Poster MDS-1159

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Long-term safety with iptacopan treatment in patients with paroxysmal nocturnal hemoglobinuria (PNH): Pooled analysis of data from phase 2 and 3 studies and the roll-over extension program

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KEY FINDINGS & CONCLUSIONS

- The safety profile of iptacopan in this pooled analysis of long-term safety data is consistent with that previously reported, with no new safety findings with up to 6 years of follow-up
- The rate of treatment discontinuation due to AEs was low
- MAVEs and serious BTH events were infrequent
- There were minimal changes in LDL cholesterol levels
- These findings demonstrate that iptacopan is well tolerated in the long-term treatment of PNH

This study is sponsored by Novartis AG, Basel, Switzerland.
Originally presented at: EHA2026 Congress; June 11-14, 2026; Stockholm, Sweden
Poster presented at: Society of Hematologic Oncology (SOHO) Annual Meeting 2026; September 9-12, 2026; Houston, TX, USA

INTRODUCTION

- Iptacopan is an oral proximal complement inhibitor approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) that targets factor B to selectively inhibit the alternative pathway of the complement system[1]
- Iptacopan demonstrated sustained hemolysis control and was well tolerated in patients with PNH in three phase 3 studies (APPOINT-PNH [NCT04820530], APPLY-PNH [NCT04558918], and APPULSE-PNH [NCT05630001]),[1,2] two phase 2 studies (X2201 [NCT03439839] and X2204 [NCT03896152]),[3,4] and the roll-over extension program (PNH-REP; NCT04747613)[5,6]
- While previous results have shown iptacopan to be well tolerated, long-term safety data are currently limited
- This analysis presents long-term safety of iptacopan 200 mg with up to 6 years of follow-up in patients with PNH using pooled data from the phase 2 studies (X2201, X2204), phase 3 studies (APPLY, APPOINT, APPULSE), and the PNH-REP[2-7]

METHODS

- The methods and patient populations of the APPLY-PNH, APPOINT-PNH, APPULSE-PNH, X2201, and X2204 studies have been described previously[1-4]
- Patients received iptacopan monotherapy 200 mg twice daily in the PNH-REP. Patients were eligible for this analysis if they had received iptacopan 200 mg at least once during any of the parent studies or the PNH-REP; all patients who completed the extension period of one of the parent studies were eligible to continue treatment in the PNH-REP[5,6]
- The date of the patient's first dose of iptacopan 200 mg was considered as the baseline date for the analysis
- Assessments included incidence and exposure-adjusted occurrence rates (OccR, expressed as number of events/100 patient-years [PY]) of breakthrough hemolysis (BTH), major adverse vascular events (MAVEs), treatment-emergent adverse events (TEAEs), and serious TEAEs
- To evaluate changes in lipid levels with iptacopan treatment, cholesterol levels were assessed. Total cholesterol was calculated in the overall population; high- (HDL) and low-density lipoprotein (LDL) cholesterol end points were calculated in the pooled phase 3 populations only

RESULTS

Patient Disposition and Treatment Exposure

- In total, the analysis population included 223 patients
- At data cutoff (October 2025), 95 (42.6%) patients had completed the PNH-REP, 106 (47.5%) remained on study, and 22 (9.9%) had discontinued treatment, including 3 (1.3%) due to adverse events (AEs), 2 (0.9%) due to pregnancy, and 8 (3.6%) due to death (no deaths were deemed study drug-related) (**Table 1**)
  - The AEs that led to treatment discontinuation were anti-glomerular basement membrane nephritis, worsening of platelet count decreased, and palpitation
- Total iptacopan exposure was 673.8 PY; 163 (73.1%) patients were exposed to iptacopan for ≥2 years, 126 (56.5%) for ≥3 years, and 34 (15.2%) for ≥4 years (**Table 2**)

Table 1. Patient Disposition

	N = 223 n (%)
Completed study	95 (42.6)
Ongoing study	106 (47.5)
Discontinued treatment	22 (9.9)
Death	8 (3.6)
Physician decision	5 (2.2)
Adverse event	3 (1.3)
Patient/guardian decision	3 (1.3)
Pregnancy	2 (0.9)
Lack of efficacy	1 (0.4)

The disposition status is based on the latest status at data cutoff for the pooled study, ie, a subject is a completer if completed the core/parent study and decided not to enter the REP or the subject completed the parent study, entered the roll-over extension, and completed.

Table 2. Treatment Exposure

	N = 223 n (%)
Total number of patients receiving study treatment, n (%)	223 (100)
Duration of exposure (months)	
Mean (SD)	36.3 (16.8)
Median (Q1-Q3)	40.3 (22.6-44.9)
Min-max	3.4-87.2
Duration of exposure, n (%)	
≥12 months	205 (91.9)
≥24 months	163 (73.1)
≥36 months	126 (56.5)
≥48 months	34 (15.2)
≥60 months	16 (7.2)
≥72 months	8 (3.6)
Subject time, years	673.8

Q, quartile; SD, standard deviation.
Duration of exposure in months is defined as days on exposure/(365.25/12) and duration of exposure in years is days on exposure/365.25, where days on exposure is derived as (last dose in the corresponding treatment period minus first dose date plus 1 minus days on temporary treatment interruptions). Subject-time is the sum of each subject's treatment exposure in years.

