26 March 2024
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EMADOC-1700519818-1348651
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Fabhalta (iptacopan)
Treatment of paroxysmal nocturnal haemoglobinuria
EU/3/20/2281

Sponsor: Novartis Europharm Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Designated active substance(s)	(4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1))
Other name(s)	Iptacopan hydrochloride
International Non-Proprietary Name	Iptacopan
Tradename	Fabhalta
Orphan condition	Treatment of paroxysmal nocturnal haemoglobinuria
Sponsor's details:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 D04 A9N6 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited
COMP opinion	23 April 2023
EC decision	4 June 2020
EC registration number	EU/3/20/2281
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Martina Weise / Kristina Dunder
Applicant	Novartis Europharm Limited
Application submission	21 April 2023
Procedure start	18 May 2023
Procedure number	EMA/H/C/005764
Invented name	Fabhalta
Proposed therapeutic indication	Fabhalta is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Fabhalta
CHMP opinion	21 March 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Elisabeth Johanne Rook
Sponsor's report submission	16 June 2023
COMP discussion	13-15 February 2024
COMP opinion (adoption via written procedure)	26 March 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) was considered justified based on clinical data showing a normalisation of haemoglobin levels;
- the condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in different organs. Vascular complications in the central nervous system are the most common cause of death;
- the condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product on top of eculizumab prevents both intra- and extravascular complement-driven haemolysis. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) an orphan medicinal product for the orphan condition: treatment of paroxysmal nocturnal haemoglobinuria".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematological disorder. It is a clonal haematopoietic stem cell (HSC) disease that presents with haemolytic anaemia, thrombosis and smooth muscle dystonias, as well as bone marrow failure in some cases.

Patients with PNH have clonal blood cells with defective surface expression of various GPI-anchored proteins. GPI is synthesized in the endoplasmic reticulum from phosphatidylinositol through the Orphan Maintenance Assessment Report EMA/OD/0000051430 Page 5/12 sequential additions of monosaccharide molecules and other components via 11 reaction steps. Nascent GPI-anchored proteins undergo several remodelling reactions in the endoplasmic reticulum and the Golgi apparatus during transport to the cell surface. At the cell surface, the GPI-anchored proteins are primarily localized to microdomains that are rich in glycosphingolipids and cholesterol, termed lipid rafts. In PNH-affected cells, the first step in GPI biosynthesis is defective; as a result, PNH cells have defective surface expression of various GPI-anchored proteins. (Hill et al, Nat Rev Dis Primers. 2017 May 18;3:17028. doi: 10.1038/nrdp.2017.28.)

PNH cells carry a loss-of-function mutation in PIGA. PNH-linked PIGA mutations are somatic mutations, as patients with PNH can harbour blood cells with normal levels of GPI-anchored proteins. PIGA is located on Xp22.2. The X chromosome localization explains why one somatic PIGA mutation can be sufficient to cause GPI deficiency in most patients with PNH, as only one allele is functional in both men and women. The main consequences of clonal expansion of PIGA-mutant HSCs are intravascular haemolysis and thrombosis; bone marrow failure can develop independently and extravascular haemolysis only manifests under eculizumab therapy. Anaemia in PNH is often multifactorial and can result from a combination of haemolysis and bone marrow failure. Abdominal pain, back pain, oesophageal spasm, dysphagia (difficulty swallowing) and erectile dysfunction are common manifestations associated with haemolytic PNH and are often a direct consequence of intravascular haemolysis and the release of free haemoglobin. Disabling fatigue is a common feature of PNH and can be disproportionate to the degree of anaemia. Fatigue is often most intense during a haemolytic attack but is usually present at all times. Episodes of jaundice and haemoglobinuria are reported by almost 50% of patients. Patients with PNH have an increased risk of chronic kidney disease as a result of long-term intravascular haemolysis. Renal tubular damage can occur from microvascular thrombosis, accumulation of iron deposits or both. Mild-to-moderate pulmonary hypertension has also been reported, but the association between chronic kidney disease and clinically significant pulmonary hypertension is still controversial.

The COMP continues to accept PNH as an orphan condition.

The approved therapeutic indication "*FABHALTA is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia"* falls within the scope of the designated orphan condition "treatment of paroxysmal nocturnal haemoglobinuria".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The condition continues to be chronically debilitating and is associated with higher mortality in patients who do not respond to C5-inhibitor treatment.

