Zilucoplan, a Subcutaneously Self-Administered Peptide Inhibitor of Complement Component 5 (C5), for the Treatment of Generalized Myasthenia Gravis: Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial and Open-Label Long-Term Extension

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INTRODUCTION
- Generalized myasthenia gravis (gMG) is an autoimmune disorder of neuromuscular transmission characterized by autoantibodies against the neuromuscular junction (Figure 1).
- Acetylcholine receptor (AChR) autoantibodies activate complement, which destroys the neuromuscular junction and blocks signal transmission from nerves to muscles.
- The incidence of gMG is 150-250/million, including ~60,000 cases in the United States, ~128,000 cases in Europe, and ~64,000 cases in Japan.
- gMG can be a serious, progressive, and life-threatening disease, which significantly impacts quality of life.
- Approximately 50% of patients experience cardiac weakness.

OBJECTIVES
- To evaluate the safety, tolerability, and efficacy of zilucoplan in patients with anti-AChR antibody-positive gMG.
- To assess the durability of the treatment effect in an open-label extension.
- To cause improvement in efficacy measures for placebo subjects crossing over to active zilucoplan week 12.

METHODS
Study Design
- Randomized, double-blind, placebo-controlled, multicenter Phase 2 study followed by an open-label long-term extension study (NCT03315130, Figure 3).
- Patients with clinical indications of immunoglobulin (IgG) or complement (C3/C4) autoantibodies were not allowed to adjust their standard of care (SOC) therapies, but could receive rescue therapy with IgG or PLEX as needed.

Pharmacodynamics and Pharmacokinetics
- Zilucoplan 0.3 mg/kg dose consistently led to rapid, sustained, and complete (≥50%) complement inhibition.
- Zilucoplan 0.1 mg/kg dose reached rapid, sustained, but submaximum (≥40%) complement inhibition.
- Based on superior pharmacokinetics, pharmacodynamics, and efficacy, 0.3 mg/kg dose was selected for Phase 3.

RESULTS
- Placebo subjects crossing over to zilucoplan 0.3 mg/kg after 12 weeks experienced rapid, clinically meaningful, and statistically significant improvements in QMG, MG-ADL, MG Composite, and MGQoL15r compared with placebo, with no significant differences between zilucoplan doses.
- Results of 0.3 mg/kg dose were consistent with the results of the Phase 2 dose-escalation study, as well as with the long-term extension study.

DISCUSSIONS
- These data support the potential therapeutic role of zilucoplan in gMG and its further evaluation in a registration Phase 3 trial.

ACKNOWLEDGMENTS
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- No competing interests.

REFERENCES

Figure 2. Zilucoplan inhibits C5

Figure 3. Multicenter Phase 2 Study Targets a Broad gMG Patient Population

Figure 4. Highly Consistent and Reproducible Pharmacokinetics and Pharmacodynamics Support Use of Zilucoplan 0.3 mg/kg Daily Dose in gMG

Table 1. Baseline Characteristics

Table 2. Safety and Tolerability Profile

Figure 5. Broad, Clinically Meaningful, Statistically Significant, and Sustained Reductions in gMG, MG-ADL, MG Composite, and MGQoL15r

Figure 6. Responsiveness Analysis—Improvement or Worsening in QMG (A) and Minimal Symptom Expression as Measured by MG-ADL of 0 or 1 (B) (Weeks 0-12)