EXPLORING THE SWITCH TO FABHALTA® (iptacopan) IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

> **I believe that FABHALTA is the next big wave for PNH management.** Prior to its approval, we were limited in our treatment options, but now, I'm very excited for patients with PNH. I've seen great results in my practice, and a capsule that's given twice daily is definitely an appealing option for appropriate patients.[1]

— **Elaine M. Majerus, MD, PhD**
Cochief and Professor, Division of Hematology
Washington University School of Medicine,
St. Louis, MO

In this edition, Dr Majerus discusses the key considerations when switching patients who were previously on a C5 inhibitor (eculizumab or ravulizumab) to FABHALTA. She also shares clinical data insights for FABHALTA in complement inhibitor–naive patients with PNH and best practices on monitoring patients on treatment.

The perspectives provided within this newsletter by Dr Majerus are her own and not reflective of her affiliations. Dr Majerus has been paid by Novartis to provide her perspectives. This newsletter is not intended to be and does not serve as medical advice, guidance, or recommendations from Novartis.

C5i, complement component C5 inhibitor; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; PNH, paroxysmal nocturnal hemoglobinuria.

INDICATION

FABHALTA is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

FABHALTA® (iptacopan) 200 mg capsules

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

FABHALTA, a complement inhibitor, increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccinations for encapsulated bacteria at least 2 weeks prior to the first dose of FABHALTA, unless the risks of delaying therapy with FABHALTA outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients receiving a complement inhibitor.**
- **Patients receiving FABHALTA are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and evaluate immediately if infection is suspected.**

Because of the risk of serious infections caused by encapsulated bacteria, FABHALTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FABHALTA REMS.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information, including Boxed WARNING and Medication Guide.

HEAR DR MAJERUS ANSWER THESE QUESTIONS. (CLICK BELOW)

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What clinical or nonclinical factors influence your approach to PNH management?

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Important considerations for PNH management

- Hb levels below normal or indicative of anemia[2-4]*
- Ongoing hemolysis (eg, LDH and ARC levels)[4-7]
- Any RBC transfusion needs[8]
- Impact of PNH on day-to-day activities[8]

Ideally, I would like to see a normal hemoglobin level in my patients. It concerns me when hemoglobin levels are persistently below 10 g/dL, as this indicates, for me, clinically relevant anemia.[2,3] In these cases, I would discuss alternative management approaches, such as proximal inhibition with FABHALTA. In addition, if any patient requires RBC transfusions, I would consider a switch to FABHALTA as there are great data to support its use.[1]

Hemoglobin is my first-line measure, but I also look at other markers.[4] I follow absolute reticulocyte count and other markers of hemolysis at each visit.[4-7] **If my patients continue to have hemolysis, that is another reason for me to switch therapies.**

It's important to think about different treatment options for patients. Many times, I see that **PNH presents with gradual adjustments over time, and patients may not recognize the full impact.** That's concerning to me, and I want to make sure that my patients are doing the things that they enjoy.

DID YOU KNOW?

In a US cross-sectional study of C5i-experienced[a] patients with self-reported diagnosis of PNH (N=122),[8,b-d]

84% of adults had a **hemoglobin level of 12 g/dL or lower**[8,e]

35% of adults **required at least 1 transfusion in the prior 12 months**[8,f]

[a]Most patients (96.7%; eculizumab: n=35; ravulizumab: n=83) were on a C5i for ≥3 months.
[b]Potential study limitations include small sample size due to the rarity of PNH, potential selection bias where dissatisfied patients are more motivated to participate, and subjectivity of patient-reported outcomes.[8]
[c]History of aplastic anemia was reported in 33.6% (41/122) of patients.[8]
[d]Other comorbidities, such as myelodysplastic syndrome and other bone marrow disorders, were reported by <6% (n=7/122) of patients.[8]
[e]88% of patients (n=28/32) were on eculizumab, and 83% of patients (n=68/82) were on ravulizumab. Hb data were analyzed for respondents that reported Hb levels (n=114).[8]
[f]52% of patients (n=12/23) were on eculizumab, and 23% of patients (n=7/31) were on ravulizumab. Transfusion data are from survey respondents who had received at least 1 year of C5i treatment and who had experienced at least 1 transfusion in their lifetimes (n=54).[8]

ARC, absolute reticulocyte count; C5i, complement component 5 inhibitor; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.
*Normal Hb levels vary, but generally are between 12 g/dL and 16 g/dL for women and 13 g/dL and 18 g/dL for men.[2,3]

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

- Patients with serious hypersensitivity to FABHALTA or any of the excipients.
- For initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis*, or *Haemophilus influenzae* type b.

