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Substantial Increases in Paroxysmal Nocturnal Hemoglobinuria (PNH) Red Blood Cell Clone Size With Oral Iptacopan Monotherapy Confirms Control of Hemolysis in Complement Inhibitor-Naive PNH Patients

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Abstract

Background: In the Ph-3 APPOINT-PNH trial (NCT04820530), oral factor B inhibitor iptacopan led to clinically meaningful hemoglobin increases with red blood cell transfusion (RBCT) independence and control of intravascular hemolysis (IVH) in complement inhibitor-naive patients with PNH. We report the total PNH RBC clone size and C3-deposition data from the 24-week treatment period of APPOINT-PNH.

Methods: Complement inhibitor-naive adults with PNH, mean hemoglobin <10g/dL, and lactate dehydrogenase (LDH) >1.5×ULN received iptacopan 200 mg twice-a-day (N=40). The primary endpoint was a ≥2g/dL hemoglobin increase from baseline without RBCTs. Response probability was described as proportions of responders with 95% CIs calculated using bootstrap; Bayesian multiple imputation was used for missing data. Total PNH RBC clone size and C3-deposition were exploratory endpoints analyzed using descriptive statistics.

Results: The primary objective was met with an estimated 92.2% (95% CI, 82.5%-100%) of patients achieving a ≥2g/dL increase in hemoglobin. An estimated 62.8% (95% CI, 47.5%-77.5%) and 97.6% (95% CI, 92.5%-100%) of patients achieved hemoglobin ≥12g/dL and transfusion avoidance, respectively. Changes from baseline (CFB) in hemoglobin, LDH, absolute reticulocyte count, and FACIT-F scores were +4.28g/dL (95% CI, 3.87-4.70), −83.55% (95% CI, −84.90% to −82.08%), -82.48×10^9/L (95% CI, −89.33 to -75.62×10^9/L) and +10.75 (95% CI, 8.66-12.84), respectively. No clinical breakthrough hemolysis (BTH) events or MAVEs were observed. The mean (SD) CFB to week 24 in total PNH RBC clone size was 43.2% (18.9%); by week 24, it increased to 87.1% of the total RBC population. The mean C3-deposition was negligible at baseline and remained low through week 24 (0.11%). No deaths/discontinuations occurred. The most frequent treatment-emergent adverse events were headaches/COVID-19/upper respiratory tract infections/diarrhea (27.5%/15.0%/12.5%/7.5%).

Conclusion: Oral iptacopan led to clinically meaningful Hb increases without RBCTs, demonstrating control of IVH in most complement inhibitor-naive patients with hemolytic PNH. Iptacopan improved survival of PNH RBCs, indicated by increased total PNH RBC clone size; no clinical BTH was reported. No evidence of C3-mediated extravascular hemolysis was observed, supported by consistently low C3-deposition throughout the treatment period. Iptacopan exhibited a favorable safety profile. APPOINT-PNH demonstrated that iptacopan monotherapy could become a practice-changing, preferred outpatient option for patients with hemolytic PNH.

Keywords

MDS, paroxysmal nocturnal hemoglobinuria, complement inhibitor, hemolysis, Phase III