Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for FABHALTA

Active ingredient: iptacopan

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

June 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AESI	Adverse events of special interest
ARTG	Australian Register of Therapeutic Goods
AUC_{τ}	Area under the concentration time curve over one dosing interval
Bb	Fragment Bb of complement Factor B
CL/F	Apparent clearance
CI	Confidence interval
C_{max}	Maximum concentration
$C_{trough, ss}$	Pre-dose concentration, steady state
DCO	Data cut -off
GPI	Glycosylphosphatidylinositol
Hb	Haemoglobin
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
popPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
RMP	Risk management plan
SAEs	Serious adverse event(s)
SD	Standard deviation
TEAE	treatment-emergent adverse event(s)
TGA	Therapeutic Goods Administration
T_{max}	Time to reach C_{max}
V_z/F	Volume of distribution

FABHALTA (iptacopan) submission

Type of submission:	New chemical entity
Product name:	FABHALTA
Active ingredient:	iptacopan
Decision:	Approved
Date of decision:	6 August 2024
Date of entry onto ARTG:	12 August 2024
ARTG number:	410830
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Limited, 54 Waterloo Road, Macquarie Park NSW 2113
Dose form:	Capsule
Strength:	Each capsule contains 200 mg iptacopan (as 225.8 mg iptacopan hydrochloride monohydrate).
Container:	PVC/PE/PVdC (triplex) blister packs backed with aluminium foil.
Pack size:	56 capsules
Approved therapeutic use for the current submission:	FABHALTA is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH)
Route of administration:	Oral
Dosage:	200 mg taken orally twice daily For further information regarding dosage, refer to the Product Information.
Pregnancy category:	Category B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Proposed indication

This AusPAR describes the submission by Novartis Pharmaceuticals Australia Pty Limited (the Sponsor) to register FABHALTA (iptacopan) for the following proposed indication:[1]

The treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is caused by a somatic mutation in the PIG-A (phosphatidylinositol glycan class A) gene of haematopoietic stem cells.[2] This results in impaired production of the glycosylphosphatidylinositol (GPI) anchor, with subsequent loss of phosphatidylinositol-bound cell surface proteins including the complement regulatory protein CD55 and CD59 on cells including red blood cells.[3] Deficiencies of these regulators results in PNH red blood cells to be highly susceptible to complement-mediated haemolysis by the membrane attack complex (C5b-9 or MAC).[4]

Variable presentations can be mild to life-threatening and include haemolytic anaemia, thrombosis, smooth muscle dystonia, fatigue, haemoglobinuria, chronic renal impairment and pulmonary hypertension.[5] Thromboembolism is a known cause of mortality in patients with PNH and represents 40% to 67% of deaths. Anaemia is as a result of haemolysis and bone marrow failure.

PNH is estimated to affect between 10 and 20 cases/million individuals.[6] The estimated incidence in the general population is between 1.0 and 1.5 cases/million individuals[7].

Current treatment options

Therapy is directed against the venous thrombosis and the haemolytic anaemia. The treatment offered to patients may be guided by the severity of symptoms and the degree of haemolysis.

The only potentially curative treatment for PNH is allogeneic bone marrow transplantation, however not all patients can tolerate the conditioning therapy, and the graft procedure itself has its own treatment related mortality and morbidity (e.g. graft-versus-host disease and infection).

The anti-C5 monoclonal antibodies eculizumab and ravulizumab have become the standard of care for haemolytic PNH. These antibodies target the terminal component of the complement cascade, binding C5 and preventing cleavage of C5a and C5b needed for MAC formation. The

[1] This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Bessler M, Mason PJ, Hillmen P, Miyata T, Yamada N, Takeda J, Luzzatto L, Kinoshita T. Paroxysmal nocturnal haemoglobinuria (PNH) is caused by somatic mutations in the PIG-A gene. EMBO J. 1994 Jan 1;13(1):110-7. doi: 10.1002/j.1460-2075.1994.tb06240.x. PMID: 8306954; PMCID: PMC394784.

[3] Miyata T, Yamada N, Iida Y, Nishimura J, Takeda J, Kitani T, Kinoshita T. Abnormalities of PIG-A transcripts in granulocytes from patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1994 Jan 27;330(4):249-55. doi: 10.1056/NEJM199401273300404. PMID: 8272086.