WARNINGS AND PRECAUTIONS

Serious Infections Caused by Encapsulated Bacteria

- FABHALTA, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis* (caused by any serogroup, including nongroupable strains), and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors. The initiation of FABHALTA is contraindicated in patients with unresolved serious infections caused by encapsulated bacteria.

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What makes FABHALTA different?

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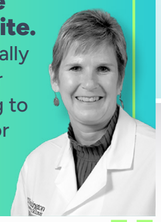
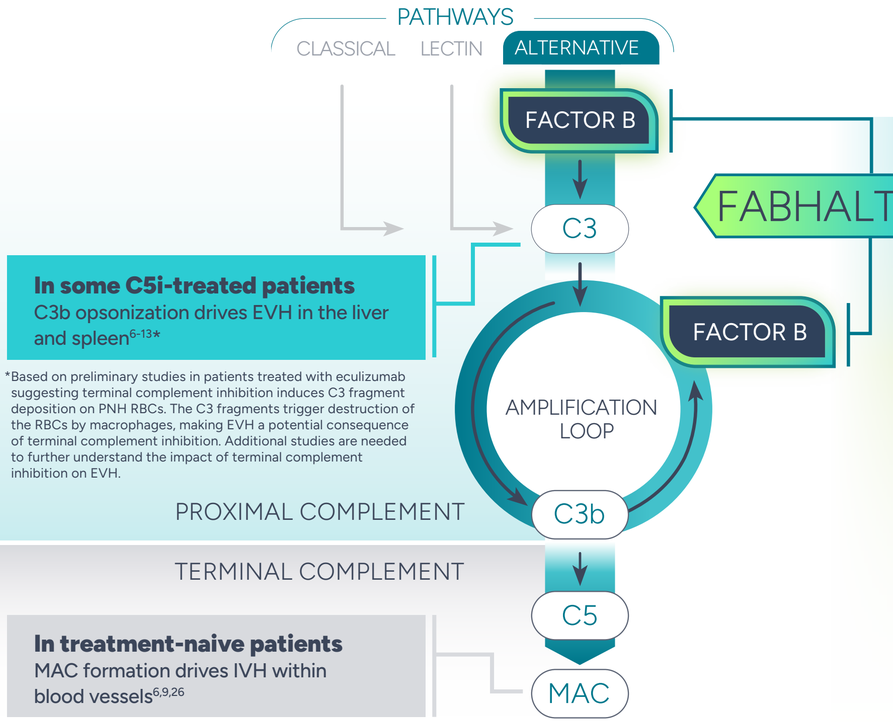
As a Factor B inhibitor, FABHALTA not only controls intravascular hemolysis (IVH), but also extravascular hemolysis (EVH), which in some patients is not as well controlled by C5 inhibition.[1,6-13]

With FABHALTA, you're getting control of both types of hemolysis (IVH and EVH).[1] Clinically significant hemolysis is associated with certain risks in PNH, so it's important to actively manage when it occurs.[14]

When appropriate, FABHALTA is also a great option for patients who prefer to not take the time to go to an infusion site.

FABHALTA is a capsule taken orally 2 times a day without regard for food. This can be very appealing to patients who travel frequently or have busy work schedules.[1,15-18]





*Based on preliminary studies in patients treated with eculizumab suggesting terminal complement inhibition induces C3 fragment deposition on PNH RBCs. The C3 fragments trigger destruction of the RBCs by macrophages, making EVH a potential consequence of terminal complement inhibition. Additional studies are needed to further understand the impact of terminal complement inhibition on EVH.

COMPREHENSIVE HEMOLYSIS CONTROL OF IVH AND EVH

FABHALTA acts proximally in the alternative complement pathway to control both C3b-mediated EVH and terminal complement–mediated IVH

C, complement component; C5i, C5 inhibitor; EVH, extravascular hemolysis; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; IVH, intravascular hemolysis; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Serious Infections Caused by Encapsulated Bacteria (continued)

- Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to the start of FABHALTA, according to the current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with FABHALTA. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent FABHALTA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible. The benefits and risks of treatment with FABHALTA, as well as the benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by encapsulated bacteria.
- Vaccination does not eliminate the risk of serious encapsulated bacterial infections, despite development of antibodies following vaccination. Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of FABHALTA in patients who are undergoing treatment for serious infections, depending on the risks of interrupting treatment in the disease being treated.

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When and why would you recommend a switch in adult patients who are currently on a C5i (eculizumab or ravulizumab) to FABHALTA?

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APPLY

Patients with PNH who are being treated with C5is often experience anemia. In fact, many patients in my practice present with Hb levels around 10 g/dL or less and show signs and symptoms of hemolysis.

