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

James F. Howard, Jr1, Richard J. Nowak, Gill I. Wolfe, Michael G. Benatar, Petro W. Duda, James MacDougall, Ramin Forazheh-Far, Henry J. Kamienski, the Zilucoplan MG Study Group

INTRODUCTION

- Generalized myasthenia gravis (gMG) is an autoimmune disorder of neuromuscular transmission characterized by antibodies against the neuromuscular junction (Figure 1).
- Anticholinesterase therapy (AChR) autonomic antibodies active complement, which destroys the neuromuscular junction and blocks acetylcholine transmission from nerve to muscle.
- The incidence of gMG is 150-250/million, including ~40,000 cases in the United States, ~160,000 cases in Europe, and ~46,000 cases in Japan.
- C5a can be a serious, progressive, and life-threatening disease, which significantly impacts quality of life.
- Approximately 20% of patients experience crisis.
- Current treatment options include: -Cholinesterase inhibitors (eg, pyridostigmine) -Corticosteroids, immunosuppressive treatments (Bis) -Plasmapheresis -Intravenous immunoglobulin (IVIg) and plasma exchange (PEX) -Eculizumab (intravenous antibody inhibitor of C5-2)
- Zilucoplan is a subcutaneously self-administered macrocyclic peptide inhibitor designed to block formation of C5-3 and binding of C5a to C5b-5 (Figure 2).

Figure 1. Autoantibodies and Complement Mediated Destruction of the Neuromuscular Junction Cause Pathology in AChR-Positive MG-4

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 on an open-label extension.
- To assess improvement in efficacy measures for placebo subjects crossing over to active zilucoplan at week 12.
- To compare the effect of a single dose of zilucoplan 0.3 mg/kg to placebo in asymptomatic gMG patients.

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 manifestations of generalized myasthenia gravis (gMG) symptoms were not allowed to adjust their standard of care (SOC) therapy, but could receive rescue therapy with IVIg or PLEX as needed.

Figure 2. Zilucoplan Inhibits C5-3

Figure 3. Multicenter Phase 2 Study Targets a Broad gMG Patient Population-5

Pharmacodynamics and Pharamacokinetics

- Zilucoplan 0.5 mg/kg dose consistently achieved sustained, and macrocyclic (-97%) complement inhibition (Figure 4).
- Zilucoplan 0.1 mg/kg dose achieved rapid, sustained, but adherent maximum (-98%) complement inhibition.
- Based on superior pharmacokinetics, pharmacodynamics, and efficacy, 0.3 mg/kg dose was selected for Phase 3.

Figure 4. Highly Consistent and Reproducible Pharmacokinetics and Pharmacodynamics Support Use of Zilucoplan 0.3 mg/kg Daily Dose in gMG-6

Key Efficacy Endpoints

- Zilucoplan 0.3 mg/kg treatment led to rapid, statistically significant, and clinically meaningful reductions in QMG, MG-ADL, MG Composite, and MGQoL15r scores vs placebo from baseline to week 12 (Figure 5).
- Sustained responses were observed for all 4 endpoints after 24 weeks of dosing with zilucoplan 0.5 mg/kg.
- Patients subjects crossing over to zilucoplan 0.3 mg/kg after 12 weeks experienced rapid, clinically meaningful, and statistically significant improvements for all 4 endpoints from weeks 12–24.

Figure 5. Broad, Clinically Meaningful, Statistically Significant, and Sustained Reductions in QMG, MG-ADL, MG Composite, and MGQoL15r-7

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=15)</th>
<th>Zilucoplan 0.3 mg/kg (n=14)</th>
<th>Placebo 0.1 mg/kg (n=15)</th>
</tr>
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<tbody>
<tr>
<td>Male, n (%)</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>7</td>
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<td>7</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>55 (17–88)</td>
<td>56 (18–88)</td>
<td>55 (18–88)</td>
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<td>Generalized MG (MGFA class)</td>
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<td>I-VII</td>
<td>I-VII</td>
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<td>QMG score ≥12</td>
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<td>Immunosuppressants</td>
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<td>Rescue therapy</td>
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<tr>
<td>Number of patients with related AEs</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2.

- All "treatment x Prior Therapy" interaction effect P-values were not significant (0.05) across all 4 endpoints (Table 3) indicating that the efficacy of zilucoplan is independent of prior therapies.
- There were few cross-over responders to include "treatment x Corticosteroid" effect in an ANCOVA model.

Table 3. Effect of Zilucoplan in Independent of Prior Therapies and Supports Early Use

- Safety and Tolerability

- No myasthenic complications occurred
- No patients experienced treatment-related serious adverse events
- Nausea and headache were more common with zilucoplan than with placebo (Table 3).

DISCLOSURES

REFERENCES

- Presented at the American Academy of Neurology (AAN) 2019 Annual Meeting; May 4-10, 2019; Philadelphia, PA.