[4] Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014 Oct 30;124(18):2804-11. doi: 10.1182/blood-2014-02-522128. Epub 2014 Sep 18. PMID: 25237200; PMCID: PMC4215311.

[5] Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers. 2017 May 18;3:17028. doi: 10.1038/nrdp.2017.28. PMID: 28516949; PMCID: PMC7879566.

[6] Cançado RD, Araújo ADS, Sandes AF, Arrais C, Lobo CLC, Figueiredo MS, Gualandro SFM, Saad STO, Costa FF. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematol Transfus Cell Ther. 2021 Jul-Sep;43(3):341-348. doi: 10.1016/j.htct.2020.06.006. Epub 2020 Jul 6. PMID: 32713742; PMCID: PMC8446255.

[7] Hill *et al.*, 2017

haematologic response to these antibodies can be variable although anti-C5 treatment inhibits intravascular haemolysis in most PNH patients and reduces the thromboembolic risk.

Ravulizumab has been found to be non-inferior to eculizumab. During maintenance therapy, eculizumab is given intravenously every 2 weeks and ravulizumab is given intravenously every 8 weeks.

Approximately two-thirds of patients treated with eculizumab have persistent anaemia with ongoing need for red blood cell transfusion[8,9]. Moreover, inhibition of C5 may result in C3-mediated extravascular haemolysis which could contribute to residual anaemia and transfusion dependence.

A new agent, pegcetacoplan which targets C3 of the complement system is also available. However, some patients remain transfusion-dependent and discontinue pegcetacoplan due to breakthrough haemolysis. Pegcetacoplan requires twice weekly subcutaneous infusion of a relatively large volume, which can be an inconvenience.

Clinical rationale

Iptacopan is a first-in-class, orally administered Factor B inhibitor of the alternative complement pathway developed for the treatment of PNH. Iptacopan targets the alternative pathway of the complement cascade proximally. In PNH, an alternative complement pathway driven disease, iptacopan through its mechanism of action has the potential to fully inhibit complement mediated haemolysis (intra- and extravascular). This may improve anaemia and decrease the associated need for transfusion, improving patient's fatigue with the potential to ultimately reduce hospital visits.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies.

The US FDA approved iptacopan on 5 December 2023 for the same indication proposed for Australia.

In the EU, the CHMP adopted a positive opinion for iptacopan on 21 March 2024 for the indication:

"FABHALTA is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia."

[8] Risitano AM, Marotta S, Ricci P, Marano L, Frieri C, Cacace F, Sica M, Kulasekararaj A, Calado RT, Scheinberg P, Notaro R, Peffault de Latour R. Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper From the SAAWP of the EBMT. Front Immunol. 2019 Jun 14;10:1157. doi: 10.3389/fimmu.2019.01157. PMID: 31258525; PMCID: PMC6587878.

[9] Debureaux et al. Bone Marrow Transplant 2021;56(10):2600-2602

Registration timeline

Table 1 captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

The active ingredient with its proposed indication was given orphan drug designation on 16 May 2023.

Table 1: Timeline for FABHALTA (iptacopan), submission PM-2023-02564-1-6

Description	Date
Designation (Orphan)	16 May 2023
Submission dossier accepted and evaluation commenced	31 July 2023
Evaluation completed	9 April 2024
Registration decision (Approved)	6 August 2024
Registration in the ARTG completed	12 August 2024
Number of working days from submission dossier acceptance to registration decision*	175 days

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA. There were no objections to approval from a quality perspective.

Nonclinical evaluation summary

The nonclinical data submitted was of high overall quality and adequate in scope, consistent with ICH M3 (R2)[10].

All pivotal safety-related studies were Good Laboratory Practice-compliant.

