NOVARTIS

1 Tradename

FABHALTA™ (iptacopan) 200 mg hard capsules

2 Description and composition

Pharmaceutical form(s)

200 mg hard capsules: pale yellow opaque, imprinted with “LNP200” on the body and “NVR” on the cap, containing white or almost white to pale purplish-pink powder.

Active substance(s)

Each capsule contains 200 mg iptacopan (as 225.8 mg iptacopan hydrochloride monohydrate).

Excipients

Capsule fill: None

Capsule shell: Hard gelatin, red iron oxide (E 172), titanium dioxide (E 171), and yellow iron oxide (E 172).

Printing ink: Black iron oxide (E 172), concentrated ammonia solution (E 527), propylene glycol (E 1520), potassium hydroxide (E 525), and shellac (E 904).

3 Indications

Fabhalta is indicated as monotherapy for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have haemolytic anaemia.

4 Dosage regimen and administration

Dosage regimen

The recommended dose is 200 mg taken orally twice daily.

If a dose or doses are missed, the patient should be advised to take one dose of Fabhalta as soon as possible (even if it is soon before the next scheduled dose) and then to resume the regular dosing schedule. Patients with PNH who have missed several consecutive doses should be monitored for potential signs and symptoms of haemolysis.

PNH is a disease that requires chronic treatment. Discontinuation of this medicinal product is not recommended unless clinically indicated (see section 6 Warnings and precautions).

Patients switching from anti-C5 (eculizumab, ravulizumab) to Fabhalta

To reduce the potential risk of hemolysis with abrupt treatment discontinuation:

- For patients switching from eculizumab, Fabhalta should be initiated no later than 1 week after the last dose of eculizumab.
- For patients switching from ravulizumab, Fabhalta should be initiated no later than 6 weeks after the last dose of ravulizumab.

Switches from complement inhibitors other than eculizumab and ravulizumab have not been studied.

Adherence to dosing schedule

Healthcare providers should advise patients with PNH about the importance of adherence to the dosing schedule in order to minimize the risk of hemolysis (see section 6 Warnings and precautions).

Special populations

Renal impairment

No dose adjustment is required in patients with mild (estimated glomerular filtration rate [eGFR] 60- <90 mL/min/1.73 m^2) or moderate (eGFR 30- <60 mL/min/1.73 m^2) renal impairment. No data are currently available in patients with severe renal impairment or on dialysis and no dose recommendations can be given. (see section 11).

Hepatic impairment

No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B). The use of iptacopan is not recommended in patients with severe hepatic impairment (Child-Pugh class C) (see section 11),

Pediatric patients

The safety and efficacy of Fabhalta in patients below the age of 18 years have not been established.

Geriatric patients (65 years of age or above)

No dose adjustment is required for patients aged 65 years and over (see section 11 Clinical Pharmacology).

Method of administration

For oral use. Fabhalta may be taken with or without food (see section 11 Clinical pharmacology).

5 Contraindications

Fabhalta is contraindicated:

- in patients with hypersensitivity to iptacopan or to any of the other excipients.
- in patients who are not currently vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae* unless the risk of delaying Fabhalta treatment outweighs the risk of developing an infection from these encapsulated bacteria (see section 6 Warnings and precautions).
- for initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type B.

6 Warnings and precautions

Co-administration with other medicinal products

Concomitant use of iptacopan with strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3 has not been studied clinically; therefore, concomitant use is not recommended due to the potential for reduced efficacy of iptacopan (see section 8). If an alternative concomitant medicinal product cannot be identified, patients should be monitored for potential signs and symptoms of haemolysis.

Serious infections caused by encapsulated bacteria

The use of complement inhibitors, such as Fabhalta, may predispose individuals to serious, life-threatening, or fatal infections caused by encapsulated bacteria. To reduce the risk of infection,

all patients must be vaccinated against encapsulated bacteria, including *Neisseria meningitidis* and *Streptococcus pneumoniae*. It is recommended to vaccinate patients against *Haemophilus influenzae* type B if available. Refer to local vaccination guideline recommendations.

Vaccines should be administered at least 2 weeks prior to administration of the first dose of Fabhalta. If Fabhalta must be initiated prior to vaccination, patients should be vaccinated as soon as possible and provided with antibacterial drug prophylaxis until 2 weeks after vaccine administration.

If necessary, patients may be revaccinated in accordance with local vaccination guideline recommendations.

Vaccination reduces, but does not eliminate, the risk of serious infection. Serious infection may rapidly become life-threatening or fatal if not recognized and treated early. Patients should be informed of and monitored for early signs and symptoms of serious infection. Patients should be immediately evaluated and treated if infection is suspected. The use of Fabhalta during treatment of serious infection may be considered following an assessment of the risks and benefits (see section 7 Adverse drug reactions).

Monitoring of PNH manifestations after discontinuation of Fabhalta

If treatment with Fabhalta must be discontinued, patients should be closely monitored for signs and symptoms of hemolysis for at least 2 weeks after the last dose. These signs include elevated lactate dehydrogenase (LDH) levels along with sudden decrease in hemoglobin or PNH clone size, fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction. If discontinuation of Fabhalta is necessary, consider alternative therapy.

