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Long-term hematologic control and safety in patients with paroxysmal nocturnal hemoglobinuria treated with iptacopan: 6-year follow-up from phase 2 studies and roll-over extension program

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KEY FINDINGS & CONCLUSIONS

- Over a 6-year follow-up, iptacopan treatment was associated with sustained hemolysis control in patients with PNH, including maintenance of Hb levels and transfusion independence
- Most patients achieved LDH <1.5 × ULN, ARC normalization, and transfusion independence through to 6 years, showing control of intravascular hemolysis and absence of treatment-emergent extravascular hemolysis
- Low rates of BTH and MAVEs were observed
- Iptacopan was well tolerated over long-term treatment, with a consistent safety profile and no new safety findings compared with previous reports
- These findings further characterize the long-term efficacy and safety of iptacopan treatment in patients with PNH

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INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening disease characterized by complement-mediated hemolysis, thrombosis, and potential concurrent bone marrow failure[1]
- Despite treatment with anti-C5 therapy, many patients with PNH remain anemic and continue to experience PNH symptoms and extravascular hemolysis[2]
- Iptacopan is an oral proximal complement inhibitor approved for the treatment of PNH that targets factor B to selectively inhibit the alternative complement pathway[2-5]
  - Iptacopan is well tolerated and has shown durable hemolysis control[4-7]
- This study reports long-term safety and efficacy outcomes with up to 6-year follow-up from patients with PNH who received iptacopan 200 mg twice daily (BID) in the phase 2 studies CLNP023X2201 and CLNP023X2204 (X2201 and X2204 henceforth)[8,9] and the roll-over extension program, PNH-REP, which is an ongoing phase 3 study[10]

METHODS

- The PNH-REP enrolled patients with PNH who completed the treatment extension periods of phase 2 and phase 3 studies[10]
- The designs of the phase 2 studies have been described previously,[11-13] which included different treatment sequences and iptacopan dosing
- All patients who entered the PNH-REP were receiving iptacopan monotherapy 200 mg BID
- The index date in this analysis was defined as the first day of patients receiving iptacopan 200 mg BID
- The PNH-REP primary endpoint was safety, including incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs per 100 patient-years, study discontinuations, and deaths
- Efficacy assessments included:
  - hemoglobin (Hb) levels and Hb levels ≥12.0 g/dL;
  - lactate dehydrogenase (LDH) levels and LDH levels <1.5 × upper limit of normal (ULN);
  - absolute reticulocyte count (ARC) and ARC normalization;
  - transfusion independence;
  - other markers of disease activity;
  - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue;
  - breakthrough hemolysis (BTH) rates; and
  - major adverse vascular event (MAVE) rates

RESULTS

Patient Characteristics and Disposition

- At data cutoff, 22/26 patients (84.6%) treated with iptacopan 200 mg BID in the phase 2 studies had entered the PNH-REP (**Figure 1**); of these, 21/22 (95.5%) were ongoing and 1/22 (4.5%) had completed the PNH-REP study. Four of 26 patients (15.4%) treated with iptacopan 200 mg BID in the phase 2 studies did not enter the PNH-REP
- Sixteen of 26 patients (61.5%) had ≥5 years and 8/26 (30.8%) had ≥6 years of exposure; median duration of exposure was ≈5.5 years

Figure 1. Patient Disposition

BID, twice daily; PNH, paroxysmal nocturnal hemoglobinuria; REP, roll-over extension program.
[a]Three patients from X2201 received iptacopan 200 mg BID but died before entering the PNH-REP (see Safety section for additional details).

Efficacy

- Hematologic response was sustained from 6 months to 6 years (**Table 1** and **Figure 2**)
  - Mean (standard deviation [SD]) Hb levels were 12.4 (1.6) and 13.0 (1.5) at years 5 and 6, respectively, and 58.3% and 85.7% of patients achieved Hb ≥12.0 g/dL irrespective of RBC transfusion
  - Most patients (23/26 [88.5%]) remained transfusion-free at 6 years
  - Mean (SD) LDH levels were 272.8 (81.0) and 309.1 (70.6) at years 5 and 6, respectively, and 83.3% and 85.7% of patients achieved LDH <1.5 × ULN levels
  - Mean (SD) ARCs were 73.5 (16.8) and 81.4 (36.1) at years 5 and 6, respectively, and 100% and 85.7% of patients achieved ARC normalization
  - Bilirubin, haptoglobin, platelet, and neutrophil levels were sustained
- FACIT-Fatigue scores were sustained from 6 months up to 6 years