If a patient's hemoglobin is less than 10 g/dL, I would recommend a switch to FABHALTA.[1]

The support for FABHALTA in patients who have been previously treated with C5is comes from the APPLY trial. FABHALTA was studied as an oral monotherapy in adult patients with PNH who have residual anemia (hemoglobin less than 10 g/dL) despite a stable regimen of C5i treatment in the last 6 months prior to randomization.[1]

In APPLY, the baseline mean hemoglobin level across both treatment groups was 8.9 g/dL, the mean LDH in both groups was below 1.5 times ULN, and 56.5% patients in the FABHALTA group and 60% patients in the C5i group required more than one transfusion in 6 months prior to randomizations.[1,19]

To me, the APPLY trial demonstrated the efficacy and safety of FABHALTA in this patient population, especially in terms of hemoglobin levels and transfusion avoidance.[1]

— **Elaine M. Majerus, MD, PhD**
St. Louis, MO

An open-label, active comparator–controlled study evaluating FABHALTA in C5i-experienced adults with PNH and residual anemia (Hb <10 g/dL)[1,19]

Key inclusion criteria

- Patients ≥18 years of age
- Diagnosed with PNH (RBC and WBC clone size ≥10%)
- Residual anemia (mean Hb <10 g/dL) despite previous treatment with a stable regimen of C5i treatment for at least 6 months prior to randomization
- Reticulocytes ≥100 × 10^9/L

(N=97)

Randomized in an 8:5 ratio*

- **Switched to FABHALTA** (n=62) — 200 mg oral monotherapy bid → **Continued FABHALTA** (n=61)
- **Continued C5is** (n=35) (US-approved and non–US-approved eculizumab n=23 or ravulizumab n=12) → **Switched to FABHALTA** (n=34)

Screening period ~8 weeks | Randomized treatment period 24 weeks | Treatment extension period 24 weeks

PRIMARY END POINTS[1,19]

- Proportion of patients achieving sustained Hb increase of ≥2 g/dL† from baseline without a need for RBC transfusions‡ after 24 weeks
- Proportion of patients achieving sustained Hb level of ≥12 g/dL† without a need for RBC transfusions‡ after 24 weeks‡

ADDITIONAL END POINTS[1,19]

- RBC transfusion avoidance§
- Change from baseline† in: Hb levels (g/dL),‖ FACIT-Fatigue scores, ARC (10^9/L), LDH level (U/L)
- Occurrence of major adverse vascular events¶
- Occurrence of clinical breakthrough hemolysis¶,#

STATISTICAL ANALYSIS[1,21]

- All end points were based on central laboratory data
- 95% CIs were based on the Sato variance estimator

*Randomization was stratified based on prior C5i treatment and transfusion history within the last 6 months.[1]
†Assessed between Days 126 and 168.[1]
‡Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[19]
§Transfusion avoidance is defined as absence of administration of packed RBC transfusions between Days 14 and 168.[1]
‖Excludes values within 30 days post transfusion.[1]
¶Throughout the study.[19]
#As per the protocol definition.[19]

ARC, absolute reticulocyte count; bid, twice a day; C5i, complement component 5 inhibitor; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; ULN, upper limit of normal; WBC, white blood cell.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

FABHALTA REMS

- FABHALTA is available only through a restricted program under a REMS called FABHALTA REMS, because of the risk of serious infections caused by encapsulated bacteria.
- Under the FABHALTA REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risks, signs, and symptoms of serious infections caused by encapsulated bacteria, provide patients with the REMS educational materials, ensure patients are vaccinated against encapsulated bacteria, prescribe antibacterial drug prophylaxis if patients' vaccine status is not up to date and treatment must be started urgently, and provide instructions to always carry the Patient Safety Card during treatment and for 2 weeks following last dose of FABHALTA.
- Further information is available by telephone: 1-833-993-2242 or online at www.FABHALTA-REMS.com.

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What does the efficacy from the APPLY trial tell you about FABHALTA as the first and only FDA-approved oral monotherapy for adults with PNH?

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The clinical data are impressive for FABHALTA on superior hemoglobin improvement without the need for transfusions after 24 weeks when compared with C5 inhibition.[1]

What stands out to me is that FABHALTA is the first PNH treatment to evaluate a primary end point of the proportion of patients achieving sustained hemoglobin increase of ≥2 g/dL in the absence of RBC transfusion, as opposed to hemoglobin stabilization.[1,15,17,18]

The second primary end point in APPLY was the proportion of patients achieving sustained hemoglobin ≥12 g/dL in the absence of RBC transfusions.[1] The definition of normal hemoglobin can vary but is generally between 12 to 16 g/dL for women and 13 to 18 g/dL for men.[2-3] We need normal levels of hemoglobin for optimal function, and so **having a lower than normal hemoglobin level is less than ideal**.[2,3,22]

If I have an opportunity to normalize someone's hemoglobin levels, like with FABHALTA, I would take that opportunity, even if it's not a guarantee that it will happen.[1] If you have the option to make it happen, it just makes sense to me to pursue it.

