

Novartis investigational iptacopan provides clinically meaningful increases in hemoglobin levels in complement-inhibitor-naïve patients with PNH

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- Phase III APPOINT-PNH study of investigational oral monotherapy iptacopan met its primary endpoint; second positive Phase III topline readout for iptacopan in paroxysmal nocturnal hemoglobinuria (PNH)¹
- Topline APPOINT-PNH data were consistent with APPLY-PNH readout and showed a significant proportion of complement-inhibitor-naïve patients treated with iptacopan achieved clinically meaningful increases in hemoglobin levels vs. baseline without the need for blood transfusions¹
- PNH has a significant unmet need not addressed by anti-C5 therapies; despite treatment with anti-C5s, a large proportion of people with PNH remain anemic, fatigued and dependent on blood transfusions²⁻⁵
- APPOINT-PNH data to be presented at upcoming medical meeting and included in iptacopan PNH global regulatory 2023 submissions

EAST HANOVER, N.J., Dec. 8, 2022 Novartis today announced the Phase III APPOINT-PNH study (NCT04820530) of investigational oral monotherapy iptacopan in complement-inhibitor-naïve (including anti-C5 therapies) adults with PNH met its primary endpoint¹. Topline results showed a significant proportion of patients treated with iptacopan (200 mg twice daily) achieved clinically meaningful hemoglobin-level increases of 2 g/dL or more from baseline without the need for blood transfusions at 24 weeks¹.

In the study, the safety profile of iptacopan monotherapy was consistent with previously reported data^{1,6,7}. Detailed data will be presented at an upcoming medical meeting and included as part of global regulatory submissions in 2023.

"We are very encouraged by the results of the complement-inhibitor-naïve data from the Phase III APPOINT-PNH trial," said David Soergel, M.D., Global Head, Cardiovascular, Renal and Metabolism Development Unit, Novartis. "This second iptacopan readout for PNH underscores the robust potential for this therapy, enabling us to submit a broad regulatory package with the goal of iptacopan potentially becoming the first oral monotherapy for PNH."

Topline results for the pivotal Phase III APPLY-PNH study were recently announced⁸. It met its two primary endpoints, with iptacopan demonstrating superiority over anti-C5 therapies (eculizumab or ravulizumab) in adults with PNH experiencing residual anemia despite prior anti-C5 treatment⁸. The study showed a statistically significant and clinically meaningful increase in the proportion of iptacopan-treated patients achieving 2 g/dL or more hemoglobin-level increases from baseline, and 12 g/dL or more hemoglobin levels, both without the need for blood transfusions at 24 weeks, compared to anti-C5 therapies⁸.

Novartis is grateful to the patients and clinical investigators whose time, trust and commitment made this PNH research possible, and is excited to continue to explore the potential of iptacopan as the first oral monotherapy

option for patients with PNH.

Iptacopan is also being investigated in Phase III studies for the complement-mediated kidney diseases (CMKDs) C3 glomerulopathy (APPEAR-C3G [NCT04817618]), IgA nephropathy (APPLAUSE-IgAN [NCT04578834]), and atypical hemolytic uremic syndrome (APPELHUS [NCT04889430]), as well as in a number of additional indications in Phase II⁹⁻¹¹.

Following presentation of the Phase III APPLY-PNH iptacopan 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.

About the study

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 (e.g., eculizumab or ravulizumab)¹².

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 weeks¹². Secondary endpoints include the proportion of participants achieving sustained hemoglobin levels of 12 g/dL or more in the absence of RBC transfusions, transfusion avoidance defined as the proportion of participants who remain 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 events¹².

About paroxysmal nocturnal hemoglobinuria (PNH)

PNH is a rare, chronic and serious complement-mediated blood disorder². 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^{2,3}. 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^{2,3}.

It is estimated that approx. 10-20 people per million worldwide live with PNH². 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 transfusions²⁻⁵.

About iptacopan

Iptacopan is an investigational first-in-class, orally administered targeted factor B inhibitor of the alternative complement pathway^{6,7,15}. It acts upstream of the C5 terminal pathway, preventing not only intravascular but also extravascular hemolysis in PNH^{6,7,15}. In doing so, iptacopan targets a key part of the biology responsible for PNH while offering an oral monotherapy option^{6,7,15}

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 C3G, IgAN, atypical hemolytic uremic syndrome (aHUS), membranous nephropathy (MN), lupus nephritis (LN), and blood disorders immune thrombocytopenic purpura (ITP) and cold agglutinin disease (CAD).

Based on disease prevalence, unmet need 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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About Novartis

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