In vitro experiments established that the drug possesses nanomolar affinity for human complement factor B; functional inhibition of the alternative pathway of the complement cascade was demonstrated, with potency similar across humans and laboratory animal species. Iptacopan was shown to inhibit the haemolysis of red blood cells obtained from patients with PNH and of normal human erythrocytes treated with anti-CD55 and anti-CD59 antibodies (to render them similarly vulnerable to complement-mediated lysis as in PNH); inhibition of C3 deposition of the surface of erythrocytes from PNH patients was also demonstrated. Inhibition of the alternative pathway after oral administration was demonstrated in animals in vivo. Relevant

[10] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Us. ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals - Scientific guideline. 2013.

animal models of PNH are not available. The pharmacology studies offer support for the utility of iptacopan for the proposed indication.

Secondary pharmacodynamic studies revealed some inhibitory activity against the mammalian target of rapamycin (mTOR; the IC_{50} being 5.5-times higher than the peak unbound plasma concentration in patients). The relevance of this finding to the observed toxicity in animals is not known, and relevance to patients unclear.

Bactericidal activity against *Neisseria meningitidis* and *Streptococcus pneumoniae* in human serum or blood obtained from non-vaccinated individuals was severely inhibited or abolished in the presence of iptacopan in vitro, consistent with the known role of the alternative complement pathway in the clearance of encapsulated bacteria. Bactericidal activity is improved with vaccination. Contraindication in patients who are not currently vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae* is included in the Product Information document and warranted.

Safety pharmacology and other studies indicated no likely pharmacologically mediated adverse effects on CNS, cardiovascular or respiratory function in patients treated with FABHALTA. Decreased blood pressure and increased heart rate were observed in dogs, but only at high multiples of the clinical C_{max} for unbound drug.

Oral absorption of iptacopan was rapid to moderate in laboratory animal species, and similar to humans. Oral bioavailability in mice, rats and dogs was moderate. Plasma protein binding was concentration-dependent, decreasing with increasing drug concentration as binding to the primary pharmacological target was saturated. Partitioning into red blood cells was seen. Rapid and wide tissue distribution of ^{14}C-iptacopan-derived radioactivity was demonstrated in rats, with negligible penetration of the blood-brain barrier and some binding to melanin apparent.

Metabolism of iptacopan involves N-dealkylation, O-deethylation, C-oxidation and glucuronidation, with a chief role for CYP2C8 identified. Excretion of iptacopan and/or its metabolites was predominantly via the faeces in rats and humans. Biliary excretion was demonstrated in rats and indicated from in vitro experiments with cultured human hepatocytes.

In vitro data indicate the potential for CYP2C8 inducers/inhibitors to alter iptacopan exposure in patients, and for iptacopan to cause interactions through inhibition of

P-glycoprotein and OATP1B1. Clinical drug-interaction studies investigating such effects have been conducted.

Iptacopan had a low order of acute toxicity by the oral route in animals.

Repeat-dose toxicity studies by the oral route were conducted in mice (up to 4 weeks), rats (up to 6 months) and dogs (up to 9 months). The thyroid, male reproductive organs, bone marrow and heart/cardiovascular system were identified as the key targets in these studies. Clinical relevance is judged to be low.

Iptacopan was not genotoxic in a standard battery of in vitro and in vivo studies, and not carcinogenic in transgenic mice or in rats.

Iptacopan did not impair male or female fertility in rats, produce malformations or other adverse effects on embryofetal development in rats and rabbits, or cause adverse effects on postnatal development in rats. Assignment to Pregnancy Category B1 (rather than Category C as the Sponsor proposes) is warranted.

While FABHALTA is not proposed for paediatric use, the submission included data on juvenile toxicity which revealed increased sensitivity of juvenile dogs to adverse effects on the heart and aorta cf. adults.

Phototoxicity is not predicted in patients, based on the results of in vitro and in vivo studies.

There are no nonclinical objections to the registration of FABHALTA for the proposed indication.

Clinical evaluation summary

Pharmacology

The pharmacology data for iptacopan comes from the following studies:

- 2 PK studies in healthy adults (CLNP023X2101 and CLNP023A2101)
- 2 studies in special populations (CLNP023A2105 (hepatic impairment) and CLNP023X1102 (healthy Japanese male subjects))
- 1 study on PK interactions (CLNP023A2104)
- 1 pharmacodynamic study on corrected QT Interval (QTc; CLNP023A2107)

There were also limited PK studies as part of the phase II and III studies i.e., in the target population

Pharmacokinetics

Iptacopan pharmacokinetics (PK) were similar in both healthy subjects and patients with PNH.