— **Elaine M. Majerus, MD, PhD**
St. Louis, MO

DID YOU KNOW?

APPLY

In APPLY, superior Hb improvements were achieved with FABHALTA over C5is (eculizumab or ravulizumab)[1]

- Primary end point: Patients with **Hb increase** of ≥2 g/dL* from baseline in the absence of RBC† transfusion after 24 weeks

Response rates

82.3% (n=51/62; 95% CI, 70.5-90.8) for patients who switched to FABHALTA

vs

0% (n=0/35; 95% CI, 0-10.0) for patients who remained on C5is (eculizumab or ravulizumab)

(Difference‡: 81.5%; 95% CI, 71.6-91.4; *P*<0.0001)

- Primary end point: Patients with **Hb normalization**§ of ≥12 g/dL* in the absence of RBC transfusions† after 24 weeks

Response rates

67.7% (n=42/62; 95% CI, 54.7-79.1) for patients who switched to FABHALTA

vs

0% (n=0/35; 95% CI, 0-10.0) for patients who remained on C5is (eculizumab or ravulizumab)

(Difference‡: 66.6%; 95% CI, 54.6-78.6; *P*<0.0001)

*Assessed between Days 126 and 168.[1]
†Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[19]
‡Adjusted difference in proportion.[1]
§Normalization defined as meeting the primary end point of Hb ≥12 g/dL. Normal Hb levels vary, but generally are between 12 g/dL and 16 g/dL for women and 13 g/dL and 18 g/dL for men.[2,3,19]

RBC TRANSFUSION DATA

C5i, complement component 5 inhibitor; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; FDA, US Food and Drug Administration; Hb, hemoglobin; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Monitoring of PNH Manifestations After FABHALTA Discontinuation

- After discontinuing FABHALTA, closely monitor patients for at least 2 weeks after the last dose for signs and symptoms of hemolysis. 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 (such as thrombosis, stroke, and myocardial infarction), dysphagia, or erectile dysfunction. If discontinuation of FABHALTA is necessary, consider alternative therapy.
- If hemolysis occurs after discontinuation of FABHALTA, consider restarting treatment with FABHALTA, if appropriate, or initiating another treatment for PNH.

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What does the efficacy from the APPLY trial tell you about FABHALTA as the first and only FDA-approved oral monotherapy for adults with PNH? (continued)

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DID YOU KNOW?

APPLY

In the APPLY trial, the response rates for RBC transfusion avoidance assessed between Weeks 2 and 24 were:[1*†]

95.2% (n=59/62; 95% CI, 86.5-99.0) for patients who switched to FABHALTA

VS

45.7% (n=16/35; 95% CI, 28.8-63.4) for patients who remained on C5is (eculizumab or ravulizumab)

(Difference‡: 49.5%; 95% CI, 32.5-66.6; *P*<0.0001)

Please note that 35 out of 62 patients in the FABHALTA arm and 21 out of 35 in the C5is arm had at least 1 RBC transfusion in the 6 months prior to trial enrollment.[1]

*Assessed between Days 14 and 168.[1]
†Transfusion avoidance is defined as absence of packed RBC transfusions between Days 14 and 168.[1]
‡Adjusted difference in proportion.[1]

Along with hemoglobin normalization, the data about RBC transfusion avoidance is another key factor that I focus on when considering switching patients to FABHALTA. I've seen great results in my practice in terms of hemoglobin improvements and transfusion requirements. It's impressive that patients on FABHALTA saw improvement in their hemoglobin levels but were also more likely to need fewer transfusions.[1]

There are risks involved with transfusions, so if we can avoid them, we should.[23-25]

FABHALTA has been shown to reduce the need for transfusions,[1] which may improve how patients feel.[24-25]

C5i, complement component 5 inhibitor; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; FDA, US Food and Drug Administration; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hyperlipidemia

- FABHALTA may increase total cholesterol, LDL cholesterol, and serum triglycerides.
- Of 88 FABHALTA-treated patients who had normal total cholesterol at baseline, 31 developed grade 1 hypercholesterolemia during the randomization or core treatment period and 1 patient worsened from baseline grade 1 to grade 2.
- Of 96 FABHALTA-treated patients with LDL cholesterol ≤ 130 mg/dL at baseline during the randomization or core treatment period, 14 patients developed LDL cholesterol > 130-160 mg/dL, 6 patients developed LDL cholesterol > 160-190 mg/dL and 4 patients developed LDL cholesterol > 190 mg/dL.

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What is your opinion on the impact of FABHALTA on markers of hemolysis in APPLY?

