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

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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).[1] Currently available therapies require life-long intravenous (IV) therapy representing a significant burden to patients.
- Pozelimab (REGN3918), a fully human monoclonal immunoglobulin G4 antibody directed against C5, has been shown to bind with high affinity to wild-type and variant (R885H/C) human C5 and blocks its activity. In a healthy volunteer study (NCT0311596), pozelimab was found to have a favorable safety profile while providing complete inhibition of *ex vivo*-assessed hemolytic activity.[2] 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.
- This finding was supportive of conducting this first-in-patient study of pozelimab in patients with active PNH.

OBJECTIVE

- To demonstrate a clinically significant reduction in intravascular hemolysis by the once weekly SC administration of pozelimab over 26 weeks of treatment in patients with active PNH who are treatment-naïve to complement inhibitor therapy or who have not recently received complement inhibitor therapy (NCT03946748).

METHODS

- This is an ongoing phase 2, open-label, single-arm, 26-week treatment study in at least 36 patients with active symptomatic 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 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**.

Table 1. Summary of baseline characteristics

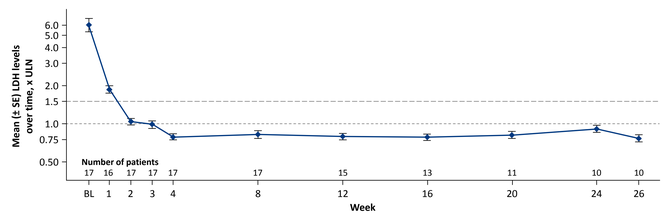
	Pozelimab (n=17)
Age, years, mean (SD)	46.2 (17.7)
Sex, male, n (%)	8 (47.1)
Race, Asian, n (%)	16 (94.1)
Race, not reported, n (%)	1 (5.9)
Weight, kg, mean (SD)	67.5 (13.5)
LDH, ULN, mean (SD) [min : max]	6.1 (3.0) [2.2 : 11.9]
Hemoglobin, g/L, mean (SD)	97.0 (18.2)
RBC transfusions during the previous year, n (%)	10 (58.8)
PNH, high sensitivity, RBC, %, mean (SD)	50.6 (26.7)
PNH, high sensitivity, WBC, monocytes, %, mean (SD)	89.2 (9.6)
PNH, high sensitivity, WBC, PMN, %, mean (SD)	82.9 (17.3)
Platelets, 10^9/L, mean (SD)	189.2 (61.3)
Reticulocytes, 10^9/L, mean (SD)	221.7 (119.4)

RBC, red blood cell; LDH, lactate dehydrogenase; PMN, polymorphonuclear leukocyte; SD, standard deviation; ULN, upper limit of normal; WBC, white blood cell.

Efficacy

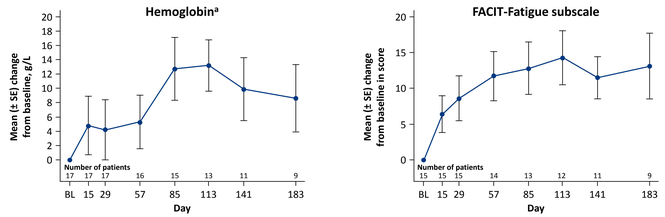
- Treatment with pozelimab led to a rapid and sustained reduction in LDH through study week 26 **(Figure 1)**. All 17 patients achieved LDH reduction to below the clinically significant threshold of LDH ≤1.5 x ULN.
- All but one patient achieved control of intravascular hemolysis (LDH ≤1.5 x ULN) at 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/L (N=9; **Figure 2**).
- Following pozelimab treatment, an improvement in the FACIT-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 [13.7]; N=9; **Figure 2**).

Figure 1. Mean (± SE) lactate dehydrogenase levels over time



BL, baseline; LDH, lactate dehydrogenase; SE, standard error; ULN, upper limit of normal.

Figure 2. Mean (± SE) change from baseline in hemoglobin levels and FACIT-Fatigue subscale score over time

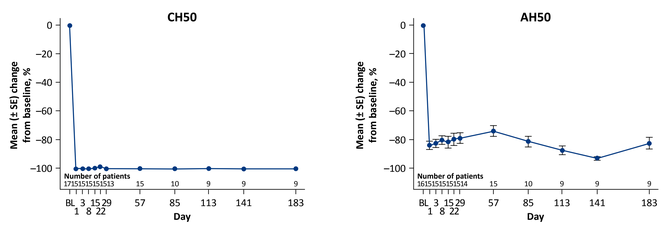


[a]During treatment, 2 patients received transfusions of PRBCs (2 units day 50; 2 units day 2 and 2 units day 57). Three patients required PRBCs (2 units each) during screening. No transfusions were associated with breakthrough hemolysis.
BL, baseline; PRBCs, packed red blood cells; SE, standard error.

Pharmacodynamics

- Suppression of CH50 and AH50 over time are shown in **Figure 3**.

Figure 3. Mean (± SE) percentage change from baseline in CH50 and AH50 over time



BL, baseline; SE, standard error.

Safety

- Treatment-emergent adverse events are summarized in **Table 2**.
- No serious adverse events or adverse events leading to treatment discontinuation were reported.
- No breakthrough hemolysis events were observed.

Table 2. Overview of treatment-emergent adverse events

n (%) of patients	Pozelimab (n=17)
Any TEAE	13 (76.5)
Any serious TEAE or TEAE leading to death	0
Any severe TEAE[a]	2 (11.8)
Any related TEAE	6 (35.3)
Any related TEAEs occurring in ≥10% of patients by PT	
Headache	4 (23.5)
Nausea	2 (11.8)

[a]One patient experienced symptomatic anemia that resolved without treatment and was not considered related to study drug. One patient experienced 2 occurrences of decreased neutrophil count that were considered related to study drug and required medication in one instance.
PT, preferred term; TEAE, treatment-emergent adverse event.

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 29 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

1. Brodsky RA. *Blood*. 2014;124:2804–2811.
2. Weyne J et al. *Blood*. 2018;S1:1039.

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DISCLOSURES

Jun-Ho Jang has no disclosures to report. Yan G. Ni, Ming-Dauh Wang, Umesh Chaudhari, Olivier Harari, Andrew J. Rankin, Lori Morton, Jonathan Weyne, David M. Weinreich, and George D. Yancopoulos 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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