Poster MDS-273

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Oral iptacopan monotherapy increases paroxysmal nocturnal hemoglobinuria (PNH) red blood cell clone size via control of intra- and extravascular hemolysis in anti-C5–treated PNH patients with anemia

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Key Findings and Conclusions

- Oral iptacopan monotherapy significantly improved hemoglobin (Hb) levels without the need for red blood cell (RBC) transfusions compared with anti-C5 treatment (eculizumab or ravulizumab).
- Iptacopan monotherapy was superior to anti-C5 treatment for RBC transfusion avoidance and patient-reported fatigue.
- C3 fragment deposition decreased with iptacopan monotherapy, which along with improved absolute reticulocyte counts (ARCs) indicate the resolution of extravascular hemolysis (EVH).
- Iptacopan treatment led to an increase in the proportion of type II and III PNH RBCs in > 90% of the total RBC population by Week 24, indicating increased survival of these cells and therefore comprehensive control of hemolysis.
- Clinical breakthrough hemolysis (BTH) was more commonly reported with anti-C5 treatment than with iptacopan monotherapy.
- Iptacopan monotherapy was well tolerated and had a favorable safety profile.
- Iptacopan monotherapy may become a practice-changing, oral, outpatient treatment for patients with PNH who had a suboptimal response to anti-C5 treatment and a preferred option for patients with hemolytic PNH.

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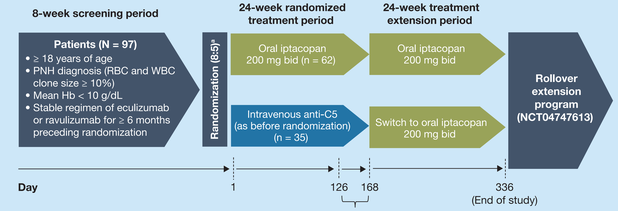
Introduction

- The intravenously administered monoclonal antibodies eculizumab and ravulizumab (also available as a subcutaneous formulation) are approved treatments for patients with PNH and inhibit C5 in the terminal complement pathway.[1-4]
- Eculizumab and ravulizumab have been shown to reduce intravascular hemolysis (IVH) and subsequent PNH symptoms; however, up to two-thirds of patients do not achieve normal Hb levels, primarily because of the emergence of EVH.[5,6]
- Iptacopan is the first oral, proximal complement inhibitor that targets factor B to selectively inhibit terminal complement-mediated IVH and prevent C3b-mediated EVH and thus achieve comprehensive hemolysis control.[7-9]
- In the 24-week randomized period of the open-label, multicenter, phase III APPLY-PNH trial (NCT04558918) in patients with PNH who have persistent anemia despite anti-C5 treatment, iptacopan monotherapy had superior efficacy to intravenous eculizumab and ravulizumab.[9]
- We report total PNH RBC clone size and C3 fragment deposition data from the 24-week randomized period of APPLY-PNH (data cutoff: September 26, 2022).

Methods

- APPLY-PNH enrolled adult patients (N = 97) with a confirmed diagnosis of PNH, a mean Hb < 10 g/dL and who were receiving a stable regimen of eculizumab or ravulizumab for ≥ 6 months preceding randomization.
- Enrolled patients received iptacopan monotherapy 200 mg twice daily or continued with their eculizumab or ravulizumab regimen for 24 weeks (**Figure 1**).
- The primary end points in APPLY-PNH were hematological response defined as a ≥ 2 g/dL Hb increase from baseline (assessed between Days 126 and 168) and Hb ≥ 12 g/dL (assessed between Days 126 and 168), in the absence of RBC transfusions (between Days 14 and 168).
- Secondary end points included RBC transfusion avoidance (between Days 14 and 168), change from baseline in Hb level (excluding values within 30 days of RBC transfusion), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) score, and ARC, percentage change from baseline in lactate dehydrogenase (LDH) level (assessed as a mean between Days 126 and 168), the annualized rate of BTH and major adverse vascular events (MAVEs) throughout the study, and safety and tolerability throughout the study.
- A prespecified testing procedure adjusted for multiplicity in the primary and secondary end points; unadjusted, two-sided *P* values are reported for significant end points.
- 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.