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Management of both IVH and EVH is important in PNH.[6-13,26]

There are data showing that hemolysis is associated with signs and symptoms of PNH, whether or not the patient is anemic.[8,23,27,28]

LDH is an important marker of IVH, while ARC is one of the markers of both IVH and EVH, so I follow these labs in my patients at every visit. If the LDH is >1.5 × ULN, it concerns me, and if absolute reticulocyte count is higher than the desired value for my patient, I think about other factors and whether the treatment is effective or a switch in therapy should be considered.[4,29]

DID YOU KNOW?

APPLY

In the APPLY study, patients in the FABHALTA group had a greater reduction in ARC compared to those on C5is (eculizumab or ravulizumab) **between Weeks 18 and 24***

The adjusted mean change from baseline of ARC levels assessed between Weeks 18 and 24 were[1]

-116 × 10^9/L
for patients in the FABHALTA group
(N=62; 95% CI, -127 to -105)
Baseline mean: 193 x 10^9/L

VS

0 × 10^9/L
for patients in the C5is group*
(N=35; 95% CI, -13 to 14)
Baseline mean: 191 x 10^9/L

(Adjusted mean difference: -116 x 10^9/L; 95% CI, -132 to -100; *P*<0.0001)
Values include post-transfusion data.[21]

No statistically significant difference in LDH was seen between FABHALTA and C5is[21]

0.96
FABHALTA (N=62)
Baseline mean: 269 U/L

0.97
C5is (N=35)
Baseline mean: 273 U/L

Adjusted geometric mean ratio to baseline in LDH assessed between Weeks 18 and 24*

- **Data for LDH were descriptive in nature, presented for observation only. No formal conclusions or comparisons between the 2 treatment arms can be made from these data**
- In both the FABHALTA and C5i-treated groups, the mean and median LDH values were below 1.5 x ULN at 24 weeks[21]

*Assessed between Days 126 and 168.[1]

ARC, absolute reticulocyte count; EVH, extravascular hemolysis; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; IVH, intravascular hemolysis; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hyperlipidemia (continued)

- Of 89 FABHALTA-treated patients with normal triglycerides during the randomization or core treatment period, 22 patients developed grade 1 elevated triglycerides. Three patients experienced an increase in triglycerides from grade 1 to grade 2.
- Of the 102 FABHALTA-treated patients in APPLY-PNH and APPOINT-PNH, 2 patients required cholesterol-lowering medications.
- Monitor serum lipid parameters periodically during treatment with FABHALTA and initiate cholesterol-lowering medications, if indicated.

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What are your thoughts on patient-reported FACIT-Fatigue* score data in APPLY?

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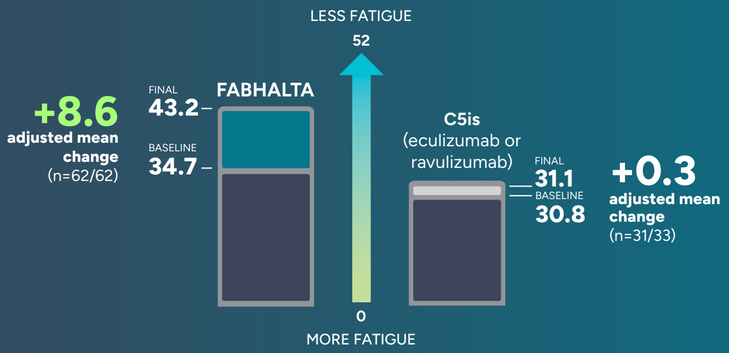
DID YOU KNOW?

APPLY

The adjusted mean change from baseline in FACIT-Fatigue score between Weeks 18 and 24[9*†‡]

Patient-reported FACIT-Fatigue scores may be an underestimation or overestimation because patients were not blinded to treatment.[19]

The data from this additional analysis are descriptive in nature, presented for observation only. At baseline, ~50% of participants reported the least severe response categories ("not at all" and "a little bit") for 10 out of 13 questions in the FACIT-Fatigue scale. Due to the small sample size, open-label design, and the low level of fatigue reported at baseline, no formal conclusions or comparisons between the 2 treatment arms can be made.



Difference: 8.34; 95% CI, 5.26-11.41

The mean FACIT-Fatigue score for the general population was **44**, based on separate large-scale surveys[31,32§]

> Patient-reported FACIT-Fatigue data in APPLY are important, as many patients who come to my clinic report feeling some degree of fatigue.[30]
>
> It's important to make sure that patients have the ability to do the things that matter to them. In my practice, **I check my patients' fatigue level by asking them if they are able work to their full potential, or do the things that they enjoy. It's usually straightforward to get this information from patients.**

C5i, complement component 5 inhibitor; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue.

*FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact on daily activities and function. The level of fatigue is measured on a 4-point Likert scale (in the study, 4=not at all fatigued to 0=very much fatigued), with 0 being the worst possible score and 52 the best.[19]

†Assessed between Days 126 and 168.[21]

‡Baseline mean FACIT-Fatigue scores were reported for 62 patients in the FABHALTA arm and 33 patients in the C5is arm. At Day 168, the adjusted mean change in FACIT-Fatigue score was reported for 62 patients in the FABHALTA arm and 31 patients in the C5is arm.[19,21]

§The FACIT-Fatigue score for the general population was determined through the assessment of 1010 adults in the US in 2002 and 2426 adults in Germany in 2018.[31,32]

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

- The most common adverse reactions (≥10%) in adults with PNH receiving FABHALTA were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash.

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What is the safety profile for FABHALTA in the APPLY trial?

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"In my practice, when patients first start a new treatment, I typically have them come in for labs every month, and then every 3 months. If patients are doing well, I will see them every 6 months. It's not possible to have a scheduled visit that coincides with adverse events, so it's important to make sure patients know how to contact us when they experience them.

It's also important to discuss with patients the importance of reporting adverse events. I find that **my PNH patients are in tune with their bodies, and they typically won't hesitate to reach out and maintain a close relationship with me.**

Because of the risk of serious infections caused by encapsulated bacteria, all prescribers need to become certified in the FABHALTA Risk Evaluation and Mitigation Strategy (REMS) program and fulfill its requirements. **In my practice, I'm very meticulous about vaccination requirements**,[1] which include required vaccination and revaccination, as needed, against encapsulated bacteria, including *Neisseria meningitidis* and *Streptococcus pneumoniae*. My nurses make sure it is noted in the header of records for all of my patients on complement inhibitors, along with a description about the vaccinations. **I educate my patients on the signs or symptoms of hemolysis and serious infection**, such as fever, as these are concerning and should be promptly addressed."

— **Elaine M. Majerus, MD, PhD**
St. Louis, MO

DID YOU KNOW?

APPLY

Adverse reactions reported in >5% of adult patients with PNH treated with FABHALTA are as follows[1,19]

ADVERSE REACTIONS	FABHALTA (N=62) n (%)	C5is (eculizumab or ravulizumab) (N=35) n (%)
Headache[a]	12 (19)	1 (3)
Nasopharyngitis[b]	10 (16)	6 (17)
Diarrhea	9 (15)	2 (6)
Abdominal pain[a]	9 (15)	1 (3)
Bacterial infection[c]	7 (11)	4 (11)
Viral infection[d]	6 (10)	11 (31)
Nausea	6 (10)	1 (3)
Arthralgia	5 (8)	1 (3)
Thrombocytopenia[a]	4 (6)	0
Dizziness	4 (6)	0
Systemic hypertension[a]	4 (6)	0
Lipid disorder[e]	4 (6)	0

- Serious adverse reactions were reported in 2 (3%) patients with PNH who received FABHALTA. They included pyelonephritis, urinary tract infection, and COVID-19[1]
- Rash was reported in 2 patients (3%)[1]
- Of the 37 FABHALTA-treated patients who had normal platelet counts at baseline, 43% experienced any grade thrombocytopenia[1]
- Three FABHALTA-treated patients experienced decreased platelets that worsened to grade ≥3 from baseline (1 patient with normal platelets that worsened to grade 4; 1 patient with baseline grade 1 that worsened to grade 4; and 1 patient with baseline grade 3 that worsened to grade 4)[1]
- **No patient discontinued FABHALTA or C5is due to an adverse reaction during the randomized control period of the trial.** One patient in APPLY discontinued FABHALTA due to pregnancy[19]

[a]Includes similar terms.[1]
[b]Nasopharyngitis contains: rhinitis allergic, upper respiratory tract infection, pharyngitis, rhinitis.[1]
[c]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.[1]
[d]Viral infection contains: COVID-19, herpes zoster, oral herpes, nasal herpes, influenza A virus test positive, influenza.[1]
[e]Lipid disorder contains: dyslipidemia, blood cholesterol increased, low-density lipoprotein increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia.[1]

How to get your patients started

- **Get REMS certified to prescribe to FABHALTA[1]**
- **Complete or update your patient's vaccinations before starting treatment with FABHALTA[1]**
- **Prescribe FABHALTA through a limited network of specialty pharmacies[1]**

For more detailed information on these steps, please visit FABHALTA-hcp.com/pnh or speak to your local Novartis representative to learn more.

C5i, complement component 5 inhibitor; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; PNH, paroxysmal nocturnal hemoglobinuria.

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

- Concomitant use of CYP2C8 inducers (eg, rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy of FABHALTA. Monitor the clinical response and discontinue use of the CYP2C8 inducer if loss of efficacy of FABHALTA is evident.
- Concomitant use of strong CYP2C8 inhibitors (eg, gemfibrozil) may increase iptacopan exposure, which may result in increased risk for adverse reactions with FABHALTA. Coadministration with a strong CYP2C8 inhibitor is not recommended.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information, including Boxed WARNING and Medication Guide.