Thrombosis is the most common cause of mortality in PNH (accounting for almost 50% of deaths before complement inhibition therapy was introduced). Anaemia in PNH is often multifactorial and can result from a combination of haemolysis and bone marrow failure. Disabling fatigue is a common feature of PNH and can be disproportionate to the degree of anaemia. It is associated with smooth muscle dystonia. Abdominal pain, back pain, oesophageal spasm, dysphagia (difficulty swallowing) and erectile dysfunction are common manifestations associated with haemolytic PNH and are often a direct consequence of intravascular haemolysis and the release of free haemoglobin. Fatigue is often most intense during a haemolytic attack but is always usually present. Episodes of jaundice and haemoglobinuria are reported by almost 50% of patients.

Number of people affected or at risk

The sponsor has conducted a literature search to establish the prevalence. The sponsor has provided a list of publications mainly from Europe but with additions from the United Kingdom and United States.

Table 1. Reported incidence of PNH in Europe and the US

Country, study period	PNH definition	No of patients	Annual incidence / 100,000 population	Reference
Denmark, 2008-2016	ICD-10 code D59.5	NR	0.08†	Hansen et al (2020)
Nordic countries, 2011-2016	Detectable PNH clones by flow cytometry (>0.1%)	NR	All Nordic: 0.23* Denmark: 0.21* Finland: 0.30* Norway: 0.25* Sweden: 0.17*	Korkama et al (2018)
Spain, 2011-2014	Detectable PNH clones by flow cytometry (>0.01%)	563	0.25*	Morado et al (2017)
UK, 2004-2018	Detectable PNH clones by flow cytometry (>0.01%)	197	0.35	Richards et al (2021)
UK, 1991-2006	Detectable PNH clones by flow cytometry	76	0.13	Hill et al (2006)
US, 2015-2018	ICD-10 D59.5	257	0.57†*	Jalbert et al (2019)

†Reported with patient-years (PY) in denominator
*Reported per 1 million, recalculated to cases per 100,000 population or per 100,000 PY to standardize presentation
ICD=International Classification of Disease; PNH=Paroxysmal nocturnal hemoglobinuria; UK=United Kingdom; US=United States, NR=Not reported

The mean annual incidence per 100,000 population of newly detected PNH clones (>0.1%) was 0.23 in the Nordic countries (Denmark 0.21, Finland 0.30, Norway 0.25, and Sweden 0.17) (Korkama et al 2018). The mean age at detection of the clone was 52 years (range: 6 to 90), with no gender difference.

In a study using the data from 24 laboratories from 2011 to 2014 in Spain Morado et al (2018) reported the overall incidence of newly detected PNH clones (>0.01%) of 0.25 per 100,000 population (ranging between 0.23 and 0.28 cases per 100,000 in 2011 and 2014, respectively).

It is acknowledged that the exact incidence of PNH is not currently established in Europe.

For information it is noted that in a retrospective population-based study using data from the Hematological Malignancy Research Network (HMRN) between 2004 and 2018, Richards et al (2021) reported an annual incidence for any detectable PNH clones of 0.35 per 100,000 in the UK. The median age of patients was 59 years (range: 5 to 91).

The incidence of the condition appears to be stable in Europe ranging between 0.23 to 0.35 per 100,000 as reported from 1977 to 2016.

In a recent publication by Sørensen A et al (October 17, 2023) Early Mortality in Paroxysmal Nocturnal Hemoglobinuria. Cureus 15(10): e47225.DOI 10.7759/cureus.47225, where data was analysed from 1977 to 2016, it was noted that years (IQR: 62.3-72.2), ten years lower than the median age at death among comparators (77.7 years (IQR:77.0-78.3)). After the first year, overall survival was 92.2% (95% CI) in patients with PNH and 99.4% (95% CI) among comparators. After 10 years, 68.4% (95% CI) of patients with PNH were still alive versus 85.8% (95% CI) of the comparators. The authors did not observe the difference in survival for patients with PNH diagnosed before and after 2006 when eculizumab became available. However, only 11 patients were registered with exposure to eculizumab either as monotherapy or in combination with warfarin.

Overall prevalence was derived from publications from Europe, the UK and the US. Please see Table 2 below.

