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The 2-year safety and efficacy of iptacopan monotherapy in patients with paroxysmal nocturnal hemoglobinuria (PNH) from APPLY- and APPOINT-PNH studies who entered the roll-over extension program (REP)

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KEY FINDINGS & CONCLUSIONS

- The 2-year data showed that iptacopan was well tolerated with no new safety signals and no increase in exposure-adjusted rates of AEs or SAEs with longer treatment duration.
- Sustained Hb ≥12 g/dL and LDH <1.5 x ULN in most of the patients at 2 years reflect comprehensive hemolysis control with iptacopan, accompanied by improvement in patient-reported fatigue.
- These findings continue to support oral iptacopan monotherapy as a potentially practice-changing treatment for patients with PNH.

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BACKGROUND

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening disease characterized by complement-mediated hemolysis and consequent anemia.[1]
- Iptacopan is an oral proximal complement inhibitor that targets factor B to selectively inhibit the alternative pathway of the complement system.[2]
- Sustained normalization of hemoglobin ([Hb] ≥12 g/dL), lactate dehydrogenase (LDH) <1.5 x upper limit of normal (ULN) levels, transfusion independence, and decreased patient-reported fatigue (as measured by Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-F] score) were observed after 48 weeks of iptacopan monotherapy in phase 3 trials in patients with PNH, who had persistent anemia despite anti-C5 treatment (APPLY-PNH; NCT04558918) or who were complement inhibitor naïve (APPOINT-PNH; NCT04820530).[2–5]
- The oral administration and unique mechanism of action of iptacopan present potential advantages over current treatments, supporting an evaluation of its long-term therapeutic outcomes.
- Herein, we present the 2-year follow-up data on safety, tolerability, and efficacy of iptacopan monotherapy in patients with PNH from the APPLY- and APPOINT-PNH studies (data cut-off: 13 September 2024).

METHODS

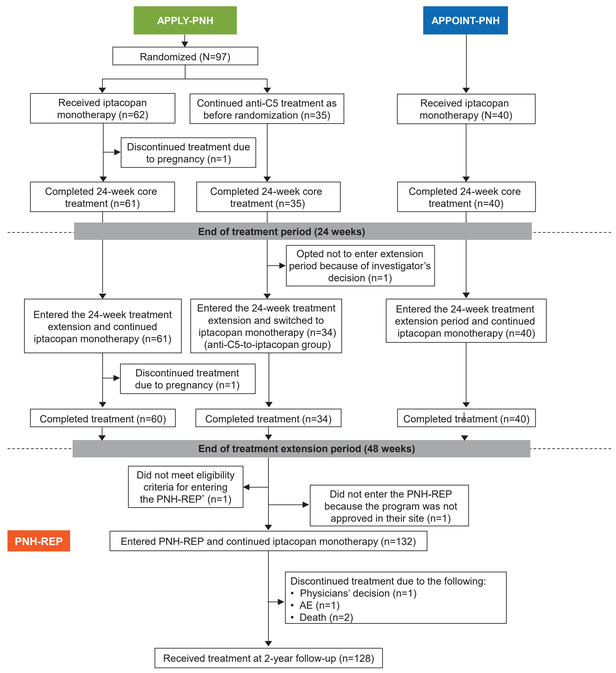
- The roll-over extension (PNH-REP) study (NCT04747613) is an ongoing, open-label, single-arm, multicenter, phase 3 study involving 59 centers globally.
- The study enrolled patients who completed phase 2 and 3 trials (including APPLY- and APPOINT-PNH) and benefited from iptacopan treatment, which is the source for this analysis. The first day of iptacopan treatment in the parent studies is considered as the baseline.
- All patients received iptacopan monotherapy 200 mg twice daily during the treatment extension period of APPLY- and APPOINT-PNH as well as during the PNH-REP.
- The following efficacy assessments were included:
  - Hematological responses, defined as the percentage of patients with an increase of ≥2 g/dL in Hb level from baseline and percentage of patients achieving a Hb level of ≥12 g/dL, without RBC transfusion in the prior 12 months or irrespective of RBC transfusions received during the treatment period
  - Proportion of patients achieving transfusion independence
  - Changes from baseline in Hb levels, FACIT-F scores, and LDH levels
  - Occurrences of clinical breakthrough hemolysis (BTH) and major adverse vascular events (MAVEs)
- Safety assessments included the frequency of treatment-emergent adverse events (TEAEs), serious TEAEs, treatment discontinuations, and deaths.