Is FABHALTA also suitable for my complement inhibitor–naive adult patients with PNH?

FABHALTA® (iptacopan) 200 mg capsules

DID YOU KNOW?

Yes, FABHALTA was also studied in adult patients with PNH who have not been treated with complement inhibitors in the APPOINT trial.[1]

Patients in this trial had a baseline mean hemoglobin of 8.2 g/dL, mean LDH of 1699 U/L, and 70% (n=28/40) of patients required at least 1 RBC transfusion in the 6 months prior to enrollment.[20] Based on the hemoglobin levels, as well as the safety profile from the APPOINT trial, I feel there is a strong argument for FABHALTA use in this patient population, especially if they are experiencing PNH signs and symptoms.[1,20,21]

— **Elaine M. Majerus, MD, PhD**
St. Louis, MO

A phase 3, single-arm, open-label, uncontrolled study evaluating FABHALTA in complement inhibitor–naive adults with PNH[1,20]

Key inclusion criteria
- Patients ≥18 years of age
- Complement inhibitor–naive
- PNH diagnosis (RBC and WBC clone size ≥10%)
- Mean Hb <10 g/dL‡
- LDH >1.5 × ULN§ (N=40)

FABHALTA (N=40) 200 mg oral monotherapy bid → **Continued FABHALTA** (n=40)

Screening period ~8 weeks | Core treatment period 24 weeks | Treatment extension period 24 weeks

PRIMARY END POINT[20]
- Proportion of patients achieving sustained Hb increase of ≥2 g/dL* from baseline without a need for RBC transfusions‡ after 24 weeks

APPOINT

PRIMARY END POINT

In the APPOINT trial, the majority of patients taking FABHALTA experienced Hb improvements* from baseline in the absence of RBC transfusions[1†]

77.5% (n=31/40; 95% CI, 61.5-89.2) of patients achieved a sustained increase in Hb levels from baseline of at least 2 g/dL in the absence of RBC transfusions after 24 weeks[1]

87.5% (n=35/40; 95% CI, 73.2-95.8) of patients achieved this end point based on a sensitivity analysis that included local laboratory Hb values when central laboratory Hb values were not available[1]

Adverse reactions reported in >5% of adults with PNH treated with FABHALTA (24-week treatment period) in APPOINT trial[1]

ADVERSE REACTIONS	FABHALTA (N=40) n (%)
Headache[a]	11 (28)
Viral infection[b]	7 (18)
Nasopharyngitis[c]	6 (15)
Rash[d]	4 (10)
Abdominal pain[a]	3 (8)
Diarrhea	3 (8)
Lipid disorder[e]	3 (8)

- Serious adverse reactions were reported in 2 (5%) patients with PNH who received FABHALTA. They included COVID-19 and bacterial pneumonia[1]
- Bacterial infection[f] and nausea were reported in 2 patients each (5%). Dizziness and urticaria were reported in 1 patient each (3%)[1]
- **No patient discontinued FABHALTA due to an adverse reaction in the core treatment period**[20]

[a]Includes similar terms.[1]
[b]Viral infection contains: COVID-19, herpes zoster, oral herpes, nasal herpes, influenza A virus test positive, influenza.[1]
[c]Nasopharyngitis contains: rhinitis allergic, upper respiratory tract infection, pharyngitis, rhinitis.[1]
[d]Rash contains: dermatitis allergic, acne, erythema multiforme, rash maculopapular, rash erythematous.[1]
[e]Lipid disorder contains: dyslipidemia, blood cholesterol increased, low-density lipoprotein increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia.[1]
[f]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.[1]

bid, twice a day; C5i, complement component 5 inhibitor; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; ULN, upper limit of normal.

*Assessed between Days 126 and 168.[1]
†Assessed between Days 14 and 168. Requiring RBCs refers to any patient receiving transfusions or meeting protocol-defined criteria.[1]
‡Confirmed by 2 measurements 2 to 8 weeks apart for patients not receiving an RBC transfusion during screening, or by 1 measurement during the first screening visit for patients receiving an RBC transfusion.[20]
§Confirmed by at least 2 measurements 2 to 8 weeks apart during the screening period.[20]

IMPORTANT SAFETY INFORMATION (continued)

USE IN SPECIFIC POPULATIONS

- Because of the potential for serious adverse reactions in a breastfed child, breastfeeding should be discontinued during treatment and for 5 days after the final dose.
- FABHALTA is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information, including Boxed WARNING and Medication Guide.