Table 2. Reported prevalence estimates of PNH **in Europe and the US**

Country, study period	**PNH definition**	**Prevalence per 100,000 population**	**Reference**
Denmark, 2015	ICD-10 code D59.5	1.04	Hansen et al (2020)
UK, 1991-2006	Detectable PNH clones by flow cytometry	1.69 (15-y period prevalence)	Hill et al (2006)
UK, 2004-2018	Detectable PNH clones by flow cytometry (clone size >0.01%)	3.81 (15-y period prevalence)	Richards et al (2021)
US, 2016-2017	ICD-10 code D59.5	1.2-1.3*	Jalbert et al (2019)
US, 2010	Clinical PNH (mono- or multiclonal), PNH clone size >20%	1.76	Mon Pere et al (2018)

Hansen et al (2020) reported prevalence of PNH in several time periods between years 1977 and 2016 using Danish national registries. Most recently reported prevalence of PNH was 1.04 per 100,000 individuals (95% CI: 0.79,1.34) for year 2015; 1.09 per 100,000 in women (95% CI: 0.74,1.54) and 1.00 per 100,000 in men (0.66-1.44).

Supporting data from the UK has been submitted. In a retrospective population-based study using data from HMRN, Richards et al (2021) reported a prevalence of 3.81 per 100,000 individuals in UK for detectable PNH clones between 2004 and 2018.

The sponsor therefore proposes a prevalence based on the review of recent publications from Europe and the US revealed that the prevalence of PNH ranges from 1.0 to 1.8 per 100,000 individuals and the annual incidence rate ranges from 0.13 to 0.35 per 100,000 population in these regions. They note

that the rates of diagnosis and diagnostic criteria used to ascertain PNH cases impact the results strongly.

The COMP accepted the highest reported prevalence of 0.2 in 10,000 which is a bit lower than what had been designated previously.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Currently the three products authorised for this condition are C5 inhibitors eculizumab and ravulizumab and C3 inhibitor pegcetacoplan (Aspaveli). The only curative treatment for PNH is hematopoietic stem cell transplantation (HSCT) using allogeneic donors.

Since the introduction of eculizumab therapy, patients with PNH can live a relatively normal lifespan and patients with haemolytic PNH receiving eculizumab have a more favourable prognosis than patients with a more profound bone marrow failure component, such as aplastic anaemia. The reason for this difference is that eculizumab does not treat the underlying production deficit in the bone marrow (Hill et al 2017).

For completeness, the approved indications of eculizumab and ravulizumab, as reflected in the respective summaries of product characteristics, are as follows:

"*Soliris is indicated in adults and children for the treatment of:- Paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1)*"; and

"Ultomiris is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH): - in patients with haemolysis with clinical symptom(s) indicative of high disease activity. - in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (see section 5.1)".

Pegcetacoplan (Aspaveli) is a complement 3 (C3) inhibitor that addresses both the intravascular haemolysis (IVH) and extravascular haemolysis (EVH) of PNH by providing upstream inhibition of the complement cascade. Although eculizumab and ravulizumab share a similar mechanism of action, the structure and mechanism of action of pegcetacoplan is different from these 2 therapies. Pegcetacoplan binds to human C3 and C3b, resulting in proximal inhibition of the complement cascade and control of both IVH and EVH, leading to additional clinical outcomes to currently used C5 inhibitors in patients with PNH. The approved indication for Aspaveli is: *"Aspaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months"*.

The sponsor's product has the following proposed indication: *FABHALTA is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia*."

The COMP considered that there was complete overlap between the sponsor's product and the authorised C5 inhibitors eculizumab and ravulizumab, both considered satisfactory methods. The current indication of Aspaveli is only second line, after C5 therapy. As Fabhalta is not restricted to

second line, there is no complete overlap between the two indications and therefor Aspaveli is not considered a satisfactory method to be considered for the significant benefit assessment.

Significant benefit

The sponsor is proposing that their product can offer a clinically relevant advantage due to better efficacy in the treatment of paroxysmal nocturnal haemoglobinuria who have haemolytic anaemia. This would also include patients who are complement C5 inhibitor naïve. The sponsor is targeting both first line treatment and patients who no longer respond adequately to C5 inhibitor treatment.

