(PF696) COMPARISONS OF TERMINAL COMPLEMENT INHIBITION WITH POZELIMAB + CEMDISIRAN VERSUS RAVULIZUMAB IN PARTICIPANTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: PHARMACODYNAMIC RESULTS FROM COHORT A

Topic: 12. Bone marrow failure syndromes incl. PNH - Clinical

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Background

Pozelimab is a human monoclonal IgG4P antibody directed against the terminal complement protein C5; cemdisiran is a synthetic siRNA targeting C5 mRNA that inhibits production of C5 protein in the liver. The combination of pozelimab and cemdisiran (combination therapy) is being investigated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), an ultra-rare disorder caused by dysregulation of the complement system and characterized by hemolysis and/or thrombosis. We report pharmacodynamic (PD) data from Cohort A of a randomized, open-label study of combination therapy compared to ravulizumab.

Aims

To compare the effect of combination therapy versus ravulizumab on PD complement markers in participants with PNH.

Methods

In this 26-week, open-label, ravulizumab-controlled study, participants with PNH were randomized (1:1) to receive either combination therapy (single IV loading dose of pozelimab 30 mg/kg plus subcutaneous [SC] pozelimab 400 mg plus cemdisiran 200 mg [Day 1], followed by SC pozelimab 400 mg plus cemdisiran 200 mg every 4 weeks) or ravulizumab (single weight-based IV loading dose [Day 1] followed by weight-based maintenance dose [Day 15] and every 8 weeks thereafter). Key secondary endpoints, assessed using validated assays, included concentration of total C5, and change and percentage change in total complement hemolytic activity assay (CH50) and alternative pathway hemolytic activity (AH50) from baseline to Week 26. Exploratory endpoints included the measurement of complement activation marker (sC5b-9) from baseline to Week 26.

Results

A total of 48 participants were enrolled (n=25 combination therapy; n=23 ravulizumab). Total C5 concentration was reduced rapidly with combination therapy to below the limit of detection and was sustained through Week 26 due to cemdisiran reducing C5 hepatocyte production. By contrast, ravulizumab led to a >2-fold rise in mean total C5 protein concentration by Day 15, reaching steady-state by Week 6 (due to C5 binding to ravulizumab, increasing the half-life; differential pharmacology will be discussed).
CH50 complement activity was completely inhibited by Day 15, with ~100% suppression maintained through Week 26 following combination therapy. With ravulizumab, CH50 was reduced by approximately 90% at Day 15, and sustained suppression of 89.3–97.4% through Week 26, but did not achieve complete inhibition.
Mean AH50 activity reduced by approximately 80% at Week 4 and maintained robust suppression (77.3–83.7%) through Week 26 following combination therapy. Ravulizumab led to a more modest decrease (approximately 45%) at Week 4 and was maintained at 38.8–46.5% through Week 26.
Terminal complement complex (sC5b-9) levels decreased by 76.0% at Day 15 and maintained reductions of 72.9–80.8% through Week 26 following combination therapy. In contrast, sC5b-9 increased by 22.9% at Day 15 and levels were maintained at 0–25% from Week 4 through Week 26 with ravulizumab. The consistent reductions observed with combination therapy indicate less terminal complement activation compared to ravulizumab.

Summary/Conclusion

Combination therapy produced more rapid and durable effects across CH50 and AH50 versus ravulizumab in participants with PNH. These data indicate earlier onset and superior complement pathway control with the combination therapy compared to ravulizumab, supporting its potential to provide uninterrupted terminal complement activity suppression over 26 weeks.