Table 1. Long-Term Consistency of Key Hematologic Responses With up to 6 Years of Iptacopan Treatment

	Index date	6 months	4 years	5 years	6 years	Last available
Hb ≥12.0 g/dL, n/N (%)[a]	0/26 (0)	14/20 (70.0)	9/13 (69.2)	7/12 (58.3)	6/7 (85.7)	17/26 (65.4)
Hb (g/dL), mean (SD)	8.8 (1.4)	12.8 (1.9)	12.6 (2.1)	12.4 (1.6)	13.0 (1.5)	12.4 (1.7)
LDH <1.5 × ULN, n/N (%)	7 (26.9)	18/19 (94.7)	11/13 (84.6)	10/12 (83.3)	6/7 (85.7)	23/26 (88.5)
LDH (U/L), mean (SD)	1157.7 (1045.1)	246.1 (59.9)	302.9 (119.0)	272.8 (81.0)	309.1 (70.6)	274.9 (87.3)
ARC (× 10^9/L), mean (SD)	204.5 (84.6)	94.8 (39.5)	77.4 (30.1)	73.5 (16.8)	81.4 (36.1)	91.4 (92.2)
ARC normalization, n/N (%)	NA[b]	14/19 (73.7)	11/11 (100)	12/12 (100)	6/7 (85.7)	24/26 (92.3)
No RBC transfusions, n/N (%)	12/26 (46.2)[c]	NR	24/26 (92.3)	23/26 (88.5)[d]	23/26 (88.5)[e]	23/26 (88.5)
Bilirubin (µmol/L), mean (SD)	36.8 (18.7)	13.1 (8.1)	12.7 (7.0)	11.2 (5.8)	13.4 (8.5)	14.6 (7.8)
Haptoglobin (g/L), mean (SD)	0.1 (0)	0.2 (0.3)	0.5 (1.2)	0.5 (0.6)	0.3 (0.4)	0.3 (0.3)
Platelets (× 10^9/L), mean (SD)	132.3 (62.2)	113.4 (55.2)	141.4 (56.7)	133.4 (59.4)	123.1 (61.7)	137.2 (53.7)
Neutrophils (× 10^9/L), mean (SD)	2.3 (1.0)	2.5 (1.8)	3.3 (2.3)	3.1 (1.4)	2.3 (0.6)	2.8 (1.2)
FACIT-Fatigue score, mean (SD)	36.7 (10.9)	44.3 (8.6)	47.3 (4.2)	45.4 (5.3)	45.3 (7.6)	44.3 (10.1)

ARC, absolute reticulocyte count; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LDH, lactate dehydrogenase; NA, not available; NR, not reported; RBC, red blood cell; SD, standard deviation.
[a]Irrespective of having received RBC transfusion. [b]ARC normalization was considered 13.5-123.0 × 10^9/L. [c]In the last 12 months prior to screening. [d]During years 1-5. [e]During years 1-6.

Figure 2. Mean (SD) Levels of (A) Hb; (B) LDH; (C) ARC; and (D) FACIT-Fatigue Scores Over Time[a]

ARC, absolute reticulocyte count; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LDH, lactate dehydrogenase; LLN, lower limit of normal; SD, standard deviation; ULN, upper limit of normal.
[a]The mean FACIT-Fatigue score among the healthy general United States population is 43.6.[14] FACIT-Fatigue scores range from 0 to 52, with higher scores indicating less fatigue.[15]

BTH and MAVEs

- Overall, 6 BTH events (none serious) occurred in 5/26 patients (19.2%; 4.7/100 PY): 2 mild, 3 moderate, and 1 severe event (deemed study drug-related by investigator)
- A MAVE (unstable angina) was reported in 1/26 patients (3.8%; 0.8/100 PY) who had pre-existing hypertension, left ventricular hypertrophy, and nephropathy

Safety

- TEAEs are presented in **Table 3**; in total, 23/26 patients (88.5%) reported ≥1 TEAE, most frequently COVID-19 and pyrexia (30.8% each)

Table 3. TEAEs in Patients Treated With Iptacopan 200 mg BID in the Phase 2 Studies and PNH-REP With up to 6 Years' Follow-up (Occurring in ≥10% of Patients)