Absorption

- Iptacopan is to be orally administered as a single immediate release capsule containing 200 mg of drug b.i.d. Following a single oral 200 mg dose of iptacopan the median T_{max} was 1.13 h.
- No clinical studies have investigated the absolute bioavailability of iptacopan. The Sponsor has provided a justification for this, which was accepted by the clinical Evaluator.
- A high fat meal had no clinically relevant effect on iptacopan PKs when compared to the fasted state.
- Following ascending single or multiple doses administered bid, increases in iptacopan exposure were dose-dependent but less than dose-proportional.
- Following multiple doses administered b.i.d, the accumulation ratio for C_{max} at steady state was similar to AUC_{τ} ranged from 1.10- and 1.49-fold. Steady-state was attained following approximately 5 to 7 days of dosing.
- The proposed bid dosing regimen appears appropriate as following b.i.d dosing a consistent iptacopan trough plasma concentration was maintained throughout the multiple ascending dose study

Distribution

- Following a single dose of 200mg the mean volume of distribution (V_z/F) of iptacopan was 3.46L. The steady state V_z/F value following administration of 200mg iptacopan bid to 6 healthy subjects was 288L.
- Iptacopan bound to human serum albumin, α-1-acid glycoprotein and lipoproteins in a non-concentration dependent manner and they accounted for 28.4%, 9.25% and 16.0% of total plasma protein binding, respectively. By contrast, binding to Factor B (FB) was concentration-dependent up to the point of saturation.

Metabolism

- Following a single 100-mg oral dose of [^{14}C]LNP023 (iptacopan) to healthy subjects, two circulating metabolites were identified, which were formed via direct acyl glucuronidation (M8) and O- deethylation/acyl glucuronidation (M9).
- The most abundant circulating component of iptacopan in plasma was parent drug, which accounted for 83% of the total radioactivity, whereas the two circulating metabolites M8 and M9 accounted for 8.05% and 5.17%, respectively. These two circulating metabolites in plasma and the major metabolite identified in faeces (M2) were 27-fold and 150- fold less potent than iptacopan.

Excretion

- Iptacopan elimination primarily occurs via multiple hepatic pathways which are responsible for approximately 79.5% of its elimination, whereas the remaining 20.5% is eliminated renally.
- Iptacopan CL/F increased dose-dependently but less than dose-proportionally.
- Following a single 100-mg oral dose of [^{14}C]LNP023, radioactivity was predominantly excreted in faeces (71.5%), whereas excretion in urine was 24.8%.

Inter-subject variability

Following dosing with 25 to 200 mg bd the intra-individual variability values for iptacopan C_{max} and AUC ranged from 11.7% to 26.8%. The intra-subject variability in $C_{trough,ss}$ was 13.3%, whereas in patients with PNH, intra-subject variability on C_{max} and AUC_{τ} ranged from 26.9% to 22.6%, respectively.

Special populations

- Hepatic impairment had little effect on total iptacopan exposure, whereas iptacopan unbound exposure increased significantly with the level of hepatic impairment. The PI states that no dose adjustment is necessary for hepatic impairment, which is appropriate.
- There was no difference between iptacopan PKs in healthy Japanese males and healthy non-Japanese subjects.

Pharmacokinetic Interactions

- Both CYP2C8- and OATP-inhibition have a mild effect on iptacopan PKs and suggest that iptacopan is a relatively weak to mild substrate for CYP2C8 and OATP.
- Iptacopan had little to no effect on the PKs of P-gp-substrates nor did it inhibit uptake via the OATP transporter.

