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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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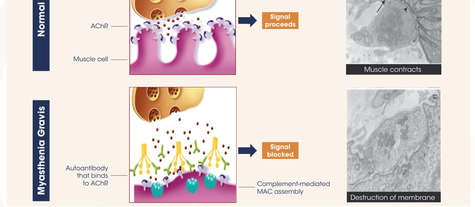
INTRODUCTION

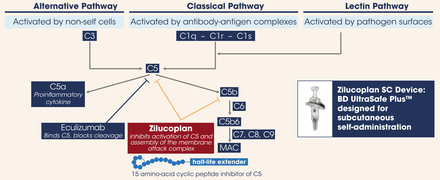
- Generalized myasthenia gravis (gMG) is an autoimmune disorder of neuromuscular transmission characterized by autoantibodies against the neuromuscular junction (**Figure 1**)[1,2]
- Acetylcholine receptor (AChR) autoantibodies activate complement, which destroys the neuromuscular junction and blocks signal transmission from nerves to muscles[1-3]
- The incidence of gMG is 150–250/million, including ~60,000 cases in the United States, ~100,000 cases in Europe, and ~24,000 cases in Japan[2]
- gMG can be a serious, progressive, and life-threatening disease, which significantly impacts quality of life[1,2]
  - Approximately 80% of patients progress to generalized muscle weakness[4]
  - Approximately 20% of patients experience crises[5]
- Current treatment options include:
  - Cholinesterase inhibitors (eg, pyridostigmine)
  - Corticosteroids, immunosuppressive treatments (ISTs)
  - Thymectomy
  - Intravenous immunoglobulin (IVIg) and plasma exchange (PLEX)
  - Eculizumab (intravenous antibody inhibitor of C5)[6]
- Zilucoplan is a subcutaneously self-administered macrocyclic peptide inhibitor designed to inhibit activation of C5 and binding of C5b to C6 (**Figure 2**)

Figure 1. Autoantibodies and Complement-Mediated Destruction of the Neuromuscular Junction Cause Pathology in AChR-Positive MG[1,2]



AChR, acetylcholine receptor; MAC, membrane attack complex; MG, myasthenia gravis.
Graphics from Science Source Images. EM pictures from Engel AG, et al. Neurology. 1977;27:307-315.

Figure 2. Zilucoplan Inhibits C5



C, complement component; SC, subcutaneous.

OBJECTIVES

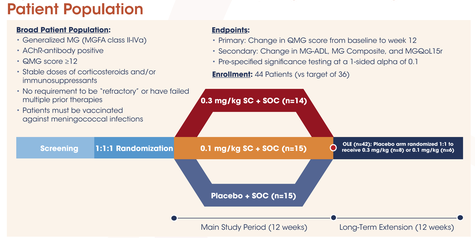
- To evaluate the safety, tolerability, and efficacy of zilucoplan in patients with anti-AChR antibody-positive gMG
- To assess the durability of the treatment effect in an open-label extension
- To assess improvement in efficacy measures for placebo subjects crossing over to active zilucoplan at week 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 deterioration of myasthenia gravis (MG) symptoms were not allowed to adjust their standard of care (SOC) therapies, but could receive rescue therapy with IVIg or PLEX as needed

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



AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MGQoL15r, 15-item Myasthenia Gravis Quality-of-Life revised scale; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous; SOC, standard of care.

Statistical Analysis

- Treatment group differences for change from baseline to week 12 in Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Activities of Daily Living (MG-ADL), MG Composite, and 15-item Myasthenia Gravis Quality-of-Life revised scale (MGQoL15r) were assessed using an analysis of covariance model (ANCOVA), with treatment as a factor and baseline QMG score as a covariate
- Pre-specified significance testing was performed at a 1-sided alpha of 0.1

RESULTS

Patient Disposition

- All 44 patients enrolled completed the 12-week study; there were no early withdrawals
  - 42/44 patients (95%) entered the open-label long-term extension (1 patient in the placebo group and 1 patient in the zilucoplan 0.3 mg/kg group withdrew prior to extension)
  - 41 patients completed the week 24 visit (1 patient in the zilucoplan 0.1→0.1 mg/kg group required repeat rescue therapy and subsequently withdrew from the extension)

Baseline Characteristics

- Baseline characteristics were similar between groups (**Table 1**)
  - Mean (±SD) baseline QMG score ranged from 18.7–19.1, reflecting a high unmet medical need
  - A broad population of patients was included (disease duration: 0 to >20 years)
    - 9% no prior steroid treatment
    - 25% no prior IST
    - 39% no prior IVIg
    - 48% no prior PLEX