The sponsor bases the claims of a clinically relevant advantage over C5 inhibitor treatment on the results from two clinical studies: the randomized, active-controlled pivotal Phase III study, APPLY-PNH in anti-C5 experienced patients, supportive by the evidence from the APPOINT-PNH Phase III study in complement inhibitor-naive patients.

The ongoing **APPOINT-PNH**, multicenter, single-arm, open-label, supportive Phase III study was designed to evaluate the efficacy and safety of iptacopan 200 mg b.i.d. orally in adult PNH patients who were naive to any complement inhibitor therapy, including anti-C5 therapy.

The following efficacy endpoints were assessed in APPOINT-PNH; haematological response defined as achieving sustained haemoglobin increase of ≥2 g/dL from baseline in the absence of RBC transfusions was the single primary endpoint in APPOINT-PNH. Haematological response defined as achieving sustained haemoglobin level of ≥12 g/dL in the absence of RBC transfusions was a secondary efficacy endpoint. Transfusion avoidance, average change from baseline in LDH, haemoglobin, ARC, and FACIT-Fatigue score, rates of clinical breakthrough haemolysis and MAVEs including thrombosis were assessed as secondary endpoints.

A treatment duration of 24 weeks for the core treatment period of APPOINT-PNH was considered appropriate to assess the effect of iptacopan on the primary and secondary efficacy endpoints, as well as for safety and tolerability.

Forty patients started iptacopan 200 mg b.i.d. monotherapy and were included in the analysis of APPOINT-PNH. Patients were enrolled from Asia (65.0%) and Europe (35.0%). The enrolled population was representative of complement-inhibitor naive PNH patients with clinically significant IVH and anaemia.

The primary haematological response endpoint defined as achieving sustained haemoglobin increase of ≥2g/dL from baseline in absence of RBC transfusions, showed the marginal proportion of patients achieving this endpoint was 92.2% (95% CI: 82.5%, 100.0%).

Results for secondary endpoints including haematological response defined as achieving sustained haemoglobin ≥12 g/dL in absence of RBC transfusions, transfusion avoidance, average change from baseline in haemoglobin, percentage LDH, ARC and FACIT-Fatigue score, rates of clinical BTH and MAVEs showed similar improvements following treatment as seen with the primary endpoint.

Table 3. Summary of APPOINT-PNH primary and secondary efficacy endpoints: 24-week core treatment period (FAS)

Endpoint	**Summary measure**	
Primary endpoint		
≥2 g/dL increase in Hb from baseline[1] in the absence of RBC transfusions[2] [4]	Marginal proportion (95% CI)	92.2% (82.5, 100.0)
Secondary endpoints		

Endpoint	Summary measure	
Hb ≥12 g/dL[1] in the absence of RBC transfusions [4]	Marginal proportion (95% CI)	62.8% (47.5, 77.5)
Transfusion avoidance[2] [4]	Marginal proportion (95% CI)	97.6% (92.5, 100.0)
Change from baseline in Hb levels (g/dL)[1] [5]	Adjusted mean (95% CI)	4.28 (3.87, 4.70)
Percentage change from baseline in LDH levels (U/L)[1] [6]	Percentage change from baseline (%) (95% CI)	-83.55 (-84.90, -82.08)
Clinical BTH[3] [6]	Adjusted annual BTH rate (95% CI)	0.00 (0.00,0.17)
Change from baseline in ARC (10^9/L)[1] [6]	Adjusted mean (95% CI)	-82.48 (-89.33, -75.62)
Change from baseline in FACIT-Fatigue scores[1] [6]	Adjusted mean (95% CI)	10.75 (8.66, 12.84)
Rates of MAVEs[3] [6] (%)	Adjusted annual MAVE rate (95% CI)	0.00 (0.00,0.17)

[1] Assessed between Day 126 and 168; [2] Assessed between Day 14 and Day 168; [3] Between Day 1 and Day 168; [4] Treatment policy estimand; [5] Direct efficacy estimand; [6] Including transfusion estimand.

The APPOINT-PNH results in patients naive to complement inhibitor therapy results showed that marginal proportions of patients achieved haematological response (as per the haematological responder primary and secondary endpoint analyses) and transfusion avoidance. APPOINT-PNH results also showed good control of complement-mediated IVH by iptacopan as shown by the large percentage change from baseline LDH.

