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MEDIA & INVESTOR RELEASE

Novartis receives FDA approval for Fabhalta® (iptacopan), offering superior hemoglobin improvement in the absence of transfusions as the first oral monotherapy for adults with PNH

Ad hoc announcement pursuant to Art. 53 LR

- *Approval based on APPLY-PNH trial in adults with PNH and anemia despite prior anti-C5 treatment, and supported by the APPOINT-PNH study in complement inhibitor-naïve patients*[1-5]
- *In APPLY-PNH, patients who switched to Fabhalta experienced superior increases of hemoglobin levels ≥ 2 g/dL (82.3% vs. 0%) and hemoglobin level ≥ 12 g/dL (67.7% vs. 0%), both in the absence of red blood cell transfusions, vs. patients who continued on anti-C5 treatment*[1,2]
- *Fabhalta, now available for both previously treated and treatment-naïve patients, is the only FDA-approved Factor B inhibitor of the immune system's complement pathway, which drives complement-mediated hemolysis in PNH*[1,6]
- *Significant unmet need remains in PNH, a chronic and rare blood disorder; despite anti-C5 therapy, a large proportion of patients can remain anemic and dependent on blood transfusions*[7,8]
- *Late-stage Fabhalta development program ongoing in multiple complement-mediated conditions*

Basel, December 6, 2023 — Novartis today announced that the U.S. Food and Drug Administration (FDA) approved Fabhalta® (iptacopan) as the first oral monotherapy for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH)[1]. Fabhalta is a Factor B inhibitor that acts proximally in the alternative complement pathway of the immune system, providing comprehensive control of red blood cell (RBC) destruction within and outside the blood vessels (intra- and extravascular hemolysis [IVH and EVH]). In clinical trials, treatment with Fabhalta increased hemoglobin levels (≥ 2 g/dL from baseline in the absence of RBC transfusions) in the majority of patients and in APPLY-PNH nearly all patients treated with Fabhalta did not receive blood transfusions[1-5].

"An efficacious oral treatment with a demonstrated safety profile could be practice-changing for physicians and help relieve burdens experienced by people with PNH," said Vinod

Pullarkat, MD, MRCP, Clinical Professor, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope. “In clinical studies, iptacopan was superior to anti-C5s in hemoglobin improvement in the absence of RBC transfusion and transfusion avoidance rate, and also effective in complement inhibitor-naïve individuals, by providing clinically meaningful hemoglobin-level increases without the need for blood transfusions.”

The FDA approval is based on the Phase III APPLY-PNH trial in patients with residual anemia (hemoglobin < 10 g/dL) despite prior anti-C5 treatment who switched to Fabhalta, which demonstrated superiority in hemoglobin improvement in the absence of RBC transfusions and in transfusion avoidance rate over patients who stayed on anti-C5 treatments[1,2]. Approval was also supported by the Phase III APPOINT-PNH study in complement inhibitor-naïve patients[1,3]. The 24-week core treatment periods in APPLY-PNH and APPOINT-PNH trials respectively showed[1-3]:

- **Patients with sustained increase of hemoglobin levels ≥ 2 g/dL[a] from baseline in the absence of transfusions:** 82.3% of anti-C5-experienced Fabhalta patients responded vs. 0% for anti-C5 (difference of 81.5%[b], P<0.0001); 77.5% of complement inhibitor-naïve patients using Fabhalta achieved this outcome (sensitivity analysis showed 87.5%[c])[1-3].
- **Patients with sustained hemoglobin level ≥ 12 g/dL[a] in the absence of transfusions:** 67.7% of anti-C5-experienced Fabhalta patients responded vs. 0% for anti-C5 (difference of 66.6%[b], P<0.0001)[1,2].
- **Patients avoiding transfusion[d,e]:** Transfusion avoidance rate 95.2% for anti-C5-experienced Fabhalta patients vs. 45.7% for anti-C5 (difference of 49.5%[b], P<0.0001)[1,2].

In the APPLY-PNH trial, the most commonly reported (≥10%) adverse reactions (ARs) with Fabhalta vs. anti-C5s were: headache[f] (19% vs. 3%), nasopharyngitis[g] (16% vs. 17%), diarrhea (15% vs. 6%), abdominal pain[f] (15% vs. 3%), bacterial infection[h] (11% vs. 11%), nausea (10% vs. 3%), and viral infection[i] (10% vs. 31%)[1,2]. In the APPOINT-PNH trial, the most commonly reported ARs (≥10%) were headache[f] (28%), viral infection[i] (18%), nasopharyngitis[g] (15%), and rash[j] (10%)[1,3]. In APPLY-PNH, serious ARs were reported in two (3%) patients with PNH receiving Fabhalta, which included pyelonephritis, urinary tract infection and COVID-19[1,2]. In APPOINT-PNH, serious ARs were reported in two (5%) patients with PNH receiving Fabhalta, which included COVID-19 and bacterial pneumonia[1,3]. Fabhalta may cause serious infections caused by encapsulated bacteria and is available only through a Risk Evaluation and Mitigation Strategy (REMS) that requires vaccinations for encapsulated bacteria[1].

People with PNH have an acquired mutation making red blood cells susceptible to premature destruction by the complement system[6,8]. PNH is characterized by hemolysis, bone marrow failure, and thrombosis in varying combinations and levels of severity[6-8]. Existing C5 inhibitor treatments, administered as infusions, may leave PNH symptoms uncontrolled[7,8]. Up to 88% of patients on anti-C5 treatment may have persistent anemia with over one-third of those patients requiring blood transfusions at least once per year[7,8].

“The U.S. approval of Fabhalta is an extraordinary moment for people living with PNH, their loved ones and the healthcare providers who care for them,” said Victor Bultó, President US, Novartis. “This new, effective oral medicine may mean that patients can reset their expectations of living with PNH, a chronic and life-altering blood disease. As Novartis continues to focus on conditions with unmet patient need, we are exploring the potential of Fabhalta in other complement-mediated diseases – with an ultimate goal to drive meaningful change for patients.”

Discovered and developed by Novartis, Fabhalta is expected to be available in the United States in December. Additional regulatory filings and reviews for Fabhalta in PNH are currently underway around the world.

[a]Assessed between Day 126 and Day 168. [b]Adjusted difference in proportion. [c]Sensitivity analysis incorporates data from local labs when central labs were not available. [d]Assessed between Day 14 and Day 168. [e]Transfusion avoidance is defined as absence of administration of packed-red blood cell transfusions between Day 14 and Day 168. [f]Includes similar terms. [g]Nasopharyngitis contains: rhinitis allergic, upper respiratory tract infection, pharyngitis, rhinitis. [h]Bacterial infection contains: pyelonephritis, urinary tract infection, bronchitis bacterial, bronchitis haemophilus, cholecystitis, folliculitis, cellulitis, arthritis bacterial, sepsis, klebsiella infection, staphylococcal infection, Pseudomonas infection, hordeolum, pneumonia bacterial. [i]Viral infection contains: COVID-19, herpes zoster, oral herpes, nasal herpes, influenza A virus test positive, influenza. [j]Rash: dermatitis allergic, acne, erythema multiforme, rash maculo-papular, rash erythematous.

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 (US-approved and non-US-approved eculizumab and 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[2,9]. 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)[2,9].

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)[3,10]. The trial enrolled 40 patients who received twice-daily, oral Fabhalta monotherapy[3,10].

About paroxysmal nocturnal hemoglobinuria (PNH)
PNH is a rare, chronic and serious complement-mediated blood disorder[6]. 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[6,8]. 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) and other debilitating symptoms[6,8].

It is estimated that approximately 10-20 people per million worldwide live with PNH[6]. Although PNH can develop at any age, it is often diagnosed in people between 30-40 years old[11,12].

PNH has a significant unmet need not fully addressed by anti-C5 therapies (eculizumab or ravulizumab): despite treatment with anti-C5s, a large proportion of people with PNH may remain anemic, and dependent on blood transfusions[6-8,13,14].

About Fabhalta® (iptacopan)
Fabhalta (iptacopan) is an oral, Factor B inhibitor of the alternative complement pathway[15-17]. Fabhalta is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

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

Based on disease prevalence, unmet needs and data from Phase II studies, Fabhalta has received FDA Breakthrough Therapy Designation in PNH, FDA Breakthrough Therapy

Designation in C3G, orphan drug designations from the FDA and EMA in PNH and C3G, EMA PRIME designation for C3G, and EMA orphan drug designation in IgAN[18-21].

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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,” “expectations,” “investigational,” “drives,” “remains,” “ongoing,” “exploring,” “goal,” “expected,” “estimated,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for FABHALTA (iptacopan), or regarding potential future revenues from FABHALTA (iptacopan). 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 FABHALTA (iptacopan) 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 FABHALTA (iptacopan)will be commercially successful in the future. In particular, our expectations regarding FABHALTA (iptacopan) 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.**

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