Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

https://www.novartis.com
https://twitter.com/novartisnews

MEDIA & INVESTOR RELEASE

Novartis Fabhalta® (iptacopan) receives positive CHMP opinion as first oral monotherapy for adult patients with paroxysmal nocturnal hemoglobinuria (PNH)

- *Positive CHMP opinion based on robust Phase III data, including APPLY-PNH, demonstrating superior hemoglobin improvement in the absence of transfusions with Fabhalta compared to anti-C5 therapy*[1-5]
- *If approved, Fabhalta® will be the first oral monotherapy available in Europe for the treatment of PNH, a chronic and rare blood disorder, in both complement inhibitor-treated and -naive PNH patients with hemolytic anemia*[1]
- *Despite anti-C5 therapy, a large proportion of patients remain anemic, fatigued and dependent on blood transfusions*[6,7]
- *Late-stage Fabhalta development program is ongoing in multiple complement-mediated diseases*

Basel, March 22, 2024 – Novartis announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion and recommended granting a marketing authorization for Fabhalta® (iptacopan) for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH) who have hemolytic anemia[1].

“With a robust body of evidence and a demonstrated safety profile, Fabhalta could be practice-changing for patients, helping relieve burdens experienced by people living with PNH,” said 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. “In clinical studies, oral iptacopan demonstrated superior hemoglobin improvement without the need for red blood cell transfusions compared to anti-C5 therapies, leading to normalization of hemoglobin in the majority of patients—a potentially groundbreaking benefit for those living with this chronic blood disorder.”

PNH is a rare and debilitating chronic blood disorder that occurs when blood cells which are intrinsically susceptible to a part of the immune system called the complement system expand over normal blood cells due to a permissive immune environment[8-11]. PNH is characterized by hemolysis, bone marrow failure, and thrombosis in varying combinations and levels of severity[6,7,12]. Current anti-C5 treatments are administered via infusion or subcutaneous injection and may leave PNH symptoms uncontrolled. Up to 50% of patients on anti-C5 treatment may have persistent anemia with 23-39% remaining dependent on blood transfusions, and the majority (75-89%) of patients on anti-C5 treatment remain fatigued[7,13-17].

The positive CHMP decision is based on robust data from the Phase III APPLY-PNH study in patients with residual anemia despite prior anti-C5 treatment who switched to Fabhalta vs. patients who stayed on anti-C5 treatment, and the Phase III APPOINT-PNH study in complement-inhibitor naïve patients[1]. In APPLY-PNH, at 24 weeks, 82.3% of anti-C5-experienced Fabhalta patients achieved a sustained increase of Hb levels ≥2 g/dL from baseline in the absence of transfusions vs. 2.0% for anti-C5 (difference of 80.2%, P<0.0001); in APPOINT-PNH, 92.2% of complement inhibitor-naïve patients using Fabhalta achieved this outcome[2,3]. Similarly, in APPLY-PNH, results highlighted a transfusion avoidance rate of 94.8% for anti-C5-experienced Fabhalta patients vs. 25.9% for those on anti-C5 (difference of 68.9%, P<0.0001)[18]. In both studies, Fabhalta was also shown to control the destruction of red blood cells (RBCs) within the blood vessels, known as intravascular hemolysis (IVH), with mean lactate dehydrogenase (LDH) levels maintained at <1.5 x upper limit of normal[2,3,19]. In APPLY-PNH, patients reported improvements in fatigue as measured by Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-F] scores[2,19]. The safety profile of iptacopan was consistent across both APPLY-PNH and APPOINT-PNH studies[2,3].

“If approved by the European Commission, Fabhalta would be the first oral monotherapy available to PNH patients in Europe,” said Patrick Horber M.D., President, International, Novartis, Basel. “With current standard of care, PNH symptoms are often uncontrolled, while patients endure regular and time-consuming infusions. This oral therapy could provide a much-needed alternative to support many people living with PNH who often have to structure their lives around managing their condition.’’

Following the CHMP’s recommendation to approve Fabhalta in adult patients with PNH who have hemolytic anemia, the European Commission (EC) will take a final decision within approximately two months.

About APPLY-PNH
APPLY-PNH (NCT04558918) was a Phase III, randomized, multinational, multicenter, active-comparator controlled, open-label trial to evaluate the efficacy and safety of twice-daily, oral Fabhalta monotherapy (200 mg) for the treatment of PNH by assessing if switching to Fabhalta was superior to continuing on anti-C5 therapies 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 [2,20]. The trial enrolled 97 patients who were randomized in an 8:5 ratio to either twice-daily, oral Fabhalta monotherapy, or intravenous anti-C5 therapies (continuing with the same regimen as they were on prior to randomization)[2,20].

About APPOINT-PNH
APPOINT-PNH (NCT04820530) was a Phase III, multinational, multicenter, open-label, uncontrolled single-arm study to evaluate the efficacy and safety of twice-daily, oral Fabhalta monotherapy (200 mg) in adult PNH patients who are naïve to complement inhibitor therapy, including anti-C5 therapies (eculizumab or ravulizumab)[3,21]. The trial enrolled 40 patients who received twice-daily, oral Fabhalta monotherapy[3,21].

About paroxysmal nocturnal hemoglobinuria (PNH)
PNH is a rare, chronic and serious complement-mediated blood disorder[12]. 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[7,12]. 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[7,12].

It is estimated that approximately 10-20 people per million worldwide live with PNH[7]. Although PNH can develop at any age, it is often diagnosed in people between 30-40 years old[8,21,22].

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, and some dependent on blood transfusions[6,7,13-17].

About Fabhalta® (iptacopan)
Fabhalta (iptacopan) is an oral, Factor B inhibitor of the alternative complement pathway[1]. Fabhalta was approved by the US Food and Drug Administration (FDA) in December 2023 for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

Discovered at Novartis, Fabhalta is currently in development for a range of other complement-mediated diseases including immunoglobulin A nephropathy (IgAN), C3 glomerulopathy (C3G), immune complex membranoproliferative glomerulonephritis (IC-MPGN) and atypical hemolytic uremic syndrome (aHUS).

Disclaimer
This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis
Novartis is an innovative medicines company. Every day, we work to reimagine medicine to improve and extend people’s lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach more than 250 million people worldwide.

Reimagine medicine with us: Visit us at **https://www.novartis.com** and connect with us on **LinkedIn**, **Facebook**, **X/Twitter** and **Instagram**.

References

1. Committee for Medicinal Products for Human Use (CHMP). Available at https://www.ema.europa.eu/en/committees/committee-medicinal-products-human-use-chmp . Accessed March 2024.
2. Ristanio AM, Röth A, Kulasekararaj A, et al. Oral Iptacopan Monotherapy Has Superior Efficacy to Anti-C5 Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria and Residual Anemia. Results from the Phase III APPLY-PNH Study. Presented at 49th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT); April 23-26, 2023; Paris, France.

3. Risitano AM, Han B, Ueda Y, et al. Oral Complement Factor B Inhibitor Iptacopan Monotherapy Improves Hemoglobin to Normal/Near-Normal Levels in Paroxysmal Nocturnal Hemoglobinuria Patients Naïve to Complement Inhibitors: Phase III APPOINT-PNH Trial. Presented at: 49th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT); April 23-36, 2023; Paris, France.
4. Risitano AM, Röth A, Soret J, et al. Addition of iptacopan, an oral factor B inhibitor, to eculizumab in patients with paroxysmal nocturnal haemoglobinuria and active haemolysis: an open-label, single-arm, phase 2, proof-of-concept trial. Lancet Haematol. 2021;8(5):e344-e354. doi:10.1016/S2352-3026(21)00028-4
5. Jang JH, Wong L, Ko BS, et al. Iptacopan monotherapy in patients with paroxysmal nocturnal hemoglobinuria: a 2-cohort open-label proof-of-concept study. Blood Adv. 2022;6(15):4450-4460. doi:10.1182/bloodadvances.2022006960
6. McKinley CE, Richards SJ, Munir T, et al. Extravascular Hemolysis Due to C3-Loading in Patients with PNH Treated with Eculizumab: Defining the Clinical Syndrome. Blood. 2017;130(Supplement 1):3471. doi:10.1182/blood.V130.Suppl_1.3471.3471
7. Dingli D, Matos JE, Lehrhaupt K, et al. The burden of illness in patients with paroxysmal nocturnal hemoglobinuria receiving treatment with the C5-inhibitors eculizumab or ravulizumab: results from a US patient survey. Ann Hematol. 2022;101(2):251-263. doi:10.1007/s00277-021-04715-5
8. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria Nat Rev Dis Primers. 2017;3:17028. doi:10.1038/nrdp.2017.28
9. Shah N, Bhatt H. Paroxysmal Nocturnal Hemoglobinuria. In: StatPearls.Treasure Island (FL): StatPearls Publishing; 2023 Jan.
10. Brodsky RA. Paroxysmal Nocturnal Hemoglobinuria. Blood. 2014;124(18):2804-2811. doi:10.1182/blood-2014-02-522128
11. Schrezenmeier H, Muus P, Socié G, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Haematologica. 2014;99(5):922-929. doi:10.3324/haematol.2013.093161
12. Cançado RD, Araújo A da S, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematol Transfus Cell Ther. 2021;43(3):341-348. doi:10.1016/j.htct.2020.06.006
13. Risitano AM, Marotta S, Ricci P, et al. Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper From the SAAWP of the EBMT. Front Immunol 2019;10:1157. doi:10.3389/fimmu.2019.01157
14. Shammo et al. HemaSphere 2023 Shammo J, Kim J, Georget M, et al. P796: Hospitalization in patients with paroxysmal nocturnal hemoglobinuria: a retrospective analysis of observational study data from the United States. Hemasphere. 2023;7(Suppl):e22585a2. doi:10.1097/01.HS9.0000970088.22585.a2
15. Debureaux PE, Kulasekararaj AG, Cacace F, et al. Categorizing hematological response to eculizumab in paroxysmal nocturnal hemoglobinuria: a multicenter real-life study. Bone Marrow Transplant. 2021;56(10):2600-2602. doi:10.1038/s41409-021-01372-0
16. Schrezenmeier H, Kulasekararaj A, Mitchell L, et al. One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study. Ther Adv Hematol. 2020;11:2040620720966137. doi:10.1177/2040620720966137
17. Young NS, Meyers G, Schrezenmeier H, Hillmen P, Hill A. The management of paroxysmal nocturnal hemoglobinuria: recent advances in diagnosis and treatment and new hope for patients. Semin Hematol. 2009;46(1 Suppl 1):S1-S16. doi:10.1053/j.seminhematol.2008.11.004
18. Novartis. Data on file
19. Risitano AM, Kulasekararaj A, Röth A, et al. Factor B Inhibition with Oral Iptacopan Monotherapy Demonstrates Sustained Long-Term Efficacy and Safety in Anti-C5-Treated Patients (pts) with Paroxysmal Nocturnal Hemoglobinuria (PNH) and Persistent Anemia: Final 48-Week Results from the Multicenter, Phase III APPLY-PNH Trial. Presented at: 65th American Society of Hematology Annual Meeting & Exposition (ASH); December 9-12, 2023; San Diego, CA.
20. Novartis Pharmaceuticals. A Randomized, Multicenter, Active-Comparator Controlled, Open-Label Trial to Evaluate Efficacy and Safety of Oral, Twice Daily LNP023 in Adult Patients With PNH and Residual Anemia, Despite Treatment With an Intravenous Anti-C5 Antibody. clinicaltrials.gov. Accessed February 14, 2024. https://clinicaltrials.gov/ct2/show/NCT04558918
21. Novartis Pharmaceuticals. A Multicenter, Single-Arm, Open-Label Trial to Evaluate Efficacy and Safety of Oral, Twice Daily Iptacopan in Adult PNH Patients Who Are Naive to Complement Inhibitor Therapy. clinicaltrials.gov. Accessed February 14, 2024. https://clinicaltrials.gov/ct2/show/NCT04820530
22. Schrezenmeier H, Röth A, Araten DJ, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. Ann Hematol. 2020;99(7):1505-1514. doi:10.1007/s00277-020-04052-z

# # #

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	Marlena Abdinoor	+1 617 335 9525

Switzerland
Satoshi Sugimoto +41 79 619 2035

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail:

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 345 4440
Isabella Zinck	+41 61 324 7188	Jonathan Graham	+1 201 602 9921
Nicole Zinsli-Somm	+41 61 324 3809	Parag Mahanti	+1 973 876 4912
Imke Kappes	+41 61 324 8269		