Population pharmacokinetics

A separate evaluation of the following population pharmacokinetics (popPK) data was conducted by a specialist popPK Evaluator:

- Population pharmacokinetics of iptacopan in PNH, C3 glomerulopathy and IgA nephropathy: Modelling Report
- Biomarker exposure-response analysis of iptacopan in healthy volunteers and patients with PNH, C3 glomerulopathy and IgA nephropathy: Modelling Report

The Evaluator concluded:

> "The modelling reports provided detailed descriptions of the data handling, methods and results and discussion of the population PK and PK-pharmacodynamic (PD) results of iptacopan in PNH, C3G and IgA nephropathy patients. However, the population PK model assumptions and parameter estimates do not align with values reported elsewhere. It is possible that there is flip- flop kinetics which influences the interpretation of the PK parameters or there is simply a scaling issue in the reporting of the PK parameters. If neither are correct, then the model should be re-estimated with initial estimates based on the results of the noncompartmental analysis. In any case, the parameters of the final population PK model require clarification. Covariate effects should be considered cautiously until the final population model is clarified.
>
> PK/PD analysis used time-matched iptacopan concentrations and complement pathway biomarkers, Wieslab activity, plasma complement factor B and plasma soluble C5b-9. There was an inhibitory effect of iptacopan on each of the three biomarkers which was dependent on the magnitude of the baseline biomarker; patient population also influenced the Wieslab and plasma fragment Bb of complement Factor B (Bb) responses. Although dose-exposure-response simulations used the population PK model together with the PK-PD model, observed data was overlaid and demonstrated the effectiveness of the 200 mg BID regimen to achieve consistent responses above the EC90 for all biomarkers. PK-PD simulations incorporating the population PK and PK-PD models were used to evaluate the proportion of subjects expected to achieve EC_{90} and the impact of missed doses on PD profiles over time.
>
> These should be re-evaluated once the final PK model is clarified."

In response, the Sponsor provided clarification regarding the data pool used for the popPK analysis, as well as the model assumptions and parameter estimates. The model was re-estimated using different initial conditions, showing similar covariate effects compared to the original model.

The limitations of the popPK model are acknowledged by the Sponsor and also the FDA in their integrated review:

> "The final population PK model and sensitivity population PK model were reproduced. The model estimated a flip-flop PK for iptacopan. A small apparent volume of distribution was estimated with a large shrinkage in the final model, which may be due to the inappropriate model structure. However, a two-compartment model would lead to large shrinkage in CL/F; therefore, a one-compartment model was selected. As a result, there are limitations to the population PK analysis."
>
> "The proposed PK/PD analyses for the three biomarkers appeared to be acceptable."

Nevertheless, the submission also contains adequate clinical evidence of the PK of iptacopan, which supports the 200mg dose, and the limitations of the popPK model are not considered a barrier to registration.

Pharmacodynamics

Mechanism of action

Iptacopan is a proximal complement inhibitor that targets FB to selectively inhibit the alternative pathway while leaving the direct signalling 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 haemolysis (IVH) is mediated by the downstream membrane attack complex (MAC), while extravascular haemolysis (EVH) is facilitated by C3b opsonization. Iptacopan acts proximally in the alternative pathway of the complement cascade to control both C3b-mediated EVH and terminal complement-mediated IVH.

Primary pharmacodynamic effects

- Following iptacopan single ascending dose from 5 to 400 mg and multiple ascending doses from 25 to 200 mg, rapid and significant (>80%) suppression of alternative pathway activity was identified 2h post-dose for all of the doses tested except for the 5mg dose and >60% suppression was generally maintained throughout the entire multiple ascending dosing period.
- In contrast to placebo dosing, administration of iptacopan induced decreases in Bb levels 2 h following dosing, which were generally maintained until 12h post-dose; however, the magnitude of decrease in Bb level was largely dependent on Bb levels at baseline.
- Decreased levels of sC5b-9 were also identified following iptacopan administration; however, decreases, albeit smaller in magnitude, were also detected in placebo treated subjects. By contrast, the CH_{50} assay showed that iptacopan had no significant effects on the classical complement pathways following the highest doses used in the multiple ascending dose study.

Secondary pharmacodynamic effects

At the geometric mean C_{max} values attained following doses of 400 mg, 800 mg and 1200 mg iptacopan, the upper bound of the two-sided 90% CI for model-derived placebo adjusted ΔFridericia-corrected QT values were 2.82 msec, 2.94 msec and 3.22 msec, respectively.

