

Novartis presents pivotal Phase III APPLY-PNH data at ASH demonstrating investigational oral monotherapy iptacopan superiority over anti-C5

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- Trial met both primary and most secondary endpoints, showing iptacopan provided transfusion-free hemoglobin-level increases in vast majority of adult paroxysmal nocturnal hemoglobinuria (PNH) patients with residual anemia despite prior anti-C5 therapy¹
- Iptacopan demonstrated an 80% difference to anti-C5 in the estimated proportion of patients* achieving 2 g/dL or more hemoglobin-level increases from baseline without the need for red blood cell transfusions¹
- Iptacopan demonstrated a 67% difference to anti-C5 in the estimated proportion of patients* achieving 12 g/dL or more hemoglobin levels without the need for red blood cell transfusions¹
- Iptacopan also provided blood-transfusion independence for almost all patients with no serious cases of breakthrough hemolysis (BTH) and clinically meaningful patient-reported-fatigue improvements¹
- Recently announced positive APPOINT-PNH Phase III study in complement-inhibitor-naïve patients adds to growing body of evidence for iptacopan in PNH²

EAST HANOVER, N.J., Dec. 13, 2022 -- Novartis today announced detailed results from the pivotal Phase III APPLY-PNH trial¹. The results showed a vast majority of patients with paroxysmal nocturnal hemoglobinuria (PNH) who received the investigational oral monotherapy iptacopan achieved clinically meaningful increases in hemoglobin levels compared to anti-C5 therapy¹. The study met both primary endpoints and most secondary endpoints, with iptacopan demonstrating superiority over anti-C5 therapy in adult patients with PNH experiencing residual anemia despite prior treatment with anti-C5 therapy¹.

In the study, the safety profile of iptacopan monotherapy was consistent with previously reported data, with no serious infections caused by encapsulated bacteria^{1,3,4}. The results, from the APPLY-PNH 24-week randomized treatment period, were featured as an oral presentation during the late-breaking abstract session and in a press briefing at the 64th American Society of Hematology Annual Meeting & Exposition (ASH).

"More than half of patients with PNH experience residual anemia despite treatment with anti-C5 therapy and many remain dependent on blood transfusions during treatment, largely due to unaddressed destruction of red blood cells in the spleen and the liver – called extravascular hemolysis," said study principal co-investigator Prof Régis Peffault de Latour, MD, PhD of Saint-Louis Hospital, Greater Paris University Hospital. "The Phase III APPLY-PNH results show oral iptacopan was superior in resolving extravascular hemolysis and maintaining intravascular hemolysis control compared to intravenous anti-C5 therapies – a potentially groundbreaking benefit for those living with this chronic blood disorder."

The study met both primary endpoints, showing superiority for iptacopan vs. anti-C5¹. For the first, an estimated 82.3%* (95% CI: 73.4, 90.2) of iptacopan-treated patients achieved hemoglobin-level increases of 2 g/dL or more from baseline without the need for red blood cell transfusions, compared to an estimated 2.0%* (95% CI: 1.1, 4.1) of anti-C5-treated patients: an estimated 80.3%* (95% CI: 71.3, 87.6; P<0.0001) difference in favor of iptacopan¹. The observed number of patients achieving this primary endpoint was 51/60[#] for iptacopan vs. 0/35 for anti-C5¹.

For the second primary endpoint, an estimated 68.8%* (95% CI: 58.3, 78.9) of iptacopan-treated patients achieved hemoglobin levels of 12 g/dL or more without the need for blood transfusions, compared to an estimated 1.8%* (95% CI: 0.9, 4.0) of anti-C5-treated patients: an estimated 67.0%* (95% CI: 56.3, 76.9; P<0.0001) difference in favor of iptacopan¹. The observed number of patients achieving this primary endpoint was 42/60[#] for iptacopan vs. 0/35 for anti-C5¹.

"Nearly every patient treated with iptacopan – 60 out of 62 – remained blood-transfusion free after six months of treatment, compared to only 14 out of 35 anti-C5-treated patients – a potentially practice-changing outcome for people with PNH," stated study principal co-investigator Antonio Risitano, M.D., Ph.D., President of the International PNH Interest Group and Head of the Hematology and Hematopoietic Transplant Unit, Reference Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria at the AORN San Giuseppe Moscati, Avellino, Italy. "This outcome, along with the exceptional hemoglobin-level increases of at least 2 g/dL in 51 out of 60 patients, suggests that, if approved, iptacopan could transform treatment and outcomes for patients with PNH."

"With combined Phase III APPLY-PNH and recently announced positive Phase III APPOINT-PNH results, Novartis has a comprehensive data package to support a 2023 regulatory submission, with the possibility of iptacopan becoming the first oral monotherapy for patients with PNH," said David Soergel, M.D., Global Head, Cardiovascular, Renal and Metabolism Development Unit, Novartis.

Iptacopan also showed superiority over anti-C5 therapy across most secondary endpoints, including change from baseline in hemoglobin levels, blood-transfusion independence, patient-reported fatigue (as measured by Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-F] scores), absolute reticulocyte (immature red blood cells) counts (ARC), and rate of clinical BTH¹.

Iptacopan-treated patients achieved a 3.59 (95% CI: 3.32, 3.86) g/dL adjusted average increase in hemoglobin levels from baseline, compared to a 0.04 (95% CI: -0.42, 0.35) g/dL decrease for anti-C5-treated patients: a 3.63 (95% CI: 3.18, 4.08; $P < 0.0001$) g/dL difference in favor of iptacopan¹. Average hemoglobin levels irrespective of blood transfusions for iptacopan-treated patients were 12.6 (standard deviation [SD]: 1.4) g/dL, compared to 9.2 (SD: 1.4) g/dL for anti-C5-treated patients¹.

In the six months prior to randomization, 57.7% of patients had received blood transfusions¹. After 24 weeks of treatment, an estimated 96.4%* (95% CI: 90.7, 100.0) of iptacopan-treated patients remained blood-transfusion free, compared to an estimated 26.1%* (95% CI: 12.4, 42.7) of anti-C5-treated patients: an estimated 70.3%* (95% CI: 52.6, 76.9; $P < 0.0001$) difference in favor of iptacopan¹. The observed number of patients achieving this endpoint was 60/62 for iptacopan vs. 14/35 for anti-C5¹. Iptacopan-treated patients achieved an 8.59 (95% CI: 6.72, 10.47) point adjusted average increase in FACIT-F score from baseline, compared to a 0.31 (95% CI: -2.20, 2.81) point increase for anti-C5-treated patients: an 8.29 (95% CI: 5.28, 11.29; $P < 0.0001$) point difference in favor of iptacopan¹.

There was no significant difference between iptacopan monotherapy and anti-C5 for rate of major adverse vascular events or change from baseline in lactate dehydrogenase levels – with the latter showing maintenance of intravascular hemolysis control¹.

The most commonly reported adverse events (AEs) with iptacopan were headache (iptacopan: 16.1%; anti-C5: 2.9%) and diarrhea (iptacopan: 14.5%; anti-C5: 5.7%), while the most commonly reported AEs with anti-C5s were COVID-19 (anti-C5: 25.7%; iptacopan: 8.1%) and clinical BTH events (anti-C5: 17.1%; iptacopan: 3.2%)¹. Two anti-C5-treated patients had serious AEs of hemolysis, compared with no iptacopan-treated patients¹. No patients discontinued iptacopan or anti-C5s because of AEs¹.

Separately, Novartis recently announced the Phase III APPOINT-PNH trial was positive, with iptacopan providing clinically meaningful increases in hemoglobin levels in complement-inhibitor-naïve patients with PNH^{2,5}. Data from APPLY-PNH and APPOINT-PNH will be included as part of global regulatory submissions in 2023.

Following presentation of the APPLY-PNH data at ASH, Novartis will host an investor conference call on December 13, 2022 at 18:30 CET / 12:30 ET. A simultaneous webcast may be accessed by visiting the Novartis website at <https://www.novartis.com/investors/event-calendar>, and a replay will be available after the call.

*These estimated proportions of patients are marginal proportions, calculated using a pre-specified logistic regression model (this also applies for the differences in marginal proportions and 95% CIs)¹. Marginal proportions reflect the population average probability of a patient meeting the endpoint criteria¹. The values are adjusted for baseline covariates and missing data have been imputed¹.

#Evaluable/non-missing data was available for 60 iptacopan-treated patients (out of the total 62 iptacopan-treated patients in the trial)¹.

About the study

APPLY-PNH (NCT04558918) is a Phase III, randomized, multinational, multicenter, active-comparator controlled, open-label trial to evaluate the efficacy and safety of twice-daily, oral iptacopan monotherapy (200 mg) for the treatment of PNH by demonstrating the superiority of iptacopan compared to anti-C5 therapies (eculizumab or ravulizumab) in adult patients presenting with residual anemia (Hb <10 g/dl) despite a stable regimen of anti-C5 treatment in the last six months prior to randomization^{1,6}.

About paroxysmal nocturnal hemoglobinuria (PNH)

PNH is a rare, chronic, and serious complement-mediated blood disorder⁷. People with PNH have an acquired mutation in some of their hematopoietic stem cells (which are located in the bone marrow and can grow and develop into red blood cells (RBCs), white blood cells and platelets) that causes them to produce RBCs that are susceptible to premature destruction by the complement system^{7,8}. This leads to intravascular hemolysis (destruction of RBCs within blood vessels) and extravascular hemolysis (destruction of RBCs mostly in the spleen and liver), which cause anemia (low levels of circulating RBCs), thrombosis (formation of blood clots), fatigue, and other debilitating symptoms that can impact people's quality of life^{7,8}.

It is estimated that approx. 10-20 people per million worldwide live with PNH⁷. Although PNH can develop at any age, it is often

diagnosed in people between 30-40 years old^{9,10}.

PNH has a significant unmet need not addressed by anti-C5 therapies (eculizumab or ravulizumab): despite treatment with anti-C5s, a large proportion of people with PNH remain anemic, fatigued, and dependent on blood transfusions^{7,8,11,12}.

About iptacopan

Iptacopan is an investigational first-in-class, orally administered targeted factor B inhibitor of the alternative complement pathway^{1,3,4,13}. It acts upstream of the C5 terminal pathway, preventing not only intravascular but also extravascular hemolysis in PNH^{1,3,4,13}. In doing so, iptacopan targets a key part of the biology responsible for PNH while offering an oral monotherapy option^{1,3,4,13}.

Discovered at the Novartis Institutes for BioMedical Research, iptacopan is currently in development for a number of other complement-mediated diseases (CMDs) where significant unmet needs exist, including kidney diseases C3 glomerulopathy (C3G), IgA nephropathy (IgAN), atypical hemolytic uremic syndrome (aHUS), membranous nephropathy (MN), lupus nephritis (LN), and blood disorders immune thrombocytopenic purpura (ITP) and cold agglutinin disease (CAD). First results for Phase III trials in C3G (APPEAR-C3G) and IgAN (APPLAUSE-IgAN) are expected in 2023^{14,15}.

Based on disease prevalence, unmet needs and data from Phase II studies, iptacopan has received FDA Breakthrough Therapy Designation in PNH, orphan drug designations from the FDA and EMA in PNH and C3G, EMA PRIME designation for C3G, and EMA orphan drug designation in IgAN¹⁶⁻¹⁹.

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List of links present in page

1. <https://prod1.novartis.com/us-en/us-en/news/media-releases/novartis-presents-pivotal-phase-iii-apply-pnh-data-ash-demonstrating-investigational-oral-mono-therapy-iptacopan-superiority-over-anti-c5>
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