If hemolysis occurs after discontinuation of Fabhalta, restarting Fabhalta treatment should be considered.

7 Adverse drug reactions

Summary of the safety profile

The safety profile of Fabhalta is based on analysis of pooled safety data from 164 patients with PNH treated with Fabhalta 200 mg twice daily across multiple studies. The median duration of Fabhalta exposure was 10.2 months. The most commonly reported adverse reactions in patients treated with Fabhalta were upper respiratory tract infection (18.9%), headache (18.3%) and diarrhea (11.0%).

Adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions from clinical trials in patients with PNH

MedDRA System Organ Class	Adverse reactions	Pool of PNH studies N=164 n (%)	Frequency category
Blood and lymphatic system disorders	Platelet count decreased[1]	12 (7.3)	Common
	Diarrhoea	18 (11.0)	Very Common

MedDRA System Organ Class	Adverse reactions	Pool of PNH studies N=164 n (%)	Frequency category
Gastrointestinal disorders	Abdominal pain[2]	16 (9.8)	Common
	Nausea	12 (7.3)	Common
Infections and infestations	Upper respiratory tract infection[3]	31 (18.9)	Very Common
	Pneumonia bacterial	1 (0.6)	Uncommon
	Urinary tract infection[4]	8 (4.9)	Common
	Bronchitis[5]	4 (2.4)	Common
Musculoskeletal and connective tissue disorders	Arthralgia	9 (5.5)	Common
Nervous system disorders	Headache[6]	30 (18.3)	Very Common
	Dizziness	5 (3.0)	Common
Skin and subcutaneous tissue disorders	Urticaria	1 (0.6)	Uncommon

[1]Platelet count decreased includes preferred terms of thrombocytopenia and platelet count decreased.

[2]Abdominal pain includes preferred terms of abdominal pain, abdominal pain upper, abdominal tenderness and abdominal discomfort.

[3]Upper respiratory tract infection includes preferred terms of influenza, nasopharyngitis, pharyngitis, rhinitis, sinusitis and upper respiratory tract infection.

[4]Urinary tract infection includes preferred terms urinary tract infection and cystitis escherichia.

[5]Bronchitis includes preferred terms bronchitis, bronchitis haemophilus and bronchitis bacterial.

[6]Headache includes preferred terms headache and head discomfort.

Description of select adverse drug reactions

Platelet count decreased

Decreases in platelet counts were generally mild and transient. Some patients with pre-existing thrombocytopenia had further decreases to Grade 3 or 4 (based on CTCAE version 4.03).

Infections

In PNH clinical studies, including Phase 2 and Phase 3 studies, 1 out of 164 PNH patients reported serious bacterial pneumonia while receiving treatment with Fabhalta. The patient had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B and recovered following treatment with antibiotics while continuing treatment with Fabhalta.

Laboratory and vital signs

Blood cholesterol and blood pressure increased

In patients treated with iptacopan 200 mg twice a day in PNH clinical studies, mean increases from baseline of approximately 28 mg/dL were seen at month 6 for both total cholesterol and LDL-cholesterol. The mean values remained within the normal ranges. Increases in blood pressure, particularly diastolic blood pressure (DBP), were observed (mean increase 4.7 mmHg at month 6). The mean DBP did not exceed 80 mmHg. Total cholesterol, LDL-cholesterol and DBP increases correlated with increases in hemoglobin (improvement in anemia) in patients with PNH (see section 12 Clinical studies). The clinical relevance of such findings should be assessed based on individual patient characteristics and the patient should be managed accordingly.

8 Interactions

Effects of other medicinal products on iptacopan

Strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3

Although concomitant administration of iptacopan with strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3, such as rifampicin, has not been studied clinically, concomitant use with iptacopan is not recommended due to the potential for reduced efficacy of iptacopan.

Effects of iptacopan on other medicinal products

CYP3A4 substrates

In vitro data showed iptacopan has potential for induction of CYP3A4 and may decrease the exposure of sensitive CYP3A4 substrates. The concomitant use of iptacopan and sensitive CYP3A4 substrates has not been studied clinically. Caution should be exercised if co-administration of iptacopan with sensitive CYP3A4 substrates is required, especially for those with a narrow therapeutic index (e.g. carbamazepine, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

CYP2C8 substrates

In vitro data showed iptacopan has potential for time-dependent inhibition of CYP2C8 and may increase the exposure of sensitive CYP2C8 substrates, such as repaglinide, dasabuvir or paclitaxel.

The concomitant use of iptacopan and sensitive CYP2C8 substrates has not been studied clinically. Caution should be exercised if co-administration of iptacopan with sensitive CYP2C8 substrates is required.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

There are no or limited amount of data from the use of iptacopan in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures between 2- and 8-fold the human exposure at the maximum recommended human dose (MRHD) (see section 13).

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, as well as adverse foetal outcomes, including foetal death and premature delivery.

The use of iptacopan in pregnant women or women planning to become pregnant may only be considered following a careful assessment of the risk and benefits, if necessary.