RESULTS

Patient Characteristics and Disposition

- Of 136 patients treated with iptacopan in APPLY-PNH (n=96) and APPOINT-PNH (n=40), 132 (97.0%) entered the PNH-REP. Eight patients (5.9%) discontinued treatment due to pregnancy (n=2), physicians' decision (n=1), adverse events (AEs) (n=1), delayed institutional review board approval (n=1), did not meet eligibility criteria for entering the PNH-REP (n=1), and death (n=2). At the 2-year follow-up, 128 (94.1%) were still on treatment (**Figure 1**).

Figure 1. Patient Disposition



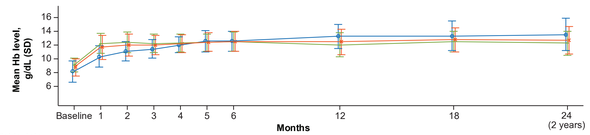
AE, adverse event; PNH, paroxysmal nocturnal hemoglobinuria; REP, roll-over extension program.
*Patient was ineligible for the REP due to a myelodysplastic syndrome diagnosis.

Efficacy

APPLY-PNH in REP

- At 2 years, 69% (58 of 84) of patients achieved a sustained Hb level of ≥12 g/dL, while an increase of ≥2 g/dL in Hb was observed in 79.8% (67 of 84) of patients without RBC transfusion in the prior 12 months.
- Similar proportion of patients (69% [58 of 84]) achieved a sustained Hb level of ≥12 g/dL, and a Hb increase of ≥2 g/dL was observed in 82.1% (69 of 84), both irrespective of RBC transfusions at 2 years.
- The mean (SD) Hb level (irrespective of RBC transfusion) at 2 years was 12.28 g/dL (1.734), with mean (SD) change from baseline of 3.20 g/dL (1.855) (**Figure 2**).
- The mean (SD) LDH level at 2 years was 300.74 U/L (217.457) with a change from baseline of 33.0 U/L (230.261) (**Figure 3**). LDH level of <1.5 ULN was observed in 90.5% (76 of 84) of patients.
- Transfusion independence at 2 years was achieved in 88.5% of patients.
- The mean (SD) FACIT-F score at 2 years was 41.7 (9.99), with a mean change (SD) from baseline of 8.4 (11.31) (**Figure 4**).

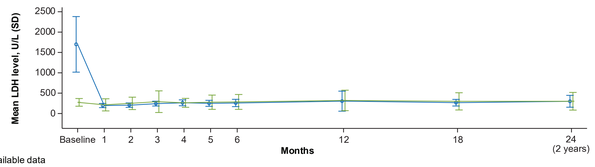
Figure 2. Mean Hb Level Over Time Irrespective of RBC by Study and Combined



Patients with available data										
APPLY-PNH in REP	96	93	93	94	93	92	87	71	79	84
APPOINT-PNH in REP	40	40	38	39	39	39	40	39	30	40
Combined in REP	136	133	131	133	132	131	127	110	109	124

Hb, hemoglobin; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; REP, roll-over extension program; SD, standard deviation.

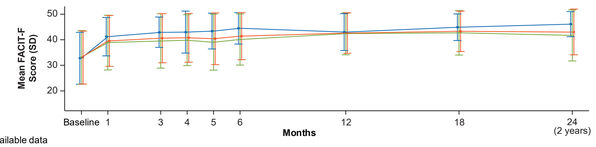
Figure 3. Mean LDH Levels Over Time by Study



Patients with available data										
APPLY-PNH in REP	96	94	96	95	95	93	89	73	82	84
APPOINT-PNH in REP	40	40	37	40	39	39	40	40	30	40

LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; REP, roll-over extension program; SD, standard deviation.