Efficacy

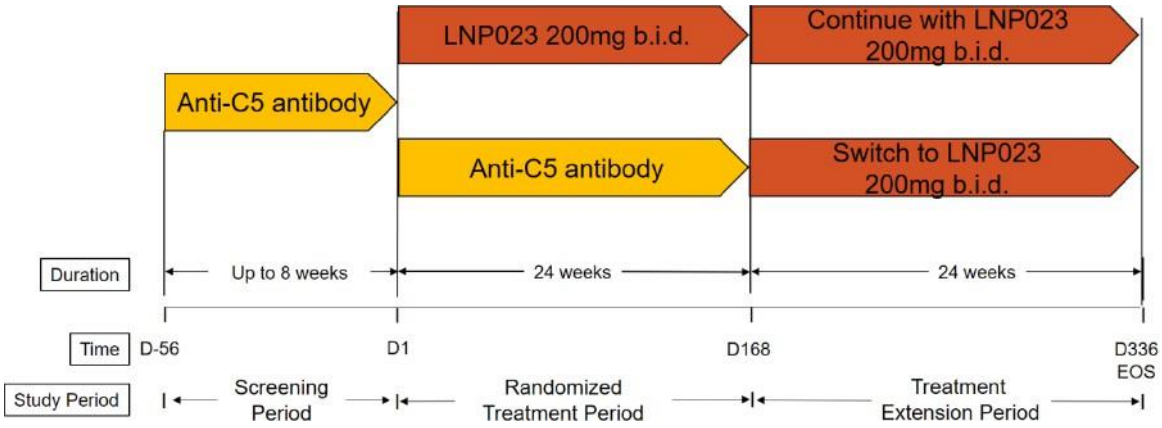
The primary efficacy and safety data supporting the PNH indication were provided by the pivotal phase III study CLNP023C12302 (the APPLY-PNH study), a randomised, active-controlled study comparing iptacopan monotherapy 200mg bd to anti-C5 treatment in PNH patients with residual anaemia despite prior anti-C5 therapy. In addition, there was a supportive study CLNP023C12301 (the APPOINT-PNH study), a single arm, open-label study evaluating iptacopan monotherapy 200mg b.d. in PNH patients who were complement inhibitor treatment-naïve.

There were 2 additional, open-label phase II studies to support efficacy (study CLNP023X2204 in complement inhibitor-naïve PNH patients and study CLNP023X2201 in anti-C5 exposed PNH patients).

Pivotal study: APPLY-PNH

APPLY-PNH was a randomised, multicentre, open-label trial comparing iptacopan with an anti-C5 antibody. The study occurred in three phases: a screening period lasting up to 8 weeks; a 24 week randomised, open-label active control treatment period for the primary efficacy and safety analyses; and a 24 week open-label extension period (Figure 1):

Figure 1: Study design: CLNP023C12302, APPLY-PNH



Key aspects of the study are described in the PICO table (Table 2):

Table 2: PICO table: CLNP023C12302, APPLY-PNH

Population	Adult patients with PNH with residual anaemia (haemoglobin [Hb] <10g/dL) despite stable treatment regimen with an anti-C5 antibody (eculizumab or ravulizumab) for at least 6 months prior to randomisation. Vaccination against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* were required at least 2 weeks prior to first dose. If iptacopan treatment had to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment was initiated. Patients were enrolled in Brazil, Czech, France, Germany, Italy, Japan, South Korea, Netherlands, Spain, Taiwan, United Kingdom and the United States. The first patient first visit occurred on 25 January 2021, and the data cut-off (DCO) for the data provided in the original submission was 26 September 2022. During evaluation, the final data for the entire 48-week study was provided with a DCO of 6 March 2023. Patients were randomised 8:5 to the iptacopan or control groups, respectively
Intervention	Iptacopan 200mg orally bd
Control	IV anti-C5 antibody
Outcome	Primary endpoints: increase from baseline Hb ≥2g/dL (assessed between day 126 and 168) in the absence of red blood cell transfusion between day 14 and 168 Hb levels ≥12g/dL (assessed between day 126 and 168) in the absence of red blood cell transfusion between day 14 and 168 Multiplicity adjustment: weighted permutation test with equal weights to each of the two primary endpoints Secondary endpoints: Absence of administration of packed red blood cell transfusion transfusions between Day 14