Table 1. Baseline Characteristics

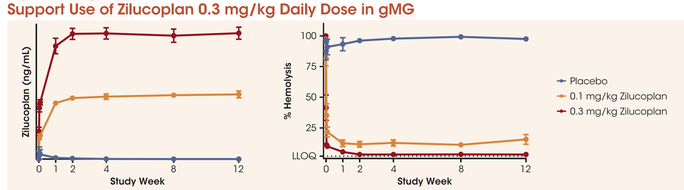
Variable	Placebo (n=15)	Zilucoplan 0.1 mg/kg (n=15)	Zilucoplan 0.3 mg/kg (n=14)
Age, years, mean (SD)	48 (15.7)	46 (15.7)	55 (15.5)
Male, n (%)	4 (27)	7 (47)	10 (71)
Race, n (%)			
White	12 (80)	13 (87)	11 (79)
Asian	1 (7)	0	1 (7)
Black or African American	2 (13)	2 (13)	2 (14)
MGFA class at screening, n (%)			
II	7 (47)	5 (33)	5 (36)
III	8 (53)	10 (67)	5 (36)
IVa	0	0	4 (29)
Duration of disease, years, mean (min, max)	8.0 (0.1, 20.9)	8.7 (1.6, 24.1)	8.3 (0.5, 26.0)
Baseline QMG score, mean (SD)	18.7 (4.0)	18.7 (4.0)	19.1 (5.1)
Baseline MG-ADL score, mean (SD)	8.8 (3.6)	6.9 (3.3)	7.6 (2.6)
Baseline MG Composite score, mean (SD)	18.7 (5.7)	14.5 (6.3)	14.6 (6.3)
Baseline MGQoL15r score, mean (SD)	15.9 (7.4)	19.1 (5.0)	16.5 (7.3)
Prior MG therapies (SOC), n (%)			
Pyridostigmine	14 (93)	15 (100)	14 (100)
Corticosteroids	13 (87)	13 (87)	14 (100)
Immunosuppressants	12 (80)	12 (80)	9 (64)
Prior IVIg, n (%)	9 (60)	8 (53)	10 (71)
Prior PLEX, n (%)	7 (47)	9 (60)	7 (50)
Prior thymectomy, n (%)	5 (33)	8 (53)	7 (50)
Prior MG crisis requiring intubation, n (%)	3 (20)	4 (27)	2 (14)

IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MGQoL15r, 15-item Myasthenia Gravis Quality-of-Life revised scale; PLEX, plasma exchange; SD, standard deviation; SOC, standard of care.

Pharmacokinetics and Pharmacodynamics

- Zilucoplan 0.3 mg/kg dose consistently achieved rapid, sustained, and near-complete (~97%) complement inhibition (**Figure 4**)
- Zilucoplan 0.1 mg/kg dose achieved rapid, sustained, but submaximal (~88%) complement inhibition (**Figure 4**)
- 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

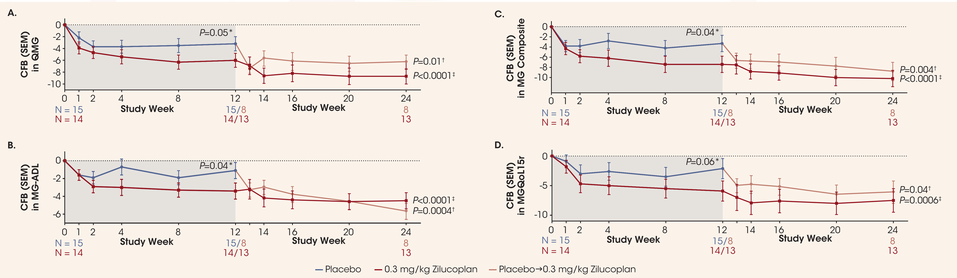


gMG, generalized myasthenia gravis; LLOQ, lower limit of quantitation.

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 0.3 mg/kg
  - Placebo 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

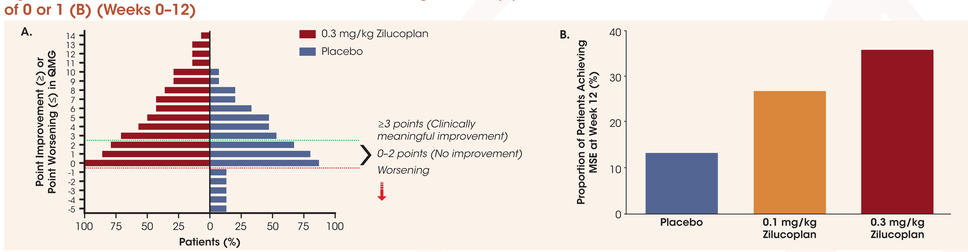
Figure 5. Rapid, Clinically Meaningful, Statistically Significant, and Sustained Reductions in QMG, MG-ADL, MG Composite, and MGQoL15r



*1-sided ANCOVA for LS mean change from baseline for 0.3 mg/kg arm vs placebo; placebo patients re-baselined to zero upon completion of 12-week main study; †2-sided *t* test for LS mean change from weeks 12–24 for placebo patients crossing over to 0.3 mg/kg (n=8); ‡2-sided *t* test for LS mean change from weeks 0–24 for 0.3 mg/kg arm.*
ANCOVA, analysis of covariance; LS, least squares; CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGQoL15r, 15-item Myasthenia Gravis Quality-of-Life revised scale; QMG, Quantitative Myasthenia Gravis; SEM, standard error of the mean.