The controlled pivotal Phase III study **APPLY-PNH** was designed in accordance with recommendations from global Health Authorities. Agreement was reached on the overall study design aspects, including patient population, primary and secondary efficacy endpoints, choice of comparator, dose evaluated, and sample size.

The sponsor obtained CHMP Scientific Advice, 12-Dec-2019 (EMEA/H/SA/3968/3/2019/III). They did not raise a question on significant benefit.

APPLY-PNH is an ongoing Phase III, randomized, multicenter, active comparator-controlled, open-label study, designed to demonstrate the efficacy and safety of iptacopan compared to anti-C5 antibody treatment (eculizumab/ravulizumab) in PNH patients with residual anaemia despite prior anti-C5 treatment through demonstration of superiority.

The study population consisted of PNH patients with residual anaemia, defined by a mean haemoglobin value below 10 g/dL, despite treatment with anti-C5. This represents a population for which there remains a high need for improved efficacy. The majority of patients in APPLY-PNH was transfusion dependent during the six months prior to randomization. A multicenter setting was chosen to ensure adequate recruitment and enrolment into the study in this rare indication. A randomized, active-comparator controlled study design for the main treatment period (24 weeks) was selected to appropriately assess the efficacy and safety of iptacopan and demonstrate superior efficacy compared to anti-C5 antibody treatment in support of its registration.

Anti-C5 therapy with monoclonal antibodies eculizumab or ravulizumab is considered the current standard of care for haemolytic PNH and were the only approved PNH therapies at time of study initiation.

Ninety-seven patients were randomized and included in the analysis of APPLY-PNH (62 patients to iptacopan and 35 to anti-C5). Demographics and baseline characteristics were generally balanced across treatment groups; there were no relevant differences between treatment groups that would be expected to influence or bias the results.

The two primary endpoints defined haematological response by 1) achieving a sustained haemoglobin increase of ≥2 g/dL from baseline in the absence of RBC transfusions and 2) achieving a sustained haemoglobin level of ≥12 g/dL in absence of RBC transfusions. These responder endpoints include 1) haemoglobin improvement/haemoglobin ≥12 g/dL approximating haemoglobin normalization and 2) transfusion independence, both criteria necessary to consider a patient as having achieved response.

Secondary endpoints included transfusion avoidance, average change from baseline in haemoglobin, ARC, LDH and FACIT-Fatigue, rates of breakthrough haemolysis (BTH) and Major Adverse Vascular Events (MAVEs) including thrombosis.

Results

In APPLY-PNH, iptacopan 200 mg b.i.d. monotherapy demonstrated a statistically significant superiority compared to standard of care anti-C5 therapy eculizumab or ravulizumab for the two primary haematological response endpoints and the majority of secondary endpoints (including transfusion avoidance, average change from baseline in haemoglobin, FACIT-Fatigue scores, ARC and adjusted annualized rate in clinical BTH). Iptacopan maintained control of IVH similar to anti-C5 as determined by the ratio to baseline in LDH.

Table 4. Summary of APPLY-PNH primary and secondary endpoints – randomized treatment period (FAS)

	LNP023 (N=62)	**Anti-C5 (N=35)**	**LNP023 vs. anti-C5 treatment effect (95% CI) adjusted for covariates**		
Endpoints	**Number of patients meeting criterion**[4]	**Number of patients meeting criterion** [4]	**Difference between response rates, %***	**Unadjusted two-sided p-value**	**Stat. sig. under testing strategy**
Primary endpoints					
≥2 g/dL increase in Hb from baseline[1] in the absence of RBC transfusions[2] [5]	51/60	0/35	80.3 (71.3, 87.6)	<0.0001	Yes
Hb ≥12 g/dL[1] in the absence of RBC transfusions[2] [5]	42/60	0/35	67.0 (56.3, 76.9)	<0.0001	Yes

