Zilucoplan is a convenient, subcutaneously self-administered macrocyclic peptide designed to bind and inhibit the channery of complement component C5 (C5). In a Phase 2 trial, 44 patients (vs target of 36) failed multiple prior therapies and were randomized to Zilucoplan (0.3 mg/kg SC + SOC) or placebo. Levels of zilucoplan did not increase upon completion of the 12-week main study. Patients must be vaccinated against varicella-zoster virus and include healthy volunteers, patients with conditions associated with myasthenia gravis (MG), patients with MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MGQoL15r, 15-item Myasthenia Gravis Quality of Life Questionnaire; C5-R885H, C5 variant R885H.

**OBJECTIVES**

Demonstrate mechanism of action of zilucoplan in gMG by showing the ability of zilucoplan to block formation of complement components C6 through C9, which are induced by anti-AChR antibodies in an in vitro model of the neuromuscular junction (NMJ).

Investigate pharmacological differentiation between zilucoplan and eculizumab by measuring mechanism of actions, including impact of clinically relevant human C5 polymorphisms, in vitro permeability using a basal lamina model, and in vivo clearance of zilucoplan in an intact mouse model (Ntf-ctK, Fc). These data support the possible mechanism that zilucoplan, through mechanisms independent of C5 convertase, may more effectively access the NMJ and locally inhibit C5 at the site of action.

The study design included 168 healthy volunteers, 25-50 years of age, and 50 patients (25 patients per group) who were anti-AChR 637-hIgG1 or control patients. These data support the possible mechanism that zilucoplan, through mechanisms independent of C5 convertase, may more effectively access the NMJ and locally inhibit C5 at the site of action.

**RESULTS**

**Mechanistic and Pharmacological Differentiation of Zilucoplan:**

- **Figure 1.** Zilucoplan inhibited C5b-9 deposition induced by anti-AChR antibody in an in vitro NMJ model using co-cultures of human myotubes, neuroblastoma cells, and human myasthenic sensory motor nerve terminal. These data suggest that zilucoplan displays non-canonical (non-convertase) C5 cleavage.

- **Figure 2.** Zilucoplan binds a C5b domain and destabilizes C5b6 complex to inhibit hemolysis. Figure 3 shows that zilucoplan can bind to C5 variants R885H (A) and R885W (B) in vitro, whereas eculizumab (C) does not bind to C5 variants R885H or R885W. Together, these data suggest that zilucoplan, but not eculizumab, can block induction of C5 convertases C678, C679, and C679 (D) through non-canonical (non-convertase) C5 cleavage.

- **Figure 4.** Eculizumab does not bind to C5 variants R885H or R885W. Inhibition of C5 by zilucoplan is shown by the ability of zilucoplan to inhibit C5b-9 deposition induced by anti-AChR antibody in an in vitro NMJ model using co-cultures of human myotubes, neuroblastoma cells, and human myasthenic sensory motor nerve terminal.

- **Figure 5.** Anti-FcRn antibody treatment did not impact pharmacokinetics of zilucoplan in non-human primates. Administration of zilucoplan (0.3 mg/kg SC) did not alter anti-C5 mAb-mediated reduction of gMG. These data suggest that, unlike anti-C5 mAbs, it is possible to use zilucoplan concurrently with anti-FcRn agents.

**CONCLUSIONS**

- **Figure 6.** Pharmacokinetics of zilucoplan in non-human primates. Administration of zilucoplan (0.3 mg/kg SC) did not alter anti-C5 mAb-mediated reduction of gMG. These data suggest that, unlike anti-C5 mAbs, it is possible to use zilucoplan concurrently with anti-FcRn agents.

**REFERENCES**