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Poster# **MDS-1141**

APPULSE-PNH: Oral iptacopan monotherapy demonstrates clinically meaningful hemoglobin increases in patients with paroxysmal nocturnal hemoglobinuria and Hb ≥10 g/dL on anti-C5 therapy

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KEY FINDINGS & CONCLUSIONS

- APPULSE-PNH included anti-C5–experienced patients with hemoglobin (Hb) ≥10 g/dL, the majority of whom likely had ongoing extravascular hemolysis (EVH)
- Iptacopan was superior after switch from anti-C5 therapy in change from baseline in Hb and enabled most patients to achieve Hb ≥12 g/dL and maintain transfusion independence
- Targeting factor B with iptacopan controlled anti-C5–induced EVH while maintaining intravascular hemolysis control
- Patients reported improvements in fatigue and treatment satisfaction scores
- Iptacopan was well tolerated, with no new safety findings
- Iptacopan is a potentially practice-changing treatment that may become a preferred outpatient option for patients with paroxysmal nocturnal hemoglobinuria (PNH)

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BACKGROUND

- Impaired complement regulation in PNH leads to intravascular hemolysis[1-3]
- Anti-C5 treatment can lead to the emergence of EVH[1,2,4,5]
- Iptacopan targets factor B to selectively block alternative pathway C3 convertase activation and achieve comprehensive hemolysis control[1,6,7]
- Patients with PNH who achieve Hb ≥10 g/dL with anti-C5 therapy may have ongoing EVH and experience a substantial quality-of-life burden
- Oral iptacopan monotherapy has demonstrated efficacy and safety in:
  - Complement inhibitor–naive patients with Hb <10 g/dL and lactate dehydrogenase (LDH) >1.5 × upper limit of normal (ULN) (APPOINT-PNH)[8,9]
  - Anti-C5–experienced patients with Hb <10 g/dL (APPLY-PNH)[8,10]

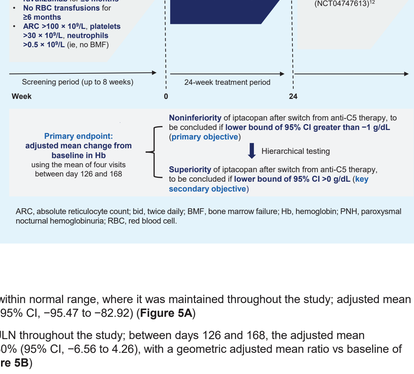
OBJECTIVE

- We report primary efficacy and safety from the single-arm, open-label, multicenter, phase 3b APPULSE-PNH trial (NCT05630001) in patients with PNH and Hb ≥10 g/dL in response to anti-C5 who switched to iptacopan

METHODS

- Adults with PNH and mean Hb ≥10 g/dL on stable anti-C5 for ≥6 months and without red blood cell (RBC) transfusions for 6 months were switched to iptacopan monotherapy 200 mg twice daily (bid) for 24 weeks (**Figure 1**)
- The primary endpoint was change from baseline (ΔBL) in Hb tested hierarchically for noninferiority (primary objective) and superiority (key secondary objective) of iptacopan vs prior anti-C5 agents using predefined thresholds (lower bound of 95% CI greater than −2 g/dL and greater than 0 g/dL, respectively)
- Secondary endpoints included adjusted mean ΔBL in absolute reticulocyte count (ARC), Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) scores, and Treatment Satisfaction Questionnaire for Medication–9 Items (TSQM-9) scores
- All endpoints, reported as adjusted mean ΔBL or ratio vs baseline, used the mean of four visits between day 126 and 168, except FACIT-Fatigue and TSQM-9, which used day 168 only

Figure 1. Study Design[11]



ARC, absolute reticulocyte count; bid, twice daily; BMF, bone marrow failure; Hb, hemoglobin; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

RESULTS

- APPULSE-PNH enrolled 52 patients. Baseline demographics and disease characteristics can be found in **Table 1**
- 98.1% (51/52) of patients completed both treatment and study
  - One patient discontinued because of a treatment-emergent adverse event (TEAE) of nonserious palpitations suspected to be related to Iptacopan
  - Mean (SD) relative dose intensity was 99.9% (0.28), defined as the ratio of received dose intensity vs planned dose intensity of 400 mg per day (200 mg bid) across all patients