Figure 4. Mean FACIT-F Scores Over Time by Study and Combined



Patients with available data									
APPLY-PNH in REP	94	92	86	86	90	92	90	73	74
APPOINT-PNH in REP	40	37	38	35	39	40	39	29	32
Combined in REP	134	129	124	121	129	132	129	102	106

FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; PNH, paroxysmal nocturnal hemoglobinuria; REP, roll-over extension program; SD, standard deviation.

APPOINT-PNH in REP

- At 2 years, 75% (30 of 40) of patients achieved a sustained Hb level of ≥12 g/dL and a Hb increase ≥2 g/dL was observed in 85% (34 of 40) without RBC transfusion in the prior 12 months.
- Similar proportion of patients (77.5% [31 of 40]) achieved a sustained Hb level of ≥12 g/dL, and a Hb increase of ≥2 g/dL was observed in 87.5% (35 of 40), both irrespective of RBC transfusions at 2 years.
- The mean (SD) Hb level (irrespective of RBC transfusion) at 2 years was 13.54 g/dL (2.327), with a mean (SD) change from baseline of 5.37 g/dL (2.919) (**Figure 2**).
- The mean (SD) LDH level at 2 years was 299.60 U/L (145.667) with a change from baseline of -1399.18 (652.417) (**Figure 3**). LDH level of <1.5 ULN was observed in 85% (34 of 40) of patients.
- Transfusion independence at 2 years was achieved in 95% of patients.
- The mean (SD) FACIT-F score at 2 years was 46.1 (4.88), with a mean change (SD) from baseline of 13.8 (10.05) (**Figure 4**).

Combined in REP

- At 2 years, 71% (88 of 124) of patients achieved a sustained Hb level of ≥12 g/dL and a Hb increase of ≥2 g/dL was observed in 81.5% (101 of 124) without RBC transfusion in the prior 12 months.
- A total of 71.8% (89 of 124) of patients achieved a sustained Hb of ≥12 g/dL, while 83.9% (104 of 124) had an Hb increase of ≥2 g/dL, both irrespective of RBC transfusions at 2 years.
- The mean (SD) Hb level (irrespective of RBC transfusion) at 2 years was 12.69 g/dL (2.022), with a mean (SD) change from baseline of 3.9 g/dL (2.461) (**Figure 2**).
- The mean (SD) LDH level at 2 years was 300.37 (196.565) U/L. LDH level of <1.5 x ULN was observed in 88.7% (110 of 124) of patients.
- Transfusion independence was achieved in 90.4% of patients.
- The mean (SD) FACIT-F score at 2 years was 43.0 (8.97) with a mean change (SD) from baseline of 10.0 (11.18) (**Figure 4**).

- Overall, the efficacy results were comparable among the APPLY-PNH REP, APPOINT-PNH REP, and the combined arms.
- The low exposure-adjusted rate of serious BTH over 2 years (1.1 events per 100 patient-years) was consistent with the absence of serious BTH observed during the 24 weeks core treatment periods of APPLY- and APPOINT-PNH studies. One serious BTH (COVID-19 associated with cold agglutinin disease) occurred during the treatment extension period of APPOINT-PNH. Additionally, 2 patients had serious BTH events (moderate severity) at 2 years (due to potential complement-amplifying conditions).[4,6] All 3 patients received transfusions, recovered from BTH without rescue medication (i.e., no anti-C5), and continued treatment; the investigators did not suspect these events to be related to iptacopan.[4,6]
- MAVEs were observed in 3 patients (4 events). Of these, one portal vein thrombosis (severe) occurred during the treatment extension period of APPLY-PNH[3] in a patient who also experienced intestinal infarction after entering the PNH-REP (see the description of death cases). Other MAVEs included transient ischemic attack in 2 patients (one mild, one severe and serious). All MAVEs resolved, except for intestinal infarction, and were not suspected to be related to iptacopan by investigators.