9.2 Lactation

It is not known if iptacopan is transferred into human milk after oral administration of Fabhalta. There are no data on the effects of Fabhalta on the breast-fed child or on milk production.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Fabhalta and any potential adverse effects (e.g., serious infections from encapsulated bacteria) on the breast-fed child from Fabhalta or from the underlying maternal condition.

9.3 Females and males of reproductive potential

Infertility

There are no data on the effect of Fabhalta on human fertility. In oral dose animal fertility studies, iptacopan did not impact fertility in male rats up to the highest dose tested (750 mg/kg/day), which corresponds to 6-fold the MRHD based on AUC. Reversible effects on

the male reproductive system (testicular tubular degeneration and hypospermatogenesis) were observed in repeated dose toxicity studies after oral administration in rats and dogs at doses >3-fold the MRHD based on AUC, with no apparent effects on sperm numbers, morphology or motility, or fertility.

In the female fertility and early embryonic developmental study in rats, iptacopan related findings were limited to increased pre- and post-implantation losses and, consequently, decreased numbers of live embryos only at the highest dose of 1,000 mg/kg/day orally, which corresponds to ~5-fold the MRHD based on AUC. The dose of 300 mg/kg/day is the no-observed-adverse-effect-level (NOAEL) which corresponds to ~2-fold the MRHD based on AUC.

10 Overdosage

Limited data are available with regard to overdose in humans. During clinical studies, a few patients took up to 800 mg Fabhalta daily and this was well tolerated. In healthy volunteers, the highest dose was 1,200 mg administered as a single dose and this was well tolerated.

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Complement inhibitors, ATC code: L04AJ08.

Mechanism of action (MOA)

Iptacopan is a proximal complement inhibitor that targets Factor B (FB) to selectively inhibit the alternative pathway while leaving the direct signaling from the lectin and classical pathways intact. Inhibition of FB prevents the activity of alternative pathway related C3 convertase and the subsequent formation of C5 convertase.

In PNH, intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC), while extravascular hemolysis (EVH) is facilitated by opsonization with C3 fragments. Iptacopan acts proximally in the alternative pathway of the complement cascade to control both C3-mediated EVH and terminal complement-mediated IVH.

Pharmacodynamics (PD)

The onset of inhibition of the alternative complement pathway biomarkers, *ex vivo* alternative pathway assay and plasma Bb (fragment Bb of FB), was ≤2 hours after a single iptacopan dose in healthy volunteers.

Iptacopan reduces serum LDH levels. In PNH patients previously treated with eculizumab, all patients treated with iptacopan 200 mg twice daily achieved a reduction of LDH levels to <1.5 times upper limit of normal (ULN) after 13 weeks and maintained the effect through the end of the study. In treatment-naïve PNH patients, iptacopan 200 mg twice daily reduced LDH by >60% compared to baseline after 12 weeks and maintained the effect through the end of the study.

Cardiac electrophysiology

In a QTc clinical study in healthy volunteers, single supra-therapeutic iptacopan doses up to 1200 mg (which provided greater than 4-fold peak concentration of the MRHD) showed no effect on cardiac repolarization or QT interval.

Pharmacokinetics (PK)

Absorption

Following oral administration, iptacopan reached peak plasma concentrations approximately 2 hours post dose. At the recommended dosing regimen of 200 mg twice daily, steady-state is achieved in approximately 5 days with minor accumulation (1.4-fold). The C_{max} and AUC data from a food-effect study involving administration of iptacopan to healthy volunteers under fasting conditions or with a high-fat meal indicated that exposure to iptacopan is not affected by food. Therefore, Fabhalta may be taken with or without food.

Distribution

Iptacopan showed concentration-dependent plasma protein binding due to binding to the target FB in the systemic circulation. Iptacopan was 75% to 93% protein bound *in vitro* at the relevant clinical plasma concentrations. After administration of iptacopan 200 mg twice daily, the apparent volume of distribution at steady state was approximately 288 L.

Biotransformation/metabolism

Metabolism is a predominant elimination pathway for iptacopan with approximately 50% of the dose attributed to oxidative pathways. Metabolism of iptacopan includes N-dealkylation, O-deethylation, oxidation, and dehydrogenation, mostly driven by CYP2C8 (98%) with a small contribution from CYP2D6 (2%). Glucuronidation (UGT1A1, UGT1A3, UGT1A8) is a minor pathway. In plasma, iptacopan was the major component accounting for 83% of the $AUC_{0\text{-}48hr}$. Two acyl glucuronides were the only metabolites detected in plasma and were minor, accounting for 8% and 5% of the $AUC_{0\text{-}48hr}$. Iptacopan metabolites are not considered pharmacologically active.

Elimination

In a human study, following a single 100 mg oral dose of [^{14}C] iptacopan, mean total excretion of radioactivity (iptacopan and metabolites) was 71.5% in the feces and 24.8% in the urine giving total mean excretion of >96% of the dose. Specifically, 17.9% of the dose was excreted as parent iptacopan into the urine and 16.8% in feces. The half-life ($t_{1/2}$) of iptacopan at steady state is approximately 25 hours after administration of Fabhalta 200 mg twice daily.