HEAR DR MAJERUS ANSWER THESE QUESTIONS. (CLICK BELOW)

HEAR MORE EXPERT PERSPECTIVES AT
https://www.FABHALTA-hcp.com/pnh/medical-expert-perspectives

INDICATION

FABHALTA is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

FABHALTA, a complement inhibitor, increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccinations for encapsulated bacteria at least 2 weeks prior to the first dose of FABHALTA, unless the risks of delaying therapy with FABHALTA outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients receiving a complement inhibitor.**
- **Patients receiving FABHALTA are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and evaluate immediately if infection is suspected.**

Because of the risk of serious infections caused by encapsulated bacteria, FABHALTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FABHALTA REMS.

CONTRAINDICATIONS

- Patients with serious hypersensitivity to FABHALTA or any of the excipients.
- For initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis,* or *Haemophilus influenza*e type b.

WARNINGS AND PRECAUTIONS

Serious Infections Caused by Encapsulated Bacteria

- FABHALTA, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis* (caused by any serogroup, including nongroupable strains), and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors. The initiation of FABHALTA is contraindicated in patients with unresolved serious infections caused by encapsulated bacteria.
- Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to the start of FABHALTA, according to the current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with FABHALTA. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent FABHALTA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible. The benefits and risks of treatment with FABHALTA, as well as the benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by encapsulated bacteria.
- Vaccination does not eliminate the risk of serious encapsulated bacterial infections, despite development of antibodies following vaccination. Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of FABHALTA in patients who are undergoing treatment for serious infections, depending on the risks of interrupting treatment in the disease being treated.

FABHALTA REMS

- FABHALTA is available only through a restricted program under a REMS called FABHALTA REMS, because of the risk of serious infections caused by encapsulated bacteria.
- Under the FABHALTA REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risks, signs, and symptoms of serious infections caused by encapsulated bacteria, provide patients with the REMS educational materials, ensure patients are vaccinated against encapsulated bacteria, prescribe antibacterial drug prophylaxis if patients' vaccine status is not up to date and treatment must be started urgently, and provide instructions to always carry the Patient Safety Card during treatment and for 2 weeks following last dose of FABHALTA.
- Further information is available by telephone: 1-833-993-2242 or online at www.FABHALTA-REMS.com.

Monitoring of PNH Manifestations After FABHALTA Discontinuation

- After discontinuing FABHALTA, closely monitor patients for at least 2 weeks after the last dose for signs and symptoms of hemolysis. 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 (such as thrombosis, stroke, and myocardial infarction), dysphagia, or erectile dysfunction. If discontinuation of FABHALTA is necessary, consider alternative therapy.
- If hemolysis occurs after discontinuation of FABHALTA, consider restarting treatment with FABHALTA, if appropriate, or initiating another treatment for PNH.

Hyperlipidemia

- FABHALTA may increase total cholesterol, LDL cholesterol, and serum triglycerides.
- Of 88 FABHALTA-treated patients who had normal total cholesterol at baseline, 31 developed grade 1 hypercholesterolemia during the randomization or core treatment period and 1 patient worsened from baseline grade 1 to grade 2.
- Of 96 FABHALTA-treated patients with LDL cholesterol ≤ 130 mg/dL at baseline during the randomization or core treatment period, 14 patients developed LDL cholesterol > 130-160 mg/dL, 6 patients developed LDL cholesterol > 160-190 mg/dL and 4 patients developed LDL cholesterol > 190 mg/dL.
- Of 89 FABHALTA-treated patients with normal triglycerides during the randomization or core treatment period, 22 patients developed grade 1 elevated triglycerides. Three patients experienced an increase in triglycerides from grade 1 to grade 2.
- Of the 102 FABHALTA-treated patients in APPLY-PNH and APPOINT-PNH, 2 patients required cholesterol-lowering medications.
- Monitor serum lipid parameters periodically during treatment with FABHALTA and initiate cholesterol-lowering medications, if indicated.

ADVERSE REACTIONS

- The most common adverse reactions (≥10%) in adults with PNH receiving FABHALTA were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash.

DRUG INTERACTIONS

- Concomitant use of CYP2C8 inducers (eg, rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy of FABHALTA. Monitor the clinical response and discontinue use of the CYP2C8 inducer if loss of efficacy of FABHALTA is evident.
- Concomitant use of strong CYP2C8 inhibitors (eg, gemfibrozil) may increase iptacopan exposure, which may result in increased risk for adverse reactions with FABHALTA. Coadministration with a strong CYP2C8 inhibitor is not recommended.

USE IN SPECIFIC POPULATIONS

- Because of the potential for serious adverse reactions in a breastfed child, breastfeeding should be discontinued during treatment and for 5 days after the final dose.
- FABHALTA is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

Please see Important Safety Information throughout this newsletter. Please click here for full Prescribing Information, including Boxed WARNING and Medication Guide.

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