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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

52-Week Open-Label Extension Data from a Phase 2 Study Evaluating the Safety and Efficacy of Pozelimab and Cemdisiran Combination Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Switched from Eculizumab

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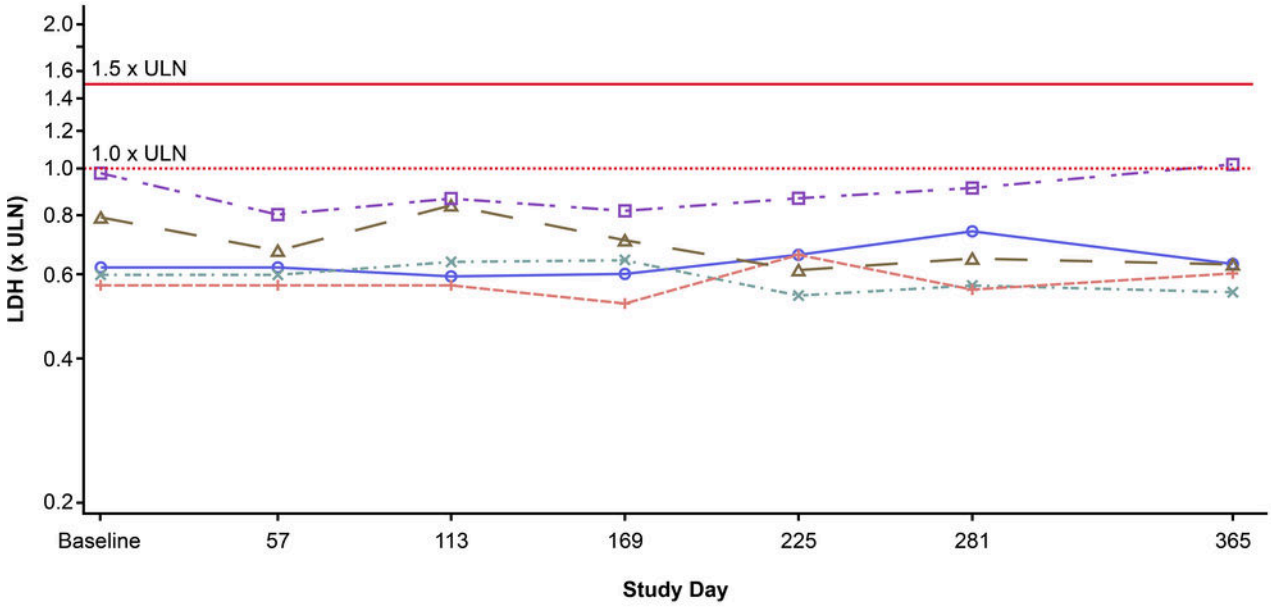
Background: Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare, acquired disorder, leading to impaired expression of complement-regulating proteins on the surface of hematopoietic cells. Complement component C5 inhibitors are part of the standard of care for patients with PNH; however, these are generally intravenous treatments. Pozelimab and cemdisiran are investigational agents with a small volume subcutaneous (SC) once every 4 weeks maintenance regimen that may be self-administered. Both inhibit terminal complement through complementary mechanisms of action. Cemdisiran is an N-acetylgalactosamine-conjugated small interfering RNA that suppresses liver production of C5, while pozelimab is a fully human monoclonal antibody inhibitor of C5. The efficacy and safety of the combination of pozelimab and cemdisiran was evaluated in an open-label, single-arm study in patients with PNH who switched from eculizumab therapy (NCT04888507). The completed safety and efficacy data of the optional 52-week open-label extension period (OLEP) are presented.
Methods: Patients who completed the 32-week open-label treatment period (OLTP) were offered to participate in an optional 52-week OLEP. Patients were adults with PNH who had switched from stable eculizumab therapy to the combination (pozelimab 400 mg and cemdisiran 200 mg) SC every 4 weeks in the OLTP. The study enrolled two patients who were previously treated with higher doses of eculizumab (1200 mg or 1500 mg every two weeks). The results of the 32-week OLTP have been previously presented; the results of the subsequent 52-week OLEP are presented here.
Results: All five patients who completed the OLTP were enrolled in and completed the OLEP. After completing the OLEP, all patients transitioned to an expanded access program to continue the combination of pozelimab and cemdisiran. At baseline of the OLTP, lactate dehydrogenase (LDH) was well controlled on eculizumab and remained controlled during the 32-week OLTP. During the 52-week OLEP, no patient had an LDH greater than 1.5 x the upper limit of normal (ULN; Figure) at any of the scheduled study visits or met the protocol criteria for breakthrough hemolysis (either by central or local laboratory values; defined as an increase in LDH [LDH $\geq$2 x ULN if pre-treatment LDH $\leq$1.5 x ULN, or LDH $\geq$2 x ULN subsequent to initial achievement of LDH $\leq$1.5 x ULN if pre-treatment LDH >1.5 x ULN] with concomitant signs or symptoms associated with hemolysis). The two patients who previously received higher doses of eculizumab also maintained control of LDH levels throughout the OLTP and OLEP. Four of five patients remained transfusion free, but one patient required a blood transfusion while hospitalized with an acute complement-activating condition. This patient experienced two serious and severe treatment-emergent adverse events of respiratory infection and consequently acute hemolysis that did not meet the trial criteria for breakthrough hemolysis but was reported as an adverse event based on clinical judgement. The investigator and sponsor assessed these events as not treatment related. CH50, a measure of terminal complement activity at fixed time points, remained suppressed throughout the study in all patients. No other serious or severe adverse events were reported. There were no meningococcal infections, thrombotic events, or TEAEs leading to death.
Conclusions: Results suggest that, in patients with PNH transitioning from eculizumab treatment, the combination of pozelimab and cemdisiran was generally well tolerated and provided long term sustained control of intravascular hemolysis without any breakthrough hemolysis events. Findings support the ongoing development of pozelimab and cemdisiran combination therapy.

Disclosures Kelly: *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Alexion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Jazz:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Pfizer:* Honoraria, Speakers Bureau; *Astellas:* Honoraria, Speakers Bureau; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Biologix:* Honoraria, Speakers Bureau; *Otsuka:* Honoraria. **Munir:** *BeiGene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau. **Muus:** *Sobi:* Other: Travel support and lecture fees; *Novartis:* Other: Advisory board member. **Aurand:** *Regeneron Pharmaceuticals, Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Mohan:** *Regeneron Pharmaceuticals, Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Senk:** *Regeneron Pharmaceuticals, Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Pavani:** *Regeneron Pharmaceuticals, Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Perlee:** *Regeneron Pharmaceuticals, Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Souttou:** *Regeneron Pharmaceuticals, Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Griffin:** *Biocryst:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Sobi:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Apellis:* Other: educational grant support ; *Regeneron Pharmaceuticals:* Consultancy; *Alexion, AstraZeneca Rare Disease:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees.

Figure 1. Spaghetti plot of LDH values (x ULN) by visit from the OLEP baseline to Day 365 in the OLEP[a]



[a]Study days for the OLEP have been renumbered starting with Day 1 at the time of the OLEP start.
LDH results were based on central laboratory values assessed at scheduled time points.
LDH, lactate dehydrogenase; OLEP, open-label extension period; ULN, upper limit of normal.

Figure 1

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