Pozelimab, a Human Antibody Against Complement Factor C5, Demonstrates Robust Inhibition of Alternative Complement Activity Both in Normal Human Serum and in Phase I Normal Healthy Volunteers

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Background and Introduction

• Blockade of complement factor C5 has demonstrated benefit in paroxysmal nocturnal hemoglobinuria,1 atypical hemolytic uremic syndrome,2 generalized myasthenia gravis,3 and neuromyelitis optica.4

• We have completed a phase I study of pozelimab, a fully human anti-C5 immunoglobulin G (IgG4), in healthy volunteers (NCT03155996).1

• Pozelimab was well tolerated and resulted in dose-dependent inhibition of hemolytic activity through the classical complement pathway in normal healthy volunteers.

• Complete inhibition of classical pathway hemolytic activity was maintained over a 4-week dosing period by a weekly subcutaneous (SC) injection of the study drug.

Objectives

• To further characterize the impact of pozelimab on the activity of the alternative complement pathway, we investigated the effect of pozelimab on alternative pathway-mediated hemolysis using an AH50 assay in the completed first-in-human (FIH) study.5

• In addition, we compared the effect of pozelimab in both alternative and classical pathway hemolysis assays with those of in-house eculizumab and in-house ravulizumab in pooled normal human serum (NHS) samples.

Methods

• In total, 56 subjects were randomized (42 received pozelimab; 14 received placebo) to 4 sequential ascending IV single-dose cohorts plus 2 sequential ascending SC single-dose cohorts followed by a multiple-dose cohort (consisting of an IV loading dose and weekly SC doses).

• Each cohort consisted of 8 subjects randomized to receive pozelimab or placebo (6 active; 2 placebo). Serum collected at multiple time-points was used to assess the effect of pozelimab on alternative pathway activity.

• In the FIH study, the alternative pathway (AP) and classical pathway (CP) hemolysis assays were performed based on lysis of rabbit red blood cells (RBCs) and sensitized sheep RBCs, respectively; both assays measure the amount of hemoglobin released from RBCs at 412 nm. The pharmacodynamic analysis set included all treated subjects who received any study drug and who had at least one non-missing analyte measurement following the first dose of study drug.

• As a result of the study, we demonstrated that pozelimab inhibited alternative pathway-mediated hemolysis in normal human serum as a function of dose. These effects were consistent with those observed in phase I normal healthy volunteers (NCT03155996).

• In the FIH study, baseline AH50 was comparable across treatment groups, with a mean ± standard deviation (SD) of 110 ± 19 U/mL (n=56).

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• The maximal suppression of hemolysis was consistently greater (32–169%) with pozelimab, in-house eculizumab, and in-house ravulizumab in AP hemolysis assays in 10, 25, or 48% NHS.

• The binding kinetics of all 3 anti-C5 antibodies are presented in Table 2.

• In-house eculizumab appeared to be less effective than in-house ravulizumab, but not for pozelimab (Figure 3).

• For ex vivo studies with pooled NHS, the peak suppression of hemolysis was observed 3–7 days post dosing, which was consistent with observed peak concentrations of pozelimab in serum following the first dose of study drug.

Results

• Baseline characteristics of subjects in the FIH study are summarized in Table 1 according to treatment group.

• In the FIH study, baseline AH50 was comparable across treatment groups, with a mean ± standard deviation (SD) of 110 ± 19 U/mL (n=56).

• Pozelimab exposure led to dose-dependent inhibition of AH50 (Figure 2).

• In all IV dosing cohorts, peak suppression of hemolysis was observed at the end of the infusion.

• Maximum suppression of hemolysis was approximately 85% change from baseline. This was achieved with the 30 mg/kg IV group and the repeat-dose 15 mg/kg IV + 400 mg SC once weekly group. In the 2 SC cohorts, peak suppression of hemolysis was observed 3–7 days post dosing, which was consistent with observed peak concentrations of pozelimab in serum following the first dose of study drug.

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Conclusions

• The phase I healthy volunteer study of pozelimab demonstrated dose-dependent and significant inhibition of AP hemolysis, with the maximal suppression of hemolysis approximately –85% change from baseline.

• Ex vivo studies with pooled NHS demonstrated that pozelimab robustly blocked both CP and AP hemolysis.

• In-house ravulizumab appeared to be less effective than in-house eculizumab in both CP and AP hemolysis assays.

• Although pozelimab and in-house eculizumab demonstrated similar effectiveness in CP hemolysis assays, pozelimab showed greater maximal suppression in AP hemolysis assays.

• As expected, all 3 antibodies provided stoichiometric inhibition of CP hemolysis; however, stoichiometric inhibition was not observed for AP hemolysis.

References


Disclosures

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