	X2201		X2204		Combined population	
	N = 16 n (%)	Total exp = 83.9 PY[a] m[b] (OccR)[c]	N = 10 n (%)	Total exp = 44.4 PY[a] m[b] (OccR)[c]	N = 26 n (%)	Total exp = 128.3 PY[a] m[b] (OccR)[c]
N patients with ≥1 AE	16 (100)	222 (264.6)	7 (70.0)	46 (103.6)	23 (88.5)	268 (208.9)
COVID-19	6 (37.5)	7 (8.3)	2 (20)	2 (4.5)	8 (30.8)	9 (7.0)
Pyrexia	6 (37.5)	13 (15.5)	2 (20.0)	3 (6.8)	8 (30.8)	16 (12.5)
BTH[d]	3 (18.8)	3 (3.6)	2 (20.0)	3 (6.8)	5 (19.2)	6 (4.7)
Hemolysis	3 (18.8)	3 (3.6)	1 (10.0)	2 (4.5)	4 (15.4)	5 (3.9)
Headache	3 (18.8)	3 (3.6)	1 (10.0)	1 (2.3)	4 (15.4)	4 (3.1)
Cough	3 (18.8)	3 (3.6)	1 (10.0)	1 (2.3)	4 (15.4)	4 (3.1)
Ear infection	3 (18.8)	4 (4.8)	0	0 (0.0)	3 (11.5)	4 (3.1)
Nasopharyngitis	2 (12.5)	2 (2.4)	1 (10.0)	1 (2.3)	3 (11.5)	3 (2.3)
Diarrhea	3 (18.8)	3 (3.6)	0	0 (0.0)	3 (11.5)	3 (2.3)
Anemia	3 (18.8)	6 (7.2)	0	0 (0.0)	3 (11.5)	6 (4.7)
Thrombocytopenia	3 (18.8)	3 (3.6)	0	0 (0.0)	3 (11.5)	3 (2.3)
Back pain	2 (12.5)	2 (2.4)	1 (10.0)	1 (2.3)	3 (11.5)	3 (2.3)
Rhinorrhea	2 (12.5)	2 (2.4)	1 (10.0)	3 (6.8)	3 (11.5)	5 (3.9)
Insomnia	2 (12.5)	3 (3.6)	1 (10.0)	1 (2.3)	3 (11.5)	4 (3.1)
Dysuria	3 (18.8)	5 (6.0)	0	0 (0.0)	3 (11.5)	5 (3.9)
Product dose omission issue	3 (18.8)	5 (6.0)	0	0 (0.0)	3 (11.5)	5 (3.9)

AE, adverse event; BID, twice daily; BTH, breakthrough hemolysis; COVID-19, coronavirus disease 2019; exp, exposure; m: number of adverse event episodes; n: number of patients with ≥1 event; OccR, occurrence rate; PNH, paroxysmal nocturnal hemoglobinuria; PY, patient-year; REP, roll-over extension program; SD, standard deviation; TEAE, treatment-emergent adverse event.
[a]Total exposure in PY is computed as (sum of the duration of on-treatment periods over patients, in days)/365.25. [b]m indicates number of AE episodes. [c]OccR = (number of episodes per 100 PY) is calculated as 100*(m divided by the total exposure in PY). [d]In the phase 2 studies, BTH was determined by investigator assessment. In the PNH-REP, BTH was protocol-defined as LDH level of 1.5 × ULN, and higher than the previous two assessments, and at least one of the following clinical criteria: either decrease in Hb level of ≥2 g/dL, or occurrence of gross hemoglobinuria, painful crisis, dysphagia, or any other significant clinical PNH-related signs or symptoms.

- Serious TEAEs occurred in 11/26 patients (42.3%; 13.2/100 PY)
  - Most common serious TEAEs were neoplasms (4/26 patients [15.4%; 3.9/100 PY]), infections (3/26 patients [11.5%; 3.9/100 PY]), and renal and urinary disorders (2/26 [7.7%; 1.6/100 PY])
- Three of 26 (11.5%) patients died during the phase 2 studies; all 3 patients died after discontinuation of iptacopan (from 52 to 343 days after last dose) and no events leading to death were deemed study drug-related. The events leading to death were squamous cell carcinoma of the oral cavity, sepsis following chemotherapy for lymphoproliferative disorder, and deterioration of general physical health following *E. coli* sepsis after surgery for aortic ulcer

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