Secondary endpoints					
Transfusion avoidance[2] [5]	60/62	14/35	70.3 (52.6, 84.9)	<0.0001	Yes
	Mean	**Mean**	**Difference between means**		
Change from baseline in Hb (g/dL)[1] [6]	3.6	-0.04	3.6 (3.2, 4.1)	<0.0001	Yes
Change from baseline in FACIT-Fatigue scores[1] [7]	8.6	0.3	8.3 (5.3, 11.3)	<0.0001	Yes
Change from baseline in ARC (10^9/L)[1] [7]	-115.9	0.37	-116.3 (-132.2, -100.4)	<0.0001	Yes
	Number of patients with an event	**Number of patients with an event**	**Annualized rate ratio**		
Clinical BTH[3] [7] (%)	2	6	0.10 (0.02, 0.61)	0.0118	Yes
MAVEs[3] [7] (%)	1	0	Not estimable	0.3173	No
	Geom. mean	**Geom. mean**	**Ratio of geom. Means**		
Ratio to baseline in LDH (U/L)[1] [7]]	0.96	0.98	0.99 (0.89, 1.10)	0.8345	No

* Model-based estimate'
[1] Assessed between Day 126 and Day 168; [2] Assessed between Day 14 and Day 168; [3] Between Day 1 and Day 168; [4] Among patients with evaluable/non-missing data; [5] Treatment policy estimand; [6] Direct efficacy estimand; [7] Including transfusion estimand.

Figure 1. Swimmer plot of patients requiring, or meeting criteria for, transfusion in randomized treatment period in APPLY-PNH (FAS)

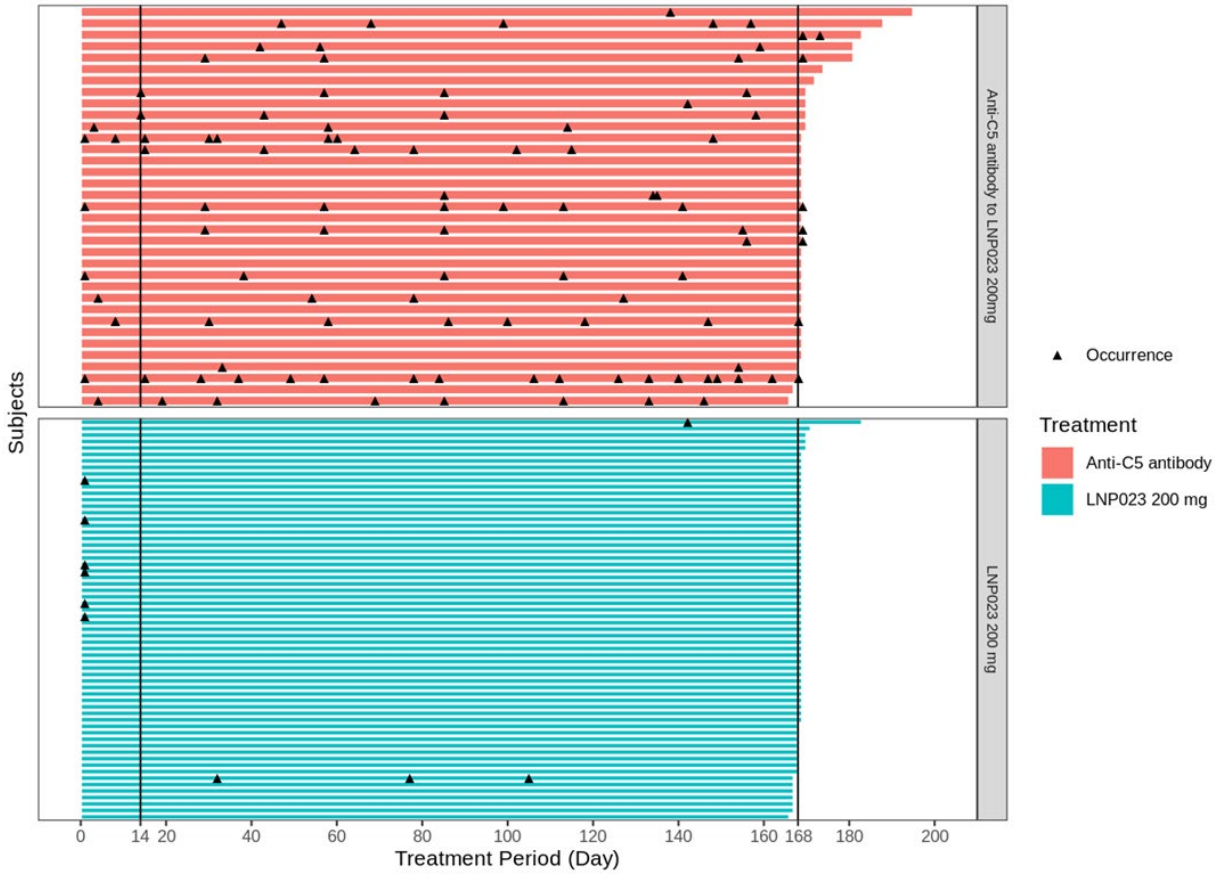
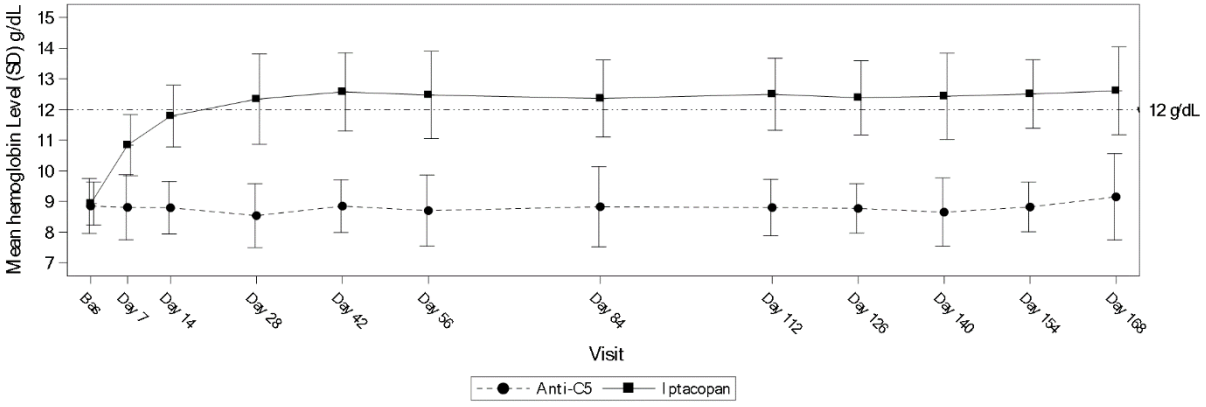