Figure 1. APPLY-PNH Study Design



ARC, absolute reticulocyte count; bid, twice daily; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; RBC, red blood cell; WBC, white blood cell.
[a]Stratified by anti-C5 regimen (eculizumab or ravulizumab) and RBC transfusions received in the preceding 6 months (yes/no).

Results

Baseline demographic and disease characteristics

- Baseline demographic and disease characteristics of the patients enrolled in APPLY-PNH can be found in **Table 1**.
- Demographics and disease characteristics at baseline were generally balanced between each arm.

Table 1. Baseline Demographic and Disease Characteristics

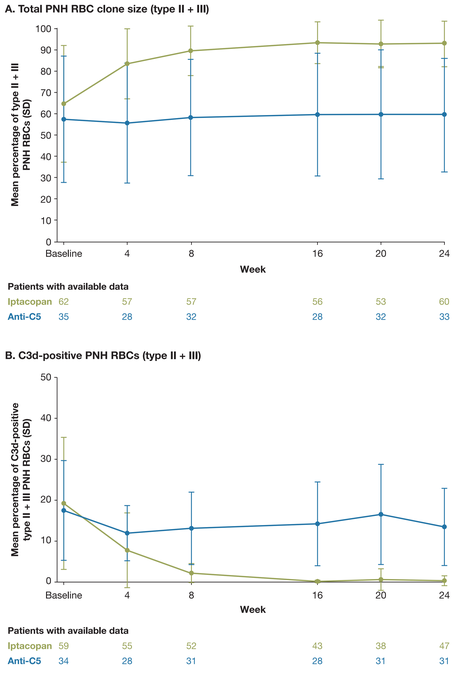
	Iptacopan 200 mg bid n = 62	Anti-C5 treatment n = 35	Overall N = 97
Mean age, years (SD)	51.7 (16.9)	49.8 (16.7)	51.0 (16.8)
Female, n (%)	43 (69.4)	24 (68.6)	67 (69.1)
Time since diagnosis, years (SD)	11.9 (9.8)	13.6 (10.9)	12.5 (10.2)
Anti-C5 treatment in the 6 months prior to randomization			
Eculizumab, n (%)	40 (64.5)	23 (65.7)	63 (64.9)
Ravulizumab, n (%)	22 (35.5)	12 (34.3)	34 (35.1)
Mean duration, years (SD)	3.8 (3.5)	4.2 (3.9)	4.0 (3.6)
Received RBC transfusions in the 6 months prior to randomization, n (%)	35 (56.5)	21 (60.0)	56 (57.7)
Mean baseline Hb, g/dL (SD) [range]	8.9 (0.7) [6.8-10.0]	8.9 (0.9) [6.2-9.9]	8.9 (0.8) [6.2-10.0]
Median baseline LDH, U/L (SD) [range]	269.1 (70.1) [150-539]	272.7 (84.8) [133-562]	270.4 (75.3) [133-562]
Baseline LDH > 1.5 × ULN, n (%)	4 (6.5)	3 (8.6)	7 (7.2)
Mean baseline ARC, 10^9/L (SD) [range]	193.2 (83.6) [51-563]	190.6 (80.9) [90-412]	192.3 (82.3) [51-563]
Mean FACIT-F score (SD) [range]	34.7 (9.8) [11-52]	30.8 (11.5) [10-50]	33.4 (10.5) [10-52]
Mean total RBC clone size (type II + III), % (SD) [range]	64.6 (27.5) [10.6-99.9]	57.4 (29.7) [9.8-99.4]	62.0 (28.4) [9.8-99.9]
Mean C3d+ RBCs (type II + III), % (SD) [range]	19.2 (16.1) [0.0-71.8]	17.5 (12.2) [1.8-51.2]	18.6 (14.8) [0.0-71.8]

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

Total PNH RBC clone size and C3 fragment deposition

- In the iptacopan monotherapy arm, mean total PNH RBC clone size increased from 64.6% at baseline to 93.2% at Week 24, an increase of 28.6% (**Figure 2A**).
- Increases in mean total PNH RBC clone size in the iptacopan monotherapy arm were seen by Week 4 and plateaued by Week 8.
- Mean percentage of C3d-positive type II and III PNH RBCs in the iptacopan monotherapy arm was 19.2% at baseline and became negligible by Week 16 (0.2%) through to Week 24 (0.3%; change from baseline: – 19.2%) (**Figure 2B**).
- Mean total PNH clone size and C3 fragment deposition on PNH RBCs through Week 24 were largely comparable with baseline in the anti-C5 arm (**Figure 2**).