Linearity/non-linearity

At doses between of 25 mg and 200 mg twice daily, iptacopan was overall under dose proportional. However, oral doses of 100 mg and 200 mg were approximately dose proportional.

Special populations

A population pharmacokinetic (PK) analysis was conducted on data from 234 patients. Age, body weight, eGFR, race and gender did not significantly influence iptacopan PK. Studies that included Asian subjects showed that the PK of iptacopan were similar to Caucasian (white) subjects.

Renal impairment

Only 17.9% of iptacopan was excreted in the urine as parent drug. Kidney is therefore a minor route of elimination. The effect of renal impairment on the clearance of iptacopan was assessed using a population pharmacokinetic analysis. There were no clinically relevant differences in the clearance of iptacopan between patients with normal renal function and patients with mild (eGFR 60- <90 mL/min/1.73m^2) or moderate (eGFR 30- <60 mL/min/1.73m^2) renal impairment, and no dose adjustment is required (see section 4 Dosage regimen and administration). Patients with severe renal impairment or on dialysis have not been studied.

Hepatic impairment

Based on a study in subjects with mild (Child-Pugh A, n=8), moderate (Child-Pugh B, n=8) or severe (Child-Pugh C, n=6) hepatic impairment, a negligible effect on the total systemic exposure of iptacopan was observed compared to subjects with normal hepatic function. Unbound iptacopan Cmax increased 1.4-, 1.7- and 2.1-fold, and unbound iptacopan AUCinf increased by 1.5-, 1.6- and 3.7-fold in subjects with mild, moderate and severe hepatic impairment, respectively.

Drug Interactions

A dedicated drug interaction study in which iptacopan was co-administered with other drugs was conducted in healthy volunteers and did not demonstrate any clinically relevant interactions:

- When co-administered with clopidogrel (a moderate CYP2C8 inhibitor), iptacopan C_{max} and AUC increased by 5% and 36%, respectively. [11]
- When co-administered with cyclosporine (a strong OATP 1B1/1B3 inhibitor), iptacopan C_{max} and AUC increased by 41% and 50%, respectively.
- In the presence of iptacopan, the C_{max} of digoxin (a PgP substrate) increased by 8% while its AUC was unchanged.
- In the presence of iptacopan, the C_{max} and AUC of rosuvastatin (an OATP substrate) remained unchanged.

12 Clinical studies

The efficacy and safety of Fabhalta in adult patients with PNH were evaluated in two multi-center, open-label, 24-week Phase 3 studies: an active comparator-controlled study (APPLY-PNH; NCT04558918) and a single arm study (APPOINT-PNH; NCT04820530).

APPLY-PNH: anti-C5 treatment experienced patients with PNH

APPLY-PNH enrolled adult PNH patients with residual anemia (hemoglobin <10 g/dL) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization.

Ninety-seven patients were randomized in 8:5 ratio either to receive Fabhalta 200 mg orally twice daily (n=62) or to continue anti-C5 treatment (eculizumab n=23 or ravulizumab n=12) throughout the duration of the 24-week randomized controlled period (RCP). Randomization was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months. Following completion of the 24-week RCP, all patients were eligible to enroll in a 24-week treatment extension period and receive Fabhalta monotherapy. Subsequently, patients were eligible to enter a separate long-term extension study.

Patients were required to be vaccinated against *Neisseria meningitidis* and recommended to be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B. If the patient had not been previously vaccinated or if a booster was required, vaccination was administered at least 2 weeks prior to first dosing. If Fabhalta treatment was initiated earlier than 2 weeks after vaccination, antibacterial drug prophylaxis was administered.

Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 12-1). The mean time on prior anti-C5 treatment was 3.8 and 4.2 years for Fabhalta and anti-C5 groups, respectively. The baseline mean PNH RBC clone size (Type II + III) was 64.6% for Fabhalta and 57.4% for the anti-C5 group. Mean baseline hemoglobin was 8.9 g/dL for both groups, with approximately 57% and 60% of patients requiring a transfusion in the 6 months prior to randomization, in the Fabhalta and anti-C5 groups, respectively. The mean baseline LDH level was 269.1 U/L for Fabhalta and 272.7 U/L

for the anti-C5 group. There were 19.4% and 28.6% of patients with a history of MAVEs in the Fabhalta and anti-C5 groups, respectively.

During the RCP, one patient in the Fabhalta group discontinued treatment due to pregnancy; no patients in the anti-C5 group discontinued.