BTH and MAVEs

- BTH occurred in 29 (13.0%) patients (OccR 6.7 events/100 PY) and serious BTH events occurred in 6 (2.7%) patients (OccR 0.9 events/100 PY)
  - All serious BTH events had an outcome of recovered/resolved
- Eight MAVEs were reported in 7 (3.1%) patients (OccR 1.2 events/100 PY). These included transient ischemic attack (3 patients); lacunar infarction, unstable angina, thrombophlebitis/deep vein thrombosis (1 patient each); intestinal infarction and portal vein thrombosis (in the same patient)
  - Of the 7 patients, 4 patients had an outcome of recovered/resolved, 2 patients had an outcome of not recovered/not resolved, and 1 patient had a fatal outcome
  - All MAVEs occurred in patients with at least 1 cardiovascular or cardiometabolic risk factor. Hypertension was the most common risk factor, reported in 5 patients
    - No patient in whom MAVEs occurred had BTH at any time

Safety

- Overall, 210 (94.2%) patients experienced ≥1 TEAE (OccR 329.4 events/100 PY) (**Table 3**)
- Sixty-seven (30.0%) patients experienced ≥1 serious TEAE (OccR 19.4 events/100 PY)
  - Infections were the most frequent serious TEAEs, reported in 29 (13.0%) patients (OccR 7.0 events/100 PY). The most common serious infections were bacterial pneumonia in 6 (2.7%) patients, and COVID-19 and pneumonia both in 5 (2.2%) patients
- In total, there were 8 deaths (3.6%). No events leading to death were classified as drug-related by the investigator
  - In the phase 3 studies, 5 deaths occurred due to cardiopulmonary failure following sepsis, gastrointestinal hemorrhage, metastatic colorectal cancer, pneumonia, and infection, followed by intestinal infarction
  - In the phase 2 studies, 3 deaths occurred; all were in study X2201 and these patients did not enter the PNH-REP. One patient died due to squamous cell carcinoma of the tongue and oral cavity, 1 due to sepsis following chemotherapy for lymphoproliferative disorder, and 1 due to deterioration of general physical health following *E.coli* sepsis after surgery for aortic ulcer
    - All 3 patients died after discontinuation of iptacopan (range: 52-343 days after last dose)

Table 3. Most Common TEAEs (Occurring in ≥10% of Patients)

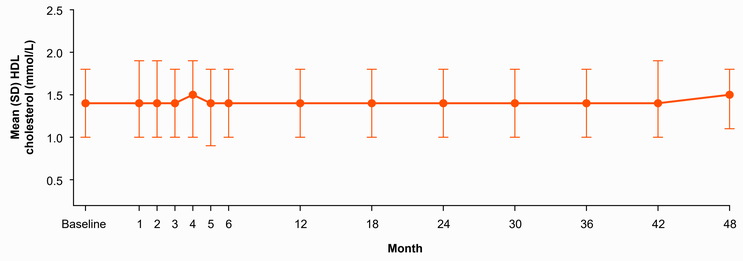
	N = 223	
	n (%)[a]	Total exp = 676.1 PY[b] m[c] (OccR)[d]
Any TEAE	210 (94.2)	2227 (329.4)
COVID-19	79 (35.4)	93 (13.8)
Nasopharyngitis	50 (22.4)	77 (11.4)
Headache	47 (21.1)	78 (11.5)
Diarrhea	37 (16.6)	51 (7.5)
Upper respiratory tract infection	33 (14.8)	54 (8.0)
Pyrexia	31 (13.9)	51 (7.5)
BTH	29 (13.0)	45 (6.7)
Abdominal pain	25 (11.2)	31 (4.6)
Nausea	25 (11.2)	33 (4.9)

BTH, breakthrough hemolysis; exp, exposure; OccR, occurrence rate; PY, patient-year; TEAE, treatment-emergent adverse event.
[a]n indicates number of patients with at least 1 event. [b]Total exposure in patient-years is computed as (sum of the duration of on-treatment periods over patients, in days)/365.25. The total is based on net on-treatment time and excludes treatment gaps. [c]m indicates number of AE episodes.
[d]OccR = (number of episodes per 100 PY) is calculated as 100*(m divided by the total exposure in PY). All occurrences are counted.

