Pozelimab Inhibits Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

INTRODUCTION
• Blockade of complement factor C5 has demonstrated benefit in patients with PNH and with elevated hemolytic activity (as assessed by serum lactate dehydrogenase [LDH] levels). Currently available therapies require long-term intravenous (IV) therapy representing a significant burden to patients.
• Pozelimab (REGN3918), a fully human monoclonal immunoglobulin G4 antibody directed against human C5 and blocks its activity. In a healthy volunteer study (NCT0311996), pozelimab was found to have a favorable safety profile while providing complete inhibition of ex vivo-processed hemolytic activity. The data from the healthy volunteer study suggested that a subcutaneous (SC) regimen of pozelimab may provide control of intravascular hemolysis in patients with active PNH and thus could provide an important new alternative to patients.

METHODS
• This is an ongoing phase 2, open-label, single-arm, 26-week treatment study in at least 36 patients with active PNH who are naïve to complement inhibitor therapy or who have received prior treatment with a complement inhibitor, but not within 6 months prior to the start of the study.
• Treatment regimen consists of pozelimab as a single IV loading dose of 30 mg/kg followed one week later by weekly SC 800 mg administration.
• For this interim analysis, a total of 17 patients were evaluated. All 17 patients had at least 71 days of treatment, with 10 patients receiving treatment for up to 183 days. All enrolled patients had baseline LDH levels ≥2 x upper limit of normal (ULN). Participants were enrolled in two cohorts: Cohort A for dose confirmation and Cohort B for further evaluation of efficacy and safety.
• The effect of pozelimab on intravascular hemolysis (monitored via LDH levels) and transfusion avoidance, as well as safety, was assessed from baseline to Week 26 (study day 183; only partial data available for some patients at this time). Pozelimab pharmacodynamics was assessed hemolytic activity assay (AH50).
• Suppression of CH50 and AH50 over time are shown in Figure 3. Pharmacodynamics of pozelimab was assessed utilizing a sheep red blood cell (RBC) complement activity assay (CH50) and rabbit RBC complement activity assay (AH50).

RESULTS
Baseline characteristics
• Baseline characteristics of patients (n=17; 8 patients ongoing) are summarized in Table 1.

Efficacy
• Treatment with pozelimab led to a rapid and sustained reduction in LDH through study week 26 (Figure 1). All 17 patients achieved LDH reduction to below the clinically significant threshold of 6.5 x ULN. All but one patient achieved control of intravascular hemolysis (LDH ≤1.5 x ULN) at week 2, and all but one patient achieved normalization of LDH (LDH ≤1.0 x ULN) at week 4 (Figure 1). Importantly, one patient who is a carrier of a C5 variant known to be resistant to blockade by eculizumab/ravulizumab, demonstrated rapid and sustained normalization of LDH.
• Hemoglobin levels increased following treatment with pozelimab, with mean (standard deviation [SD]) increase from baseline to Week 26 of 8.6 (14.1) g/dL (N=9; Figure 2).
• Following pozelimab treatment, an improvement in the FACT-Fatigue score (a 13-item, patient reported outcome measure assessing an individual’s level of fatigue over the past week) was observed (mean [SD] change from baseline at Week 26 of 13.1 [3.7]; N=9; Figure 2).

Table 1. Summary of baseline characteristics

Table 2. Overview of treatment-emergent adverse events

CONCLUSIONS
• Pozelimab administered SC once weekly provided inhibition of intravascular hemolysis in patients with active PNH, and was generally well tolerated.
• Normalization of LDH levels was observed at study day 25 in all 17 evaluated patients with active PNH, including a patient with a C5 variant known to be resistant to blockade by eculizumab/ravulizumab.
• LDH reduction was sustained below 1.5 x ULN until study day 183. These interim data are supportive of the continued development of pozelimab in PNH and potentially other complement mediated diseases. These results indicate that a SC regimen may provide an alternative to currently available IV therapies.

REFERENCES

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Jun-Ho Jang has no disclosures to report. Yan G N, Ming-Dau Wang, Umesh Chaudhari, Olivier Harari, Andrew J. Rankin, Lori Morton, Jonathan Wayne, David M. Weinreich, and George D. Vancopoulos are employees and/or stockholders in Regeneron Pharmaceuticals, Inc. Peter Hillmen has received honoraria from and has been a consultant for Alexion.

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