Safety

- All AEs had a lower or similar exposure-adjusted reporting rate during 2 years of treatment compared to the 6 months treatment period in the core APPLY- and APPOINT-PNH studies **(Table 1).**
- The exposure-adjusted reporting rate of serious AEs (SAEs: 24.7 per 100 patient-years) during the 2 years of treatment was comparable with that observed in APPLY- and APPOINT-PNH over 24 weeks (28.0 and 21.0 per 100 patient-years, respectively).
- There were 2 deaths at 2 years: one in a patient with multiple comorbidities (cardiac, respiratory, renal disorders, and pancytopenia), who died due to cardiopulmonary failure following initial sepsis, about 19 months after starting iptacopan; the other in a patient with liver cirrhosis who had developed ascites and infection followed by intestinal infarction, approximately 10 months after starting iptacopan. These events were not suspected to be related to iptacopan.
- A slightly lower rate of exposure-adjusted serious infections was observed during 2 years of exposure (9.5 events per 100 patient-years), compared with the first 6 months of APPLY-PNH and APPOINT-PNH (10.5 and 10.4 events per 100 patient-years, respectively). The following serious infections were reported within the 2 years of treatment in two or more patients: COVID-19 (n=4, 2.9%); infection and pneumonia (n=3, 2.2% each); and pneumonia bacterial and pneumonia pneumococcal (n=2, 1.5% each).
- One patient with a history of thrombocytopenia discontinued iptacopan due to a further decrease in platelet count.
- The most common TEAEs by preferred terms (reported in ≥10% of patients) included COVID-19 (46.3%), upper respiratory tract infection and nasopharyngitis (34.5%), headache (21.3%), diarrhea (19.1%), abdominal pain (12.5%), nausea and vomiting (each 11.8%), pyrexia (11.0%), and BTH (10.3%) **(Table 1)**.

Table 1. Most Frequent AEs During 2 Years of Exposure (Reported in ≥10% of Patients)

Preferred terms	AEs after 24 weeks (6 months)				AEs during 24 months (2 years)	
	APPLY-PNH		APPOINT-PNH		Combined in REP	
	N=62 n* (%)	Total exposure =28.58 PY‡ m† (OccR)§	N=40 n* (%)	Total exposure =19.29 PY‡ m† (OccR)§	N=136 n* (%)	Total exposure =263.6 PY‡ m† (OccR)§
Numbers of subjects with at least one AE	51 (82.3)	-	37 (92.5)	-	133 (97.8)	-
COVID-19	5 (8.1)	5 (17.5)	6 (15.0)	6 (31.1)	63 (46.3)	72 (27.3)
URTI + nasopharyngitis	9 (14.5)	10 (35.0)	5 (12.5)	6 (31.1)	47 (34.5)	69 (26.2)
Headache	10 (16.1)	17 (59.5)	11 (27.5)	12 (62.2)	29 (21.3)	51 (19.3)
Diarrhea	9 (14.5)	10 (35.0)	3 (7.5)	3 (15.6)	26 (19.1)	35 (13.3)
Abdominal pain	4 (6.5)	5 (17.5)	2 (5.0)	2 (10.4)	17 (12.5)	22 (8.3)
Nausea	6 (9.7)	8 (28.0)	2 (5.0)	2 (10.4)	16 (11.8)	22 (8.3)
Vomiting	2 (3.2)	2 (7.0)	2 (5.0)	2 (10.4)	16 (11.8)	20 (7.6)
Pyrexia	2 (3.2)	3 (10.5)	2 (5.0)	2 (10.4)	15 (11.0)	19 (7.2)
BTH	2 (3.2)	2 (7.0)	0	0	14 (10.3)	22 (8.3)

AE, adverse event; BTH, breakthrough hemolysis; OccR, occurrence rate; PNH, paroxysmal nocturnal hemoglobinuria; PY, patient-years; URTI, upper respiratory tract infection.
n indicates number of patients with at least one event. †m indicates number of AE episodes. ‡Total exposure in patient-years is computed as (sum of the duration of on-treatment periods over patients, in days)/365.25. §OccR = (number of episodes per 100 PY) is calculated as 100(m divided by the total exposure in PY). All occurrences are counted.

References

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