

MEDIA & INVESTOR RELEASE

Novartis Phase III APPOINT-PNH trial shows investigational oral monotherapy iptacopan improves hemoglobin to near-normal levels, leading to transfusion independence in all treatment-naïve PNH patients

- *Data at EBMT show primary endpoint met – estimated* 92.2% of complement-inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria (PNH) achieving 2 g/dL or more hemoglobin-level increase from baseline without the need for blood transfusions¹*
- *Secondary endpoints show clinically meaningful benefits, including achieving 12 g/dL or more hemoglobin levels and blood-transfusion independence in the vast majority of patients, no cases of clinical breakthrough hemolysis, reduction of lactate dehydrogenase levels, and improved patient-reported fatigue¹*
- *Phase III APPLY-PNH encore data, also presented at EBMT, demonstrate iptacopan superiority over anti-C5 treatments in PNH patients with residual anemia despite prior anti-C5 treatment, and safety and efficacy consistent with APPOINT-PNH^{1,2}*
- *APPOINT-PNH and APPLY-PNH data to be included in global regulatory submissions in H1 2023*

Basel, April 26, 2023 — Novartis today announced detailed results from the Phase III APPOINT-PNH trial of investigational oral monotherapy iptacopan in complement-inhibitor-naïve (including anti-C5 therapies) adults with paroxysmal nocturnal hemoglobinuria (PNH)¹. The trial met its primary endpoint and demonstrated clinically meaningful benefits across secondary endpoints¹. These data were presented at the 49th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT).

With iptacopan treatment, an estimated* 92.2% of patients (95% confidence interval [95%CI]: 82.5, 100) achieved a 2 g/dL or more hemoglobin-level increase from baseline without the need for red blood cell transfusions after the 24-week core treatment period¹.

“In addition to improvement of hemolysis and fatigue seen on currently available treatments, hemolytic PNH patients treated with iptacopan achieve improvement of anemia never seen before with anti-C5s; these data underscore the potential of iptacopan to be a practice-changing oral medicine for this devastating disease,” explained trial 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.

Study principal co-investigator Prof Régis Peffault de Latour, MD, PhD of Saint-Louis Hospital, Greater Paris University Hospital added: “The APPOINT-PNH results are consistent with the tolerability and safety profiles seen in APPLY-PNH and show oral iptacopan controls hemolysis while nearly eliminating the need for blood transfusions.”

PNH is a rare, chronic, and serious complement-mediated blood disorder. It has a significant unmet need despite treatment with anti-C5s, as a large proportion of people with PNH remain anemic, fatigued, and dependent on blood transfusions³⁻⁶. It is estimated that approximately 10-20 people per million worldwide live with PNH³.

The APPOINT-PNH trial also showed clinically meaningful benefits for secondary endpoints¹. An estimated* 62.8% (95%CI: 47.5, 77.5) of patients achieved hemoglobin levels of 12 g/dL or more without the need for red blood cell transfusions¹.

“We continue to be impressed by the totality of evidence from APPLY-PNH and APPOINT-PNH, which confirm the practice-changing potential of iptacopan in the treatment of PNH,” said David Soergel, M.D., Global Head, Cardiovascular, Renal and Metabolism Development Unit, Novartis. “We look forward to our first submissions to regulatory authorities for PNH in the first half of this year, and are continuing to progress our iptacopan studies for a range of other complement-mediated diseases, with Phase III results in C3 glomerulopathy and IgA nephropathy anticipated later in the year.”

Importantly, an estimated* 97.6% (95%CI: 92.5, 100) of patients achieved red blood cell transfusion independence at 24 weeks (in contrast, 70% of patients received blood transfusions in the six months prior to treatment)¹. No clinical breakthrough hemolysis (BTH) events or major adverse vascular events (MAVEs) were observed during the 24-week trial period¹.

Lactate dehydrogenase (LDH) levels decreased by 83.55% (95%CI: -84.90, -82.08) from baseline at 24 weeks, with reductions seen as early as day seven¹. At week 24, 95% of patients had LDH levels ≤ 1.5 times the upper limit of normal (ULN). LDH is a biomarker of intravascular hemolysis (destruction of RBCs within blood vessels) and these results show, when combined with other APPOINT results, iptacopan provided good control of intravascular hemolysis^{1,3}.

Patients also reported clinically meaningful improvements in fatigue, with an adjusted average 10.75 (95%CI: 8.66, 12.84) point increase from baseline in Functional Assessment of Chronic Illness Therapy – Fatigue score, reaching absolute levels similar to those reported in the general population^{1,7,8}.

Iptacopan demonstrated a tolerability and safety profile consistent with previously reported data^{1,2,9,10}. The most commonly reported adverse events (AEs) were infections (in 40.0% of patients, mainly COVID-19 [15.0%] and upper respiratory tract infection [12.5%]), headache (27.5%) and diarrhea (7.5%), with four serious AEs reported¹. No patients discontinued iptacopan in the 24-week treatment period¹.

Data from the pivotal Phase III APPLY-PNH trial (first reported at ASH 2022) were also presented, which demonstrate the superiority of iptacopan over anti-C5 therapy for the treatment of patients with PNH experiencing residual anemia despite prior anti-C5 therapy².

** Proportions estimated based on statistical modelling and accounting for missing data¹.*

About APPOINT-PNH

APPOINT-PNH (NCT04820530) is a Phase III, multinational, multicenter, open-label, single-arm study to evaluate the efficacy and safety of twice-daily, oral iptacopan monotherapy (200

mg) in adult PNH patients who are naïve to complement inhibitor therapy, including anti-C5 therapies (eculizumab or ravulizumab)^{1,11}.

The primary endpoint was to assess the proportion of participants achieving an increase in hemoglobin levels from baseline of 2 g/dL or more in the absence of red blood cell (RBC) transfusions at 24 weeks^{1,11}. Secondary endpoints include the proportion of participants achieving sustained hemoglobin levels of 12 g/dL or more in the absence of RBC transfusions, transfusion independence (defined as the percentage of people who remained free from transfusions), average change in hemoglobin levels, average percent change in lactate dehydrogenase (LDH) levels, rate of breakthrough hemolysis, average change in absolute reticulocyte counts, change in fatigue, and rates of major adverse vascular events^{1,11}.

The trial enrolled 40 patients who received twice-daily, oral iptacopan monotherapy^{1,11}.

About APPLY-PNH

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 despite a stable regimen of anti-C5 treatment in the last six months prior to randomization^{2,12}.

One primary endpoint was to assess the percentage of patients achieving an increase in hemoglobin levels from baseline of 2 g/dL or more in the absence of RBC transfusions at 24 weeks^{2,12}. Another primary endpoint was to assess the percentage of participants achieving sustained hemoglobin levels of 12 g/dL or more in the absence of RBC transfusions at 24 weeks^{2,12}. Secondary endpoints include percentage of participants who remain free from transfusions, average change in hemoglobin levels, change in fatigue, average change in absolute reticulocyte counts, average percent change in LDH levels, rate of breakthrough hemolysis, and rates of major adverse vascular events^{2,12}.

The trial enrolled 97 patients who were randomized in an 8:5 ratio to either twice-daily, oral iptacopan monotherapy, or intravenous anti-C5 therapies (continuing with the same regimen as they were on prior to randomization)^{2,12}.

About paroxysmal nocturnal hemoglobinuria (PNH)

PNH is a rare, chronic and serious complement-mediated blood disorder³. 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 RBCs, white blood cells and platelets) that causes them to produce RBCs that are susceptible to premature destruction by the complement system^{3,4}. 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^{3,4}.

It is estimated that approx. 10-20 people per million worldwide live with PNH³. Although PNH can develop at any age, it is often diagnosed in people between 30-40 years old^{13,14}.

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 transfusions³⁻⁶.

About iptacopan

Iptacopan is an investigational first-in-class, orally administered targeted factor B inhibitor of the alternative complement pathway^{1,2,9,10,15}. It acts upstream of the C5 terminal pathway, preventing not only intravascular but also extravascular hemolysis in PNH^{1,2,9,10,15}. In doing so, iptacopan targets a key part of the biology responsible for PNH while offering an oral monotherapy option^{1,2,9,10,15}.

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), 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 H2 2023^{16,17}.

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 IgAN¹⁸⁻²¹.

Disclaimer

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Novartis Media Relations

E-mail: media.relations@novartis.com

Central

North America

Richard Jarvis	+41 79 584 2326	Julie Masow	+1 862 579 8456
Anja von Treskow	+41 79 392 9697	Michael Meo	+1 862 274 5414
Anna Schäfers	+41 79 801 7267	Mary Carmichael	+1 862 200 8344
		Marlena Abdinoor	+1 744 337 0487

Switzerland
Satoshi Sugimoto +41 79 619 2035

Novartis Investor Relations

Central investor relations line: +41 61 324 7944

E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 345 4440
Nicole Zinsli-Somm	+41 61 324 3809	Parag Mahanti	+1 973 876 4912
Isabella Zinck	+41 61 324 7188		