- Robust and meaningful improvements over placebo were seen in the responder analysis (**Figure 6**)

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



MSE is a recently proposed endpoint designed to assess how many patients become free or virtually free of MG symptoms as measured by achieving an MG-ADL total score of 0 or 1 on therapy.[7]
MG-ADL, Myasthenia Gravis Activities of Daily Living; MSE, minimal symptom expression; QMG, Quantitative Myasthenia Gravis.

- All "Treatment x Prior Therapy" interaction effect *P* values were not significant (>0.20) across all 4 endpoints (**Table 2**) indicating that the efficacy of zilucoplan is independent of prior therapies; there were too few corticosteroid-naive patients to include "Treatment x Corticosteroid" effect in an ANCOVA model

Table 2. Efficacy of Zilucoplan Is Independent of Prior Therapies and Supports Early Use

	Treatment Interaction *P* value (Zilucoplan 0.3 mg/kg vs Placebo)			
Prior Therapy	QMG	MG-ADL	MG-Comp	MGQoL15r
IST	0.59	0.43	0.62	0.62
IVIg	0.74	0.68	0.64	0.77
PLEX	0.21	0.49	0.29	0.45

IST, immunosuppressive therapy; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-Comp, Myasthenia Gravis Composite Scale; MGQoL15r, 15-item Myasthenia Gravis Quality-of-Life revised scale; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis.

Rescue Therapy

- 3/15 patients (20%) on placebo required rescue therapy
- 1/15 patients (7%) on zilucoplan 0.1 mg/kg required rescue therapy
- 0/14 of the patients on zilucoplan 0.3 mg/kg required rescue therapy

Safety and Tolerability

- No meningococcal infections occurred
- No patients experienced treatment-related serious adverse events
- Nausea and headache were more common with zilucoplan than with placebo (**Table 3**)
- Safety and tolerability in the open-label extension were consistent with the placebo-controlled phase

Table 3. Safety and Tolerability Profile

	Placebo (n=15)	Zilucoplan 0.1 mg/kg (n=15)	Zilucoplan 0.3 mg/kg (n=14)
Patients with AEs	12	15	12
Patients with related AEs	3	8	3
Patients with serious AEs	3	0	5
Patients with related serious AEs	0	0	0
Patients with most common related AEs			
Nausea	0	2	2
Injection site bruising	1	2	0
Injection site scab	0	3	0
Contusion	0	1	1
Headache	1	4	2
Patients with injection site reactions	3	4	3

AE, adverse event.

CONCLUSIONS

- **In this study, zilucoplan was effective in a broadly selected gMG population (not restricted to "refractory"), supporting earlier treatment with complement inhibition**
- **Primary and key secondary endpoints were met, with rapid, clinically meaningful, and statistically significant reductions in QMG, MG-ADL, MG Composite, and MGQoL15r compared with placebo**
- **The completeness of pharmacodynamic complement inhibition, the magnitude and speed of onset of effect, and lack of requirement for rescue therapy favor zilucoplan 0.3 mg/kg as the preferred dose for Phase 3**
- **Sustained efficacy was observed over 24 weeks of dosing for all 4 endpoints, and rapid, clinically meaningful, and statistically significant improvements were observed in placebo patients crossing over to active drug at week 12**
- **Favorable safety and tolerability profile**
  - **Safety profile was consistent with Phase 1 healthy volunteer and Phase 2 paroxysmal nocturnal hemoglobinuria studies[8]**
- **These positive data support the potential therapeutic role of zilucoplan in gMG and its further evaluation in a registrational Phase 3 trial**

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Zilucoplan MG Study Group

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DISCLOSURES

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- Gil I. Wolfe is a consultant for Grifols, Takeda, ArgenX, Momenta; is on the speakers bureau for Grifols and Alexion Pharmaceuticals, and has received grant/research support from Alexion Pharmaceuticals, ArgenX, Ra Pharmaceuticals, and Immunovant
- Michael G. Benatar was site investigator for MG trials sponsored by UCB Pharmaceuticals and Alexion Pharmaceuticals, as well as an NIH-funded study of rituximab, and has provided consulting services to UCB
- Henry J. Kaminski has received grant 508240 from the Muscular Dystrophy Association; is a consultant for Alnylam Pharmaceuticals, Ra Pharmaceuticals, and UCB Pharmaceuticals; and is CEO and CMO of ARC Biotechnology, LLC based on US Patent 8,961,981
- Petra W. Duda and Ramin Farzaneh-Far are employees of Ra Pharmaceuticals; James MacDougall is a consultant of Ra Pharmaceuticals

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