Figure 2. Mean (SD) haemoglobin values (g/dL) in randomized period, including post-transfusion data in APPLY-PNH (FAS)



Bas: Baseline. SD: standard deviation. At each visit, only patients with a value at both Baseline and that visit are included. The plot shows the mean (+/- SD) based on observed central lab haemoglobin data. Haemoglobin values within 30 days following the transfusion are included.

In conclusion, the efficacy of iptacopan is derived from study APPLY-PNH in a representative population of anti-C5 experienced patients with residual anaemia (haemoglobin <10 g/dL) with the majority of patients having received RBC transfusions in the 6 months prior to randomization. The study results are consistent, statistically significant and clinically meaningful, demonstrating the superiority of iptacopan monotherapy over anti-C5 therapy across a broad spectrum of clinically relevant endpoints in haemolytic PNH, with the majority of these being objectively measured laboratory parameters.

Iptacopan monotherapy resulted in clinically meaningful increases in haemoglobin levels, with the majority of patients achieving haemoglobin levels ≥12g/dL, approximating haemoglobin normalization, significantly reduced the need for RBC transfusions with almost all patients avoiding transfusions, and improved patient-reported fatigue. These benefits of iptacopan were achieved by maintaining IVH control and inhibiting EVH.

There is supportive data from the open-label, single-arm Phase III study, APPOINT-PNH in treatment naïve patients and additional supportive evidence of effectiveness from the two PNH Phase II studies X2204 and X2201.

The sponsor has provided sufficient clinical evidence to support the basis of significant benefit for the maintenance of the orphan designation.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 26 March 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of paroxysmal nocturnal haemoglobinuria (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in different organs. Vascular complications in the central nervous system are the most common cause of death;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Fabhalta is of significant benefit to those affected by the orphan condition is established. The sponsor has provided clinical data showing that treatment with Fabhalta monotherapy resulted in clinically meaningful increases in haemoglobin levels in patients who have haemolytic anaemia as compared to treatment with Complement 5 inhibitors.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Fabhalta, (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)), iptacopan for treatment of paroxysmal nocturnal haemoglobinuria (EU/3/20/2281) is not removed from the Community Register of Orphan Medicinal Products.