Abstract: P822

Title: EFFECTS OF ORAL IPTACOPAN MONOTHERAPY, INCLUDING INCREASED PAROXYSMAL NOCTURNAL HEMOGLOBINURIA RED BLOOD CELL CLONE SIZE, ARE MAINTAINED IN COMPLEMENT INHIBITOR-NAÏVE PATIENTS: FINAL APPOINT-PNH DATA

Abstract Type: Poster Presentation

Topic: Bone marrow failure syndromes incl. PNH - Clinical

Background:

Iptacopan (a first-in-class, oral factor B inhibitor) demonstrated efficacy and safety as a monotherapy in the 24-week (wk) core treatment period of the Phase III APPOINT-PNH trial (NCT04820530) in complement inhibitor-naïve patients (pts) with hemolytic paroxysmal nocturnal hemoglobinuria (PNH).

Aims:

We report final (48-wk) efficacy and safety data from APPOINT-PNH, including PNH red blood cell (RBC) clone size and C3 fragment deposition data.

Methods:

Complement inhibitor-naïve adult PNH pts with hemoglobin (Hb) <10 g/dL and lactate dehydrogenase (LDH) >1.5 × upper limit of normal received iptacopan monotherapy 200 mg twice daily for 48 wks (24-wk core period and 24-wk extension period).

Results:

All 40 pts completed APPOINT-PNH. The proportion of pts with non-missing data achieving an Hb increase of ≥2 g/dL from baseline (irrespective of transfusions) was maintained from Wk 24 (37/39, 94.9%) to Wk 48 (38/39, 97.4%). The proportion of pts achieving Hb ≥12 g/dL (irrespective of transfusions) at Wk 48 (31/39, 79.5%) was numerically higher than at Wk 24 (26/39, 66.7%). An estimated 97.5% of pts (95% confidence interval [CI] 92.5, 100.0) achieved transfusion avoidance, with one pt requiring RBC transfusions between Wks 2 and 48. Mean Hb was 12.56 g/dL (standard deviation [SD] 1.49) at Wk 24 and increased to 13.24 g/dL (SD 1.80) at Wk 48 (mean change from baseline to Wk 48 +5.09 g/dL [SD 2.01]), showing further improvement. Increased Functional Assessment of Chronic Illness Therapy – Fatigue scores at Wk 24 were sustained through the extension period (mean change from baseline to Wk 48 +10.4 [SD 10.14]), as were reductions in LDH (median change from baseline to Wk 48 −1241.5 U/L [interquartile range −1795.0 to −925.0]; Wk 48 median 261.5 U/L [interquartile range 206.0 to 334.0]) and absolute reticulocyte count (mean change from baseline to Wk 48 −76.55 × 10^9/L [SD 50.15]).

The total PNH RBC clone size (type II and III) at Wk 24 (mean 87.06% [SD 9.89%]) was sustained through to Wk 48 (mean 87.77% [SD 11.44%]; mean change from baseline to Wk 48 +43.62% [SD 19.01%]; **Figure**); mean C3 fragment deposition on PNH RBCs remained negligible (0.11% at Wk 24 and 0.36% at Wk 48).

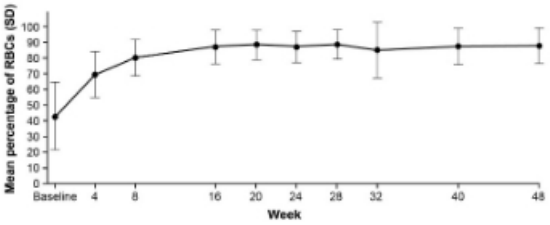
Two pts experienced a clinical breakthrough hemolysis (BTH) event during the extension period (adjusted annualized rate: 0.05 [95% CI 0.01, 0.17]), which resolved without treatment discontinuation (one resolved during APPOINT-PNH, one after the 48-wk period). Potential complement-amplifying conditions (CACs) were identified for both pts. There were no major adverse vascular events. The most common treatment-emergent adverse events in the trial were headache (30.0% of pts), COVID-19 (22.5%), upper respiratory tract infection (17.5%) and diarrhea (15.0%). There were no deaths or treatment discontinuations.

Summary/Conclusion:

Improvements in the 24-wk core treatment period of APPOINT-PNH were sustained over the extension period,

including maintenance of increased Hb, normal/near-normal mean Hb, improvements in fatigue and transfusion avoidance. The increase in total PNH RBC clone size after 24 wks of therapy was sustained through the extension period, indicating continued control of hemolysis and hence survival of PNH RBCs. Despite the increased PNH RBC clone size, clinical BTH was only observed in two pts, both of whom had potential CACs. C3 fragment deposition was negligible during 48 wks of treatment, supporting no emergence of C3-mediated extravascular hemolysis. Iptacopan was also well tolerated throughout APPOINT-PNH. These findings suggest that iptacopan monotherapy could be a practice-changing treatment for hemolytic PNH.

Figure. Total PNH RBC clone size* during 48 weeks of treatment with iptacopan monotherapy in APPOINT-PNH



Pts with available total PNH RBC clone size* data

Iptacopan 200 mg bid	40	38	35	31	34	38	37	35	37	34

*Percentage of type II and type III PNH RBCs
bid, twice daily; PNH, paroxysmal nocturnal hemoglobinuria; pt, patient; RBC, red blood cell; SD, standard deviation

Keywords: Paroxysmal nocturnal hemoglobinuria (PNH), Hemolysis, Complement, Phase III