Changes in Lipids

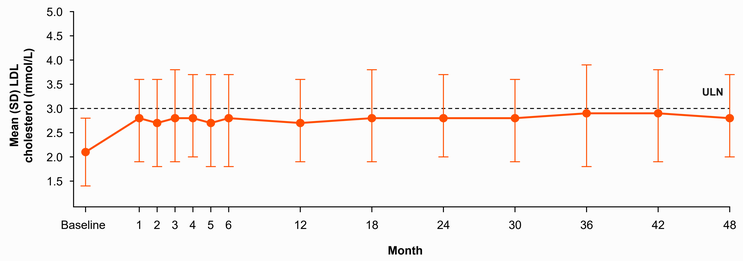
- In the overall population (n = 223), mean (SD) total cholesterol was 4.1 (0.9) mmol/L at baseline, 4.9 (1.2) mmol/L at year 3 (n = 129), and 5.0 (1.0) mmol/L at year 4 (n = 32), with respective mean (SD) elevations of 0.9 (0.9) and 1.1 (0.7) mmol/L from baseline
- In the pooled phase 3 population (n = 188), mean (SD) HDL cholesterol was 1.4 (0.4) at baseline; this remained stable, with mean (SD) change from baseline of 0.0 (0.3) and 0.1 (0.3) mmol/L at years 3 and 4, respectively (**Figure 1**)
- In the pooled phase 3 population (n = 188), mean (SD) LDL cholesterol was 2.1 (0.7) at baseline; this showed a mean (SD) increase from baseline of 0.8 (0.8) mmol/L at both year 3 and year 4 timepoints (**Figure 2**)

Figure 1. Mean HDL Cholesterol Levels Over Time (Pooled Phase 3 Population)



HDL, high-density lipoprotein; SD, standard deviation.

Figure 2. Mean LDL Cholesterol Levels Over Time (Pooled Phase 3 Population)



LDL, low-density lipoprotein; SD, standard deviation; ULN, upper limit of normal.

Pregnancies

- Nine pregnancies were reported; of these, 4 resulted in elective abortions, 2 in spontaneous abortions, 1 in ectopic pregnancy, and 2 in healthy live births

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Acknowledgments

We would like to thank the patients who participated in this study; their time, interest, and insight are greatly appreciated. Medical writing and editorial support was provided by Gary Brown, BSc, of Nucleus Global, and was funded by Novartis Pharmaceuticals Corporation. This poster was developed in accordance with Good Publication Practice (GPP) guidelines. The authors had full control of the content and made the final decision on all aspects of this publication.

Disclosures

AR reports consulting fees from Alexion, Amgen, Apellis, Bioverativ, BioCryst, Roche, Kira, Novartis, Recordati, Sanofi, and Sobi; and honoraria from Alexion, Roche, Grifols, Sanofi, Recordati, and Sobi. **AK** reports consulting fees from AbbVie, Alexion, Celgene/Bristol Myers Squibb, Janssen, Novartis, Novo Nordisk, Pfizer, Roche, Samsung, and Sobi; honoraria from Agios, Alexion, Amgen, Celgene/Bristol Myers Squibb, Novartis, Pfizer, Roche, Samsung, and Sobi; and holds stocks for Pfizer. **CF** reports honoraria from Alexion; and participation on a Data Safety Monitoring Board or Advisory Board with Novartis and Sobi. **FSdF** reports contracts or grants from Alexion, Novartis, Pfizer, and Sobi; honoraria from Alexion, Novartis, Pierre Fabre, and Sobi; travel support from Alexion, Novartis, and Sobi; participation on a Data Safety Monitoring Board or Advisory Board with Alexion, Novartis, and Samsung; and other interests in Novartis and Sobi. **PS** reports contracts or grants from AstraZeneca, Novartis, Pfizer, and Roche; honoraria from AstraZeneca, Novartis, Pfizer, and Roche; and participation on a Data Safety Monitoring Board or Advisory Board with AstraZeneca, Novartis, Pfizer, and Roche. **BSK** reports honoraria from Astellas, AstraZeneca, BeiGene, Bristol Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Meiji Seika Pharma, Novartis, Ono, and Pfizer. **AG** reports consulting fees from Alexion, Novartis, and Roche; honoraria from Alexion, Novartis, Roche, and Sobi; and participation on a Data Safety Monitoring Board or Advisory Board with Alexion, Novartis, Roche, and Sobi. **YU** reports contracts or grants from Chugai; consulting fees from Alexion, Asahi Kasei, Chugai, Johnson & Johnson (Janssen), Novartis, Ono, and Sanofi; honoraria from Alexion, Incyte, Johnson & Johnson (Janssen), Novartis, Sanofi, and Sobi; and participation on a Data Safety Monitoring Board or Advisory Board with Alexion, Johnson & Johnson (Janssen), Novartis, and Sanofi. **LWLL** reports contracts or grants from AstraZeneca, Novartis, and Regeneron. **IW** reports contracts or grants from Novartis; consulting fees from Alexion, Novartis, and Recordati; and honoraria from Alexion, Novartis, and Recordati. **PF** and **LM** are employees of and hold stocks for Novartis Pharma AG. **SS** is an employee of and holds stocks for Novartis Farmacéutica, S.A. **RJK** reports research grants from Novartis and Sobi; consulting fees from Alexion, Amgen, Florio, Novartis, Omeros, Otsuka, and Sobi; honoraria from Alexion, Amgen, Florio, Novartis, Omeros, Otsuka, Roche, and Sobi; and participation on a Data Safety Monitoring Board or Advisory Board with Alexion, Novartis, and Roche.