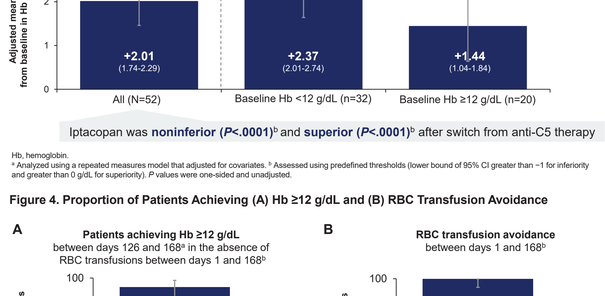
Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	Iptacopan 200 mg bid (N=52)
Mean age (SD), years	46.0 (13.7)
Female sex, n (%)	20 (38.5)
Race, n (%)	
Asian	4 (7.7)
Not reported/unknown	13 (25.0)
White	35 (67.3)
Mean time since diagnosis (SD), years	10.8 (7.5)
Prior anti-C5 treatment, n (%)	
Ravulizumab	46 (88.5)
Eculizumab	6 (11.5)
Mean duration of prior anti-C5 (SD), years[a]	3.5 (3.2)
Hb ≥12 g/dL, n (%)	20 (38.5)
Mean Hb (SD), g/dL	11.87 (1.32)
Baseline Hb <12 g/dL (n=32)	11.08 (0.5)
Baseline Hb ≥12 g/dL (n=20)	13.13 (1.2)
Mean ARC (SD), 10^9/L	154.84 (76.16)
Baseline Hb <12 g/dL (n=32)	165.27 (75.61)
Baseline Hb ≥12 g/dL (n=20)	138.16 (75.92)
Mean LDH (SD), U/L	226.8 (69.1)
Baseline Hb <12 g/dL (n=32)	223.6 (75.5)
Baseline Hb ≥12 g/dL (n=20)	211.3 (55.5)
Mean FACIT-Fatigue score (SD)	38.9 (9.4)

ARC, absolute reticulocyte count; bid, twice daily; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; SD, standard deviation.
[a] Stable regimen.

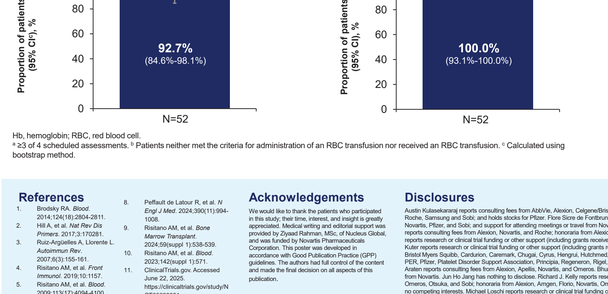
- Iptacopan monotherapy led to rapid normalization of mean Hb levels; mean (SD) Hb at baseline and 24 weeks was 11.87 (1.32) g/dL and 13.88 (1.27) g/dL, respectively (**Figure 2**)
- APPULSE-PNH met its primary and key secondary objectives; iptacopan was noninferior (*P*<.0001) and superior (*P*<.0001) after switch from anti-C5 therapy (**Figure 3**)
  - Adjusted mean ΔBL in Hb was +2.01 g/dL (95% CI, 1.74-2.29 g/dL)
- During APPULSE-PNH, most patients achieved Hb ≥12 g/dL, and all patients remained transfusion free
  - No patients required RBC transfusion between days 1 to 168 (**Figure 4A**)
  - Proportion of patients with Hb ≥12 g/dL between days 126 and 168 was 92.7% (95% CI, 84.6%-98.1%) (**Figure 4B**)

Figure 2. Mean Hb Levels During APPULSE-PNH[a]



BL, baseline; Hb, hemoglobin; SD, standard deviation.
[a] At each visit, only patients with a value at both BL and that visit are included. On-treatment period for iptacopan is counted from the date of the first dose until 7 days after the date of the last dose.

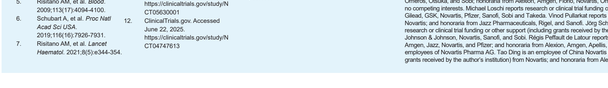
Figure 3. Adjusted Mean Change From Baseline in Hb Between Days 126 and 168[a]



Iptacopan was **noninferior (*P*<.0001)**[b] and **superior (*P*<.0001)**[b] after switch from anti-C5 therapy

Hb, hemoglobin.
[a] Analyzed using a repeated measures model that adjusted for covariates. [b] Assessed using predefined thresholds (lower bound of 95% CI greater than −1 for inferiority and greater than 0 g/dL for superiority). *P* values were one-sided and unadjusted.

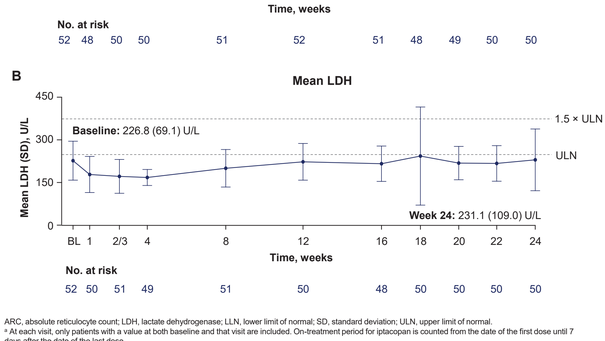
Figure 4. Proportion of Patients Achieving (A) Hb ≥12 g/dL and (B) RBC Transfusion Avoidance



Hb, hemoglobin; RBC, red blood cell.
[a] ≥3 of 4 scheduled assessments. [b] Patients neither met the criteria for administration of an RBC transfusion nor received an RBC transfusion. [c] Calculated using bootstrap method.

- Mean ARC rapidly decreased to within normal range, where it was maintained throughout the study; adjusted mean ΔBL in ARC was −89.19 × 10^9/L (95% CI, −95.47 to −82.92) (**Figure 5A**)
- Mean LDH remained below the ULN throughout the study; between days 126 and 168, the adjusted mean percentage ΔBL in LDH was −1.30% (95% CI, −6.56 to 4.26), with a geometric adjusted mean ratio vs baseline of 0.99 (95% CI, 0.93 to 1.04) (**Figure 5B**)

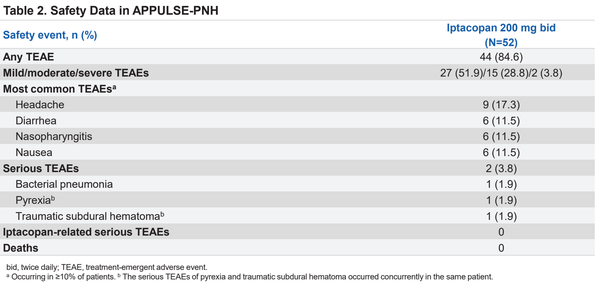
Figure 5. Mean (A) ARC and (B) LDH During APPULSE-PNH[a]



ARC, absolute reticulocyte count; LDH, lactate dehydrogenase; LLN, lower limit of normal; SD, standard deviation; ULN, upper limit of normal.
[a] At each visit, only patients with a value at both baseline and that visit are included. On-treatment period for iptacopan is counted from the date of the first dose until 7 days after the date of the last dose.

- Mean PNH RBC clone size increased to become similar to mean PNH granulocyte clone size; mean ΔBL in total PNH RBC clone size (exploratory endpoint) at day 168 was +22.2% (SD, 16.2) (**Supplemental Figure**)
- Mean C3 deposition reduced to negligible levels by Week 16; mean ΔBL in C3d+ PNH RBCs (exploratory endpoint) at day 168 was –11.6% (SD, 9.3) (**Supplemental Figure**)
- Mean FACIT-Fatigue and TSQM-9 domains scores improved
  - Adjusted mean ΔBL in FACIT-Fatigue was +4.29 (95% CI, 1.74-6.85) (**Figure 6A**)
  - Adjusted mean ΔBL in TSQM-9 effectiveness, convenience, and global satisfaction was +12.54 (95% CI, 5.58-19.49), +23.86 (95% CI, 17.62-30.10), and +18.53 (95% CI, 12.87-24.19), respectively (**Figure 6B**)

Figure 6. (A) FACIT-Fatigue and (B) TSQM-9 Scores



- Iptacopan monotherapy was well tolerated, with no new safety findings (**Table 2**)
  - No patients experienced clinical breakthrough hemolysis or major adverse vascular events
  - 42.3% (22/52) of patients had TEAEs in the infections and infestations system organ class
    - Infections likely caused by encapsulated bacteria were bacterial pneumonia (1.9%; 1/52) and otitis media (3.8%; 2/52)
  - One patient discontinued iptacopan because of a nonserious TEAE of palpitations reported as suspected to be related to iptacopan

Table 2. Safety Data in APPULSE-PNH

Safety event, n (%)	Iptacopan 200 mg bid (N=52)
Any TEAE	44 (84.6)
Mild/moderate/severe TEAEs	27 (51.9)/15 (28.8)/2 (3.8)
Most common TEAEs[a]	
Headache	9 (17.3)
Diarrhea	6 (11.5)
Nasopharyngitis	6 (11.5)
Nausea	6 (11.5)
Serious TEAEs	2 (3.8)
Bacterial pneumonia	1 (1.9)
Pyrexia[b]	1 (1.9)
Traumatic subdural hematoma[b]	1 (1.9)
Iptacopan-related serious TEAEs	0
Deaths	0

bid, twice daily; TEAE, treatment-emergent adverse event.
[a] Occurring in ≥10% of patients. [b] The serious TEAEs of pyrexia and traumatic subdural hematoma occurred concurrently in the same patient.

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