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

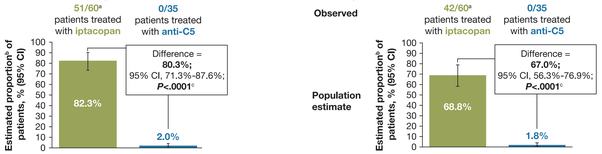


C3d, C3 deposition; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

Hematological response (primary end point)

- Iptacopan monotherapy was superior to anti-C5 treatment for both primary end points (**Figure 3**).

Figure 3. Hb Response in APPLY-PNH



Hb, hemoglobin; RBC, red blood cell.
[a]2/60 patients in the iptacopan arm had missing data between Days 126 and 168 so were not evaluable based on observed data; [b]Marginal proportions, differences in marginal proportions and 95% CIs were calculated using a logistic regression model using the Firth correction that adjusted for baseline covariates and accounted for missing data and the possibility of no patients meeting the primary end point criteria in the anti-C5 arm; consequently, the treatment effect of iptacopan is underestimated, and the treatment effect of anti-C5 is overestimated. Marginal proportions reflect the population average probability of a patient meeting the primary end point criteria; [c]*P* values are two-sided and unadjusted.

Secondary end points

- Iptacopan monotherapy was superior to anti-C5 treatment for transfusion avoidance, with an estimated 96.4% of patients treated with iptacopan avoiding transfusions between Days 14 and 168 compared with 26.1% of patients treated with anti-C5 treatment (difference: 70.3%; 95% CI, 52.6%-84.9%; *P*<.0001).
- Iptacopan monotherapy was superior to anti-C5 treatment for adjusted mean changes from baseline in Hb (difference: +3.63 g/dL; 95% CI, 3.18-4.08 g/dL; *P*<.0001), FACIT-F score (difference: +8.29; 95% CI, 5.28-11.29; *P*<.0001) and ARC (difference: –116.26 × 10^9/L; 95% CI, –132.17 to –100.36 × 10^9/L; *P*<.0001).
- Iptacopan monotherapy was superior to anti-C5 treatment when comparing annualized clinical BTH rate (annualized rate ratio: 0.10; 95% CI, 0.02-0.61; *P*=.0118).
- LDH level and the annualized MAVE rate did not differ significantly between the two treatment arms.
  - IVH was already controlled at randomization by anti-C5 therapy, as evidenced by most patients having LDH of ≤ 1.5 × upper limit of normal at baseline.
  - Only one MAVE occurred during the study. This occurred in the iptacopan treatment arm and was a serious treatment-emergent adverse event (TEAE) of transient ischemic attack. The MAVE was considered by the investigator to be unrelated to iptacopan, and the patient had a concomitant serious TEAE of sick sinus syndrome. The patient was continuing to receive iptacopan treatment at data cutoff.

Safety

- Safety data have previously been reported.[9]
- 82.3% and 80.0% of patients experienced at least one TEAE in the iptacopan and anti-C5 arms, respectively.
- Headache (16.1% vs 2.9%) and diarrhea (14.5% vs 5.7%) were more commonly reported with iptacopan vs anti-C5, and COVID-19 (25.7% vs 8.1%) and BTH (17.1% vs 3.2%) were more commonly reported with anti-C5 vs iptacopan.
- Two patients treated with anti-C5 had serious TEAEs of hemolysis compared with none in the iptacopan arm.
- No serious infections caused by *Neisseria meningitidis*, *Streptococcus pneumoniae,* or *Haemophilus influenzae* were reported.
- No TEAEs in either arm led to discontinuation of study treatment or death.

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