Poster MDS-278

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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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Key Findings and Conclusions

- Oral iptacopan monotherapy led to clinically meaningful hemoglobin (Hb) increases without the need for red blood cell (RBC) transfusions, demonstrating good control of intravascular hemolysis (IVH).
- Iptacopan monotherapy also resulted in transfusion avoidance and a clinically meaningful improvement in patient-reported fatigue.
- Treatment with iptacopan monotherapy increased total PNH RBC clone size to proportions similar to white blood cell (WBC) clone sizes, indicating improved survival of PNH RBCs; no clinical breakthrough hemolysis (BTH) was reported during the core treatment period.
- C3 fragment deposition was consistently low throughout the core treatment period, indicating no evidence of C3b-mediated extravascular hemolysis (EVH).
- Iptacopan monotherapy was well tolerated and had a favorable safety profile.
- Iptacopan monotherapy may become a potentially practice-changing, oral, outpatient treatment that could become a preferred option for complement inhibitor–naive patients with hemolytic PNH.

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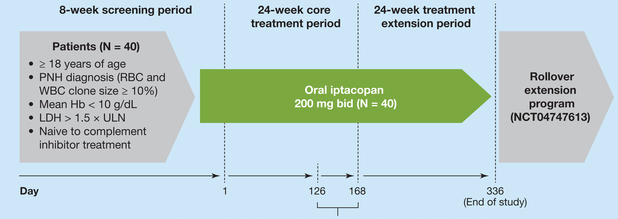
Introduction

- Iptacopan is the first oral, proximal complement inhibitor that targets factor B to selectively inhibit the alternative pathway of the complement cascade, resulting in the control of both terminal complement-mediated IVH and prevention of C3b-mediated EVH.[1–3]
- Iptacopan recently demonstrated superior efficacy to eculizumab and ravulizumab and had a favorable safety profile in patients with PNH and anemia despite anti-C5 treatment in the Phase III APPLY-PNH trial (NCT04558918).[3]
- In the 24-week core treatment period of the single-arm, open-label, multicenter, phase III APPOINT-PNH trial (NCT04820530), iptacopan monotherapy led to clinically meaningful Hb increases without the need for RBC transfusions and control of IVH in complement inhibitor–naive patients with PNH.[4]
- We report efficacy and safety results, including total PNH clone size and C3 deposition data, from the 24-week core treatment period of APPOINT-PNH (data cutoff: November 2, 2022).

Methods

- APPOINT-PNH enrolled complement inhibitor–naive adult patients with a confirmed diagnosis of PNH, a mean Hb level of < 10 g/dL, and lactate dehydrogenase (LDH) of > 1.5 × upper limit of normal.
- Forty patients received iptacopan monotherapy 200 mg twice daily (**Figure 1**).
- The primary end point was hematological response, defined as a ≥ 2-g/dL increase in Hb from baseline (assessed between Days 126 and 168) in the absence of RBC transfusions (between Days 14 and 168).
- The primary end point was analyzed by deriving an estimated proportion of responders from all imputed datasets, with 95% CIs calculated using bootstrap; bayesian multiple imputation was used to account for missing data. The lower bound of the two-sided 95% CI for the response rate was compared with a threshold of 15%; exceeding this threshold was considered sufficient demonstration that iptacopan led to hematological response in patients with PNH who had anemia in the absence of transfusions.
- Secondary end points included hematological response, defined as having Hb levels of ≥ 12 g/dL (assessed between Days 126 and 168) in the absence of RBC transfusions (between Days 14 and 168), transfusion avoidance (between Days 14 and 168), changes from baseline in Hb level, absolute reticulocyte count (ARC), and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) score, percentage change from baseline in LDH level (assessed as a mean between Days 126 and 168), annualized rates of BTH, and major adverse vascular events (MAVEs), and safety and tolerability (assessed throughout the study).
- Percentage of total PNH RBC clone size (sum of type II and III PNH RBCs) and C3 fragment deposition (type II and III PNH RBCs that were C3 deposition positive) were exploratory end points assessed by flow cytometry and analyzed using descriptive statistics.

Figure 1. APPOINT-PNH Study Design



ARC, absolute reticulocyte count; bid, twice daily; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; ULN, upper limit of normal; WBC, white blood cell.

Results

Baseline demographic and disease characteristics

- Baseline demographic and disease characteristics of the patients can be found in **Table 1**.

Table 1. Baseline Demographic and Disease Characteristics

	Iptacopan 200 mg bid N = 40
Mean age, years (SD)	42.1 (15.9)
Male, n (%)	23 (57.5)
Race, n (%) Asian White Black or African American	 27 (67.5) 12 (30) 1 (2.5)
Time since diagnosis, years (SD)	4.7 (5.5)
Received RBC transfusions, n (%)	28 (70)
Mean baseline Hb, g/dL (SD) [range]	8.2 (1.1) [5.8-10.0]
Median baseline LDH, U/L (range)	1581.5 (522-3244)
Mean baseline ARC, × 10^9/L (SD) [range]	154.3 (63.7) [59-325]
Mean FACIT-F score (SD) [range]	32.8 (10.2) [13-51]
Mean total PNH RBC clone size (type II + III), % (SD) [range]	42.7 (21.2) [9.0-92.9]
Mean C3d+ RBCs (type II + III), % (SD) [range]	0.7 (0.4) [0.1-1.9]

ARC, absolute reticulocyte count; bid, twice daily; C3d, C3 deposition; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

Total PNH RBC clone size and C3 fragment deposition

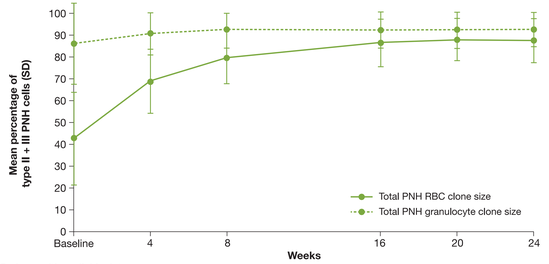
- With iptacopan monotherapy, the mean (SD) change from baseline to Week 24 in total PNH RBC clone size was 43.2% (18.9%).
- By Week 24, the total PNH RBC clone size increased to 87.1% of the total RBC population (**Figure 2A**).
- As expected in complement inhibitor–naive patients, the mean percentage of C3d-positive type II and III PNH RBCs was negligible at baseline (0.67%) and remained consistently low through Week 12 (0.05%) and Week 24 (0.11%) (**Figure 2B**).
- WBC clone sizes increased slightly from baseline to Week 24 (**Figure 2A** and **Supplementary Figure 1**).

Primary end point

- The study met its prespecified success criterion; an estimated 92.2% (95% CI, 82.5%-100%) of patients achieved a ≥ 2-g/dL Hb increase from baseline in the absence of RBC transfusions (**Figure 3**).
- The lower bound of the two-sided 95% CI exceeded the predefined 15% threshold by more than five-fold, demonstrating that iptacopan led to hematological response.

Figure 2. Total PNH Clone Size and C3 Fragment Deposition Throughout the 24-Week Core Treatment Period

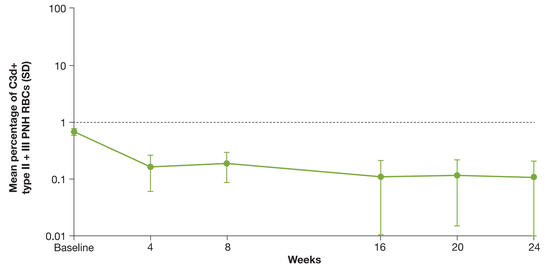
A. Total PNH RBC clone size (type II + III) and total PNH granulocyte clone size



Patients with available data

Iptacopan	40 (40)	38 (38)	35 (36)	31 (31)	34 (32)	38 (40)

B. C3d+ PNH RBCs (type II + III)[a]



Patients with available data

Iptacopan	40	36	29	23	29	28

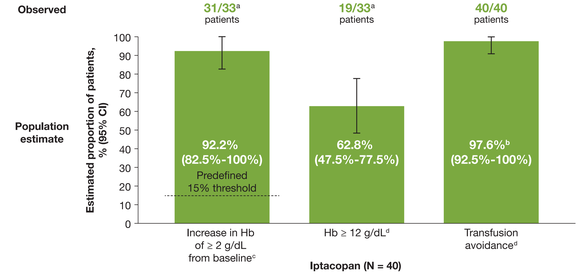
C3d, C3 deposition; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.
[a] Untreated patients with PNH typically have fewer than 1% C3d-positive PNH RBCs[5] (indicated by the dashed line).

Secondary end points

- Over half of patients achieved Hb level of ≥ 12 g/dL in the absence of RBC transfusions (**Figure 3**).
- All patients remained free from RBC transfusions between Days 14 and 168 (**Figure 3**).
- Adjusted mean change from baseline in Hb level, percentage LDH, FACIT-F scores, and ARC were +4.28 g/dL (95% CI, 3.87-4.70 g/dL), −83.55% (95% CI, −84.90% to −82.08%), +10.75 (95% CI, 8.66-12.84), and −82.48 × 10^9/L (95% CI, −89.33 to −75.62 × 10^9/L), respectively.
- No BTH events or MAVEs were observed during the core treatment period (adjusted annual rate for both end points was 0% [95% CI, 0.00%-0.17%]).

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Figure 3. Hb Response and Transfusion Avoidance



Hb, hemoglobin.
[a] 7/40 patients had missing central laboratory data between Days 14 and 168, so they were not evaluable based on observed data; [b] Transfusion was derived for one patient with imputed Hb values due to missing central laboratory Hb data; therefore, the estimated proportion is less than 100%; [c] The primary end point was analyzed by deriving an estimated proportion as the simple proportion of responders from all imputed datasets, with 95% CIs computed using the bootstrap method; [d] Hb ≥ 12 g/dL and transfusion avoidance were analyzed using a similar methodology to the primary end point.

Safety

- Safety data have previously been reported.[4]
- There were no deaths.
- Headache (27.5%), COVID-19 (15.0%), upper respiratory tract infections (12.5%), and diarrhea (7.5%) were the most frequently reported treatment-emergent adverse events (TEAEs).
- Most patients reported TEAEs that were mild in severity.
- No patients discontinued iptacopan.
- Hemolysis was not reported as a serious or nonserious TEAE.

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Disclosures

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