Table 12-1 Patient Baseline Demographics and Characteristics in APPLY- PNH

Parameters	Statistics	Fabhalta (n=62)	Anti-C5 (n=35)
Age (years)	Mean (SD) min, max	51.7 (16.9) 22, 84	49.8 (16.7) 20, 82
Sex Female	n (%)	43 (69.4)	24 (68.6)
Race Asian black or African American white or Caucasian	n (%) n (%) n (%)	12 (19.4) 2 (3.2) 48 (77.4)	7 (20.0) 2 (5.7) 26 (74.3)
Ethnicity Hispanic or Latino Not Hispanic or Latino Not reported/unknown	n (%) n (%) n (%)	8 (12.9) 51 (82.3) 3 (4.8)	2 (5.7) 27 (77.1) 6 (17.1)
Hemoglobin level (g/dL)	Mean (SD)	8.9 (0.7)	8.9 (0.9)
LDH level (U/L)	Mean (SD)	269.1 (70.1)	272.7 (84.8)
Absolute reticulocyte count (ARC) (10^9/L)	Mean (SD)	193.2 (83.6)	190.6 (80.9)
At least one transfusion in 12 months prior to screening	n (%)	37 (59.7)	22 (62.9)
At least one transfusion in 6 months prior to randomization	n (%)	35 (56.5)	21 (60.0)
Number of transfusions in 6 months prior to randomization among patients who had a transfusion	Mean (SD)	3.1 (2.6)	4.0 (4.3)
History of MAVEs (including thrombosis)	n (%)	12 (19.4)	10 (28.6)
Disease duration (years)	Mean (SD)	11.9 (9.8)	13.5 (10.9)

Abbreviations: LDH, lactate dehydrogenase; MAVEs, major adverse vascular events; SD, standard deviation.

Efficacy was based on two primary endpoints to demonstrate superiority of Fabhalta to anti-C5 in achieving hematological response after 24 weeks of treatment, without a need for transfusion, by assessing the proportion of patients demonstrating: 1) sustained increase of ≥ 2 g/dL in hemoglobin levels from baseline (hemoglobin improvement) and/or 2) sustained hemoglobin levels ≥12 g/dL. Secondary endpoints included transfusion avoidance, change from baseline in hemoglobin levels, change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores, occurrence of clinical breakthrough hemolysis and change from baseline in absolute reticulocyte counts.

Fabhalta was superior to anti-C5 treatment, with a significant difference in response rate of 80.2% (82.3% vs 2%) for hemoglobin improvement (sustained increase of hemoglobin levels ≥ 2 g/dL from baseline) and 67% (68.8% vs 1.8%) for sustained hemoglobin level ≥12 g/dL without a need for RBC transfusion for both primary endpoints, after 24 weeks of treatment ($p<0.0001$) (see Table 12-2).

Overall, more patients achieved hemoglobin improvement in the Fabhalta group (51/60) compared to the anti-C5 group (0/35), and sustained hemoglobin ≥12 g/dL (42/60 in the Fabhalta group compared to 0/35 in the anti-C5 group) without a need for RBC transfusion (see Table 12-2).

Fabhalta was also superior to anti-C5 treatment for transfusion avoidance rate with a treatment difference of 68.9% (94.8% vs 25.9% ($p<0.0001$)) and change from baseline in hemoglobin level (treatment difference of +3.66 g/dL; $p<0.0001$). The treatment effect of Fabhalta on hemoglobin was seen as early as Day 7 and sustained during the study (see Figure 12-1).

Fabhalta was superior to anti-C5 treatment in improving fatigue as assessed by FACIT-Fatigue (treatment difference of +8.29 points; $p < 0.001$), and patients treated with Fabhalta experienced clinically meaningful improvements in patient reported fatigue from baseline (+8.59 points). Fabhalta was also superior to anti-C5 treatment in annualized rate of clinical breakthrough hemolysis (treatment difference of 90%; $p=0.01$) and reduction in absolute reticulocyte count from baseline (treatment difference of -116.2×10^9/L; $p<0.0001$) consistent with the inhibition of EVH.

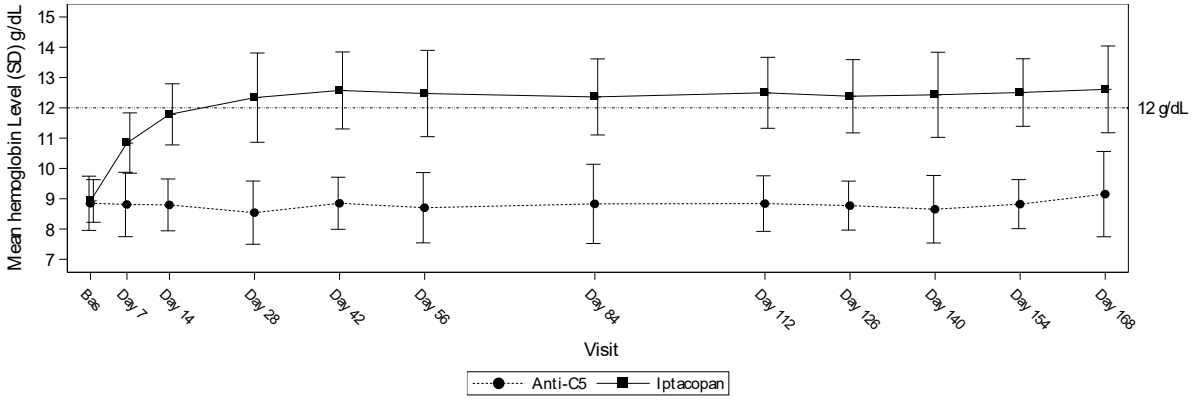
The LDH ratio to baseline was similar for both treatment groups, demonstrating that Fabhalta maintained control of IVH following discontinuation of anti-C5 treatment (see Table 12-2).

Table 12-2 Efficacy results for the 24-week randomized treatment period in APPLY-PNH

Endpoints	Fabhalta (N=62)	Anti-C5 (N=35)	Difference (95% CI) p-value
Primary endpoints			
Number of patients achieving hemoglobin improvement (sustained increase of hemoglobin levels ≥2 g/dL from baseline[a] in the absence of transfusions)	51/60[b]	0/35[b]	
Response rate[c] (%)	82.3	2.0	80.2 (71.2, 87.6) <0.0001
Number of patients achieving sustained hemoglobin level ≥12 g/dL[a] in the absence of transfusions	42/60[b]	0/35[b]	
Response rate[c] (%)	68.8	1.8	67.0 (56.4, 76.9) <0.0001
Secondary endpoints			
Number of patients avoiding transfusion[d,e]	59/62[b]	14/35[b]	
Transfusion avoidance rate[c] (%)	94.8	25.9	68.9 (51.4, 83.9)<0.0001
Hemoglobin level change from baseline (g/dL) (adjusted mean[f])	3.60	-0.06	3.66 (3.20, 4.12) <0.0001
FACIT-Fatigue score change from baseline (adjusted mean[g])	8.59	0.31	8.29 (5.28, 11.29) <0.0001
Clinical breakthrough hemolysis [h,i], % (n/N)	3.2 (2/62)	17.1 (6/35)	
Annualized rate of clinical breakthrough hemolysis	0.07	0.67	RR=0.10 (0.02, 0.61) 0.01
Absolute reticulocyte counts change from baseline (10^9/L) (adjusted mean[g])	-115.8	0.3	-116.2 (-132.0, -100.3) <0.0001
LDH ratio to baseline (adjusted geometric mean[g])	0.96	0.98	Ratio = 0.99 (0.89, 1.10) 0.84
MAVEs[h] % (n/N)	1.6 (1/62)	0	
Annualized rate of MAVEs[h]	0.03	0	0.03 (-0.03, 0.10) 0.32

Abbreviations: RR, rate ratio; LDH, lactate dehydrogenase; MAVEs, major adverse vascular events.
[a] Assessed between Day 126 and 168.
[b] Based on observed data among evaluable patients.
[c] Response rate reflects the adjusted proportion.
[d] Assessed between Day 14 and 168.
[e] Transfusion avoidance is defined as absence of administration of packed-red blood cell transfusions or meeting the criteria for transfusion between Day 14 and 168.
[f] Adjusted mean assessed between Day 126 and 168, values within 30 days after transfusion were excluded from the analysis.
[g] Adjusted mean assessed between Day 126 and 168, values within 30 days after transfusion were included in the analysis.
[h] Assessed between Day 1 and 168.
[i] Clinical breakthrough hemolysis defined as meeting clinical criteria (either decrease of Hemoglobin level ≥ 2 g/dL compared to the last assessment or within 15 days; or signs or symptoms of gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms) and laboratory criteria (LDH> 1.5-times ULN and increased as compared to the last 2 assessments).

Figure 12-1 Mean hemoglobin level* (g/dL) during 24-week randomized treatment period in APPLY-PNH



**Note: The figure includes all hemoglobin data collected in the study, including those values within 30 days after RBC transfusion.*

The results for the primary endpoints were consistent across the predefined subgroups studied, including disease duration, age, sex, baseline hemoglobin, history of MAVEs, previous anti-C5 treatment (eculizumab or ravulizumab), the need for transfusion in the last 6 months, number of transfusions in the last 6 months (<2 or ≥2), LDH level at baseline, and duration of previous anti-C5 treatment.

APPOINT-PNH: Complement inhibitor naïve study

APPOINT-PNH studied 40 adult PNH patients (RBC clone size ≥10%) with hemoglobin <10 g/dL and LDH > 1.5 ULN, who were not previously treated with a complement inhibitor. All 40 patients received Fabhalta 200 mg orally twice daily during the 24-week open-label core treatment period. Subsequently, patients were eligible to enroll in a 24-week treatment extension period and continue to receive Fabhalta, followed by a separate long-term extension study.

Patients were required to be vaccinated against *Neisseria meningitidis* and recommended to be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* Type B. If the patient had not been previously vaccinated or if a booster was required, vaccination was administered at least 2 weeks prior to or up to 2 weeks after the first dose. If Fabhalta treatment was initiated earlier than 2 weeks after vaccination, antibacterial drug prophylaxis treatment was administered.

Table 12-3 shows the patient baseline demographics and disease characteristics. No patients discontinued from the core treatment period of the study.

Table 12-3 Patient baseline demographics and characteristics in APPOINT-PNH

Parameters	Statistics	Fabhalta (n=40)
Age (years)	Mean (SD) min, max	42.1 (15.9) 18, 81
Sex Female	 n (%)	 17 (42.5)
Hemoglobin level (g/dL)	Mean (SD)	8.2 (1.1)
LDH level (U/L)	Mean (SD)	1,698.8 (683.3)
Absolute reticulocyte count (ARC) (10^9/L)	Mean (SD)	154.3 (63.7)
At least one transfusion in the last 12 months prior to screening	n (%)	27 (67.5)
At least one transfusion in the last 6 months prior to treatment	n (%)	28 (70.0)

Parameters	Statistics	Fabhalta (n=40)
Number of transfusions in last 6 months prior to treatment among patients who had a transfusion	Mean (SD)	3.1 (2.1)
History of MAVEs (including thrombosis)	n (%)	5 (12.5)
Disease duration (years)	Mean (SD)	4.7 (5.5)

Efficacy was based on the primary endpoint assessing the effect of Fabhalta treatment on the proportion of patients achieving hemoglobin improvement (sustained increase of ≥2 g/dL in hemoglobin levels from baseline, without a need for RBC transfusion, after 24 weeks). Secondary endpoints included: sustained hemoglobin ≥12 g/dL (without a need for RBC transfusion) after 24 weeks, transfusion avoidance, change from baseline in hemoglobin levels, change from baseline in FACIT-Fatigue scores, occurrence of clinical breakthrough hemolysis and change from baseline in absolute reticulocyte counts.

Fabhalta treatment resulted in a response rate of 92.2% (95% CI: 82.5, 100.0) for hemoglobin improvement, without a need for RBC transfusion, after 24 weeks. The response rate for patients achieving hemoglobin ≥12 g/ dL, without a need for RBC transfusion, was 62.8% (95% CI: 47.5, 77.5). Fabhalta treatment led to transfusion avoidance rate of 97.6% (95% CI: 92.5, 100.0). Patients treated with Fabhalta experienced clinically meaningful improvements in patient reported fatigue (FACIT-Fatigue score change from baseline +10.8; 95% CI: 8.7, 12.8). No patients experienced clinical breakthrough hemolysis or MAVEs. When compared to baseline, in patients treated with Fabhalta, hemoglobin levels increased by 4.3 g/dL (95% CI: 3.9, 4.7), absolute reticulocyte counts changed by -82.5 x 10^9/L (95% CI: -89.3, -75.6), and the LDH percent change was -83.6% (95% CI: -84.9, -82.1) after 24 weeks. The treatment effect of Fabhalta on LDH was seen as early as Day 7 and reached <1.5 ULN by Day 14, which was sustained during the study. (See Table 12-4 and Figure 12-2).

Table 12-4 Efficacy results for the 24-week core treatment period in APPOINT-PNH

Endpoints	Fabhalta (N=40) 95% CI
Primary endpoint	
Number of patients achieving hemoglobin improvement (sustained increase of hemoglobin levels ≥ 2 g/dL from baseline[a] in the absence of transfusions)	31/33[b]
Response rate[c] (%)	92.2 (82.5, 100.0)[d]
Secondary endpoints	
Number of patients achieving sustained hemoglobin level ≥12g/dL[a] in the absence of transfusions	19/33[b]
Response rate[c] (%)	62.8 (47.5, 77.5)
Number of patients avoiding transfusion[e,f]	40/40[b]
Transfusion avoidance rate[c] (%)	97.6 (92.5, 100.0)
Hemoglobin level change from baseline (g/dL) (adjusted mean[i])	+4.3 (3.9, 4.7)
FACIT-Fatigue score change from baseline (adjusted mean[j])	+10.8 (8.7, 12.8)
Clinical breakthrough hemolysis[g,h], % (n/N)	0/40

Endpoints	Fabhalta (N=40) 95% CI
Annualized rate of clinical breakthrough hemolysis	0.0 (0.0,0.2)
Absolute reticulocyte counts change from baseline (10^9/L) (adjusted mean[j])	-82.5 (-89.3, -75.6)
LDH percent change from baseline (adjusted mean[j])	-83.6 (-84.9, -82.1)
Percent of patients with MAVEs[h]	0.0

[a] Assessed between Day 126 and 168.

[b] Based on observed data among evaluable patients.

[c] Response rate reflects the adjusted proportion.

[d] The threshold for demonstration of benefit was 15%, representing the rate that would have been expected on anti-C5 treatment.

[e] Assessed between Day 14 and 168.

[f] Transfusion avoidance is defined as absence of administration of packed-red blood cell transfusions between Day 14 and Day 168 or meeting the criteria for transfusion between Day 14 and 168.

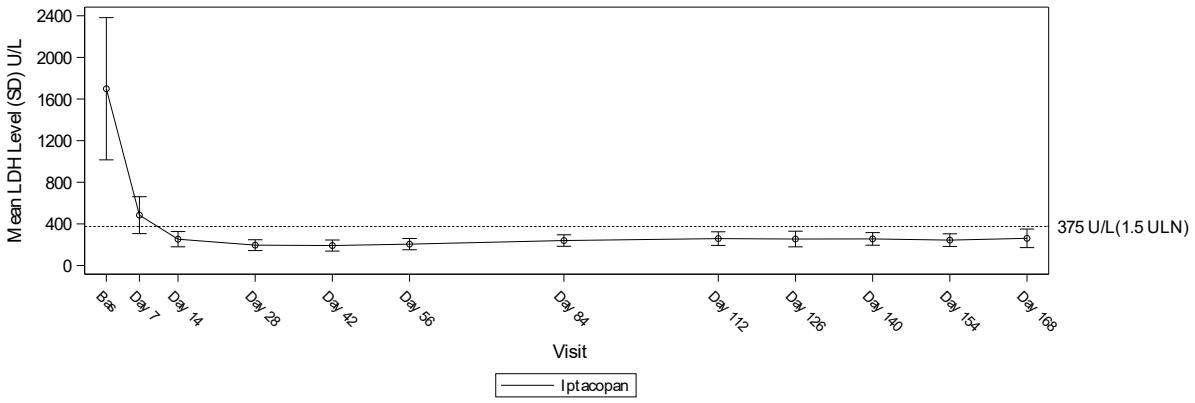
[g] Clinical breakthrough hemolysis defined as meeting clinical criteria (either decrease of hemoglobin level ≥2 g/dL compared to the latest assessment or within 15 days; or signs or symptoms of gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms) and laboratory criteria (LDH>1.5-times ULN and increased as compared to the last 2 assessments).

[h] Assessed between Day 1 and 168.

[i] Adjusted mean assessed between Day 126 and 168, values within 30 days after transfusion were excluded from the analysis.

[j] Adjusted mean assessed between Day 126 and 168, values within 30 days after transfusion were included in the analysis.

Figure 12-2 Mean LDH level (U/L) during 24-week core treatment period in APPOINT-PNH



The results for the primary endpoint were consistent across the predefined subgroups examined, including disease duration, age, sex, baseline hemoglobin, history of MAVEs, need for transfusion in the last 6 months, and number of transfusions in the last 6 months (<2 or ≥2).

13 Non-clinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

Reproductive toxicity

In oral dose animal fertility studies, iptacopan did not impact fertility in male rats up to the highest dose tested (750 mg/kg/day), which corresponds to 6-fold the MRHD based on AUC. Reversible effects on the male reproductive system (testicular tubular degeneration and hypospermatogenesis) were observed in repeated dose toxicity studies after oral administration in rats and dogs at doses >3-fold the MRHD based on AUC, with no apparent effects on sperm numbers, morphology or motility, or fertility.

In the female fertility and early embryonic developmental study in rats, iptacopan-related findings were limited to increased pre-and post-implantation losses and, consequently, decreased numbers of live embryos only at the highest dose of 1 000 mg/kg/day orally, which corresponds to ~5-fold the MRHD based on total AUC. The dose of 300 mg/kg/day is the no-observed-adverse-effect level (NOAEL) which corresponds to ~2-fold the MRHD based on AUC.

Animal reproduction studies in rats and rabbits demonstrated that oral administration of iptacopan during organogenesis did not induce adverse embryo or foetal toxicity up to the highest doses, which correspond to 5-fold (for rats) and 8-fold (for rabbits) the MRHD of 200 mg twice daily based on AUC.

Animal reproduction studies in rats and rabbits demonstrated that oral administration of iptacopan during organogenesis did not induce adverse embryo or foetal toxicity up to the highest doses, which correspond to 5-fold (for rats) and 8-fold (for rabbits) the MRHD of 200 mg twice daily based on AUC.

In the pre- and postnatal development study in rats, with iptacopan administered orally to females during gestation, parturition and lactation (from gestational day 6 to lactation day 21), there were no adverse effects on pregnant dams or offspring up to the highest dose tested of 1 000 mg/kg/day (estimated 5-fold the MRHD based on AUC).

Repeated dose

In the chronic toxicity study, one male dog at the highest dose level (margin to clinical exposure near 20-fold), was sacrificed 103 days after completed iptacopan administration due to irreversible non-regenerative severe anaemia associated with bone marrow fibrosis. During the treatment phase, haematology findings indicating inflammation and dyserythropoiesis were observed. No mechanism for the observed findings has been identified and a relation to treatment cannot be excluded.

Mutagenicity and carcinogenicity

Iptacopan was not genotoxic or mutagenic in a battery of in vitro and in vivo assays.

Carcinogenicity studies conducted with iptacopan in mice and rats via oral administration did not identify any carcinogenic potential. The highest doses of iptacopan studied in mice (1 000 mg/kg/day) and rats (750 mg/kg/day) were approximately 4- and 12-fold the MRHD based on AUC, respectively.

Phototoxicity

In vitro and in vivo phototoxicity tests were equivocal. In the in vivo phototoxicity study, with iptacopan at doses between 100 and 1 000 mg/kg (equivalent to 38-fold the human total Cmax at the MRHD), some mice showed a non-dose-response pattern of transient minimal erythema, scabs and dryness and slight increase in average ear weight subsequent to irradiation.

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

See folding box.

Information might differ in some countries.

Fabhalta must be kept out of the reach and sight of children.

Nature and contents of container

Fabhalta is supplied in PVC/PE/PVDC blisters with aluminum foil backing, packed in a box of 56 hard capsules.

Instructions for use and handling

Not applicable.

Special precautions for disposal

Not applicable.

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