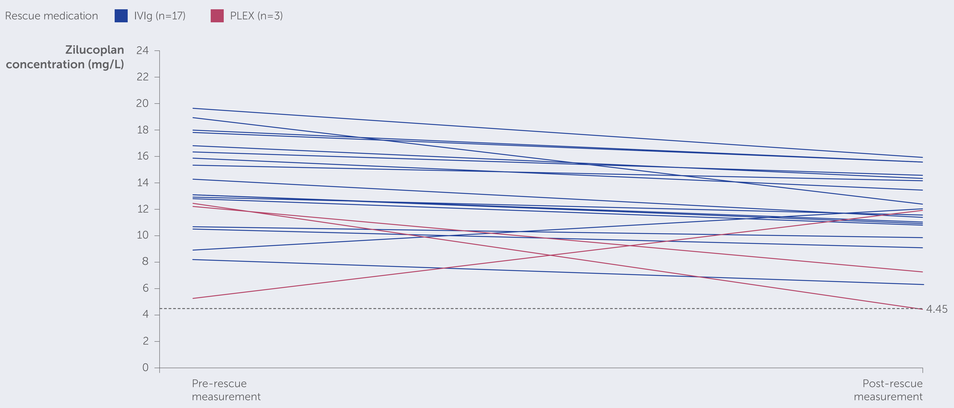
PK and PD analyses

- All IVIg rescue events (n=17/17) and two of three PLEX rescue events had pre- and post-zilucoplan concentrations within the therapeutic exposure range (above 4.45 mg/L; **Figure 1**)
  - The third PLEX rescue event had a post-rescue zilucoplan concentration just below 4.45 mg/L (4.39 mg/L)
- Mean complement inhibition remained complete (>95%) pre- and post-rescue therapy in all patients (**Figure 2**):
  - 97.1% and 97.4% for IVIg events, respectively
  - 96.3% and 95.9% for PLEX events, respectively

Safety

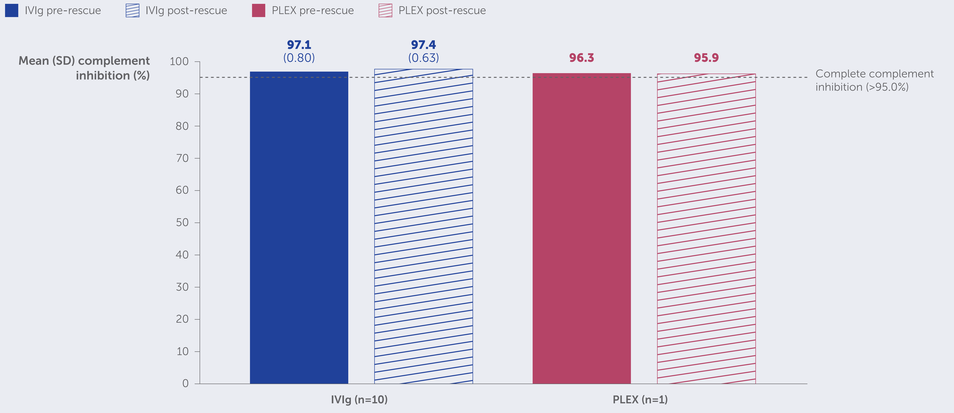
- In RAISE-XT, TEAEs occurred in 188/200 (94.0%) patients
  - The most common TEAEs occurring in ≥15% of patients overall were MG worsening (n=52 [26.0%]), COVID-19 (n=49 [24.5%]), headache (n=35 [17.5%]), diarrhea (n=30 [15.0%]) and nasopharyngitis (n=30 [15.0%])
- In total, 64/200 (32.0%) patients experienced a serious TEAE; two (1.0%) were considered treatment related (esophagitis [n=1] and injection-site infection [n=1])

Figure 1 Change in zilucoplan concentration following rescue with IVIg or PLEX



mITT population, which included all patients enrolled in RAISE-XT who received ≥1 dose of the study drug and had ≥1 post-dosing MG-ADL score. Total rescue events while on zilucoplan 0.3 mg/kg, after ≥1 week of exposure. 'n' represents the number of rescue events with data. One event per rescue; some patients contributed ≥1 event. A value of 4.45 mg/L represents the estimated zilucoplan plasma concentration at which patients were expected to achieve complete complement inhibition (>95%).[5]

Figure 2 Mean complement inhibition pre- and post-rescue with IVIg or PLEX



mITT population. Total rescue events while on zilucoplan 0.3 mg/kg, after ≥1 week of exposure. 'n' represents the number of rescue events with data. One event per rescue; some patients contributed ≥1 event.

Summary and conclusions

In this *post hoc* analysis of data from the Phase 3 RAISE and RAISE-XT OLE studies, the impact of rescue therapy (IVIg or PLEX) on zilucoplan concentration and complement inhibition in patients with AChR Ab+ gMG was assessed

Zilucoplan concentrations remained within the therapeutic exposure range for all but one post-rescue event

Complete complement inhibition (>95%) was maintained with IVIg and PLEX during treatment with zilucoplan

These data confirm that zilucoplan can be used concomitantly with IVIg and PLEX rescue therapy without the need for supplemental dosing

Abbreviations: AChR Ab+, positive for autoantibodies against the acetylcholine receptor; C5, component 5; gMG, generalized myasthenia gravis; IVIg, intravenous immunoglobulin; 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; PD, pharmacodynamic; PK, pharmacokinetic; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SD, standard deviation; sRBC, sheep red blood cell; TEAE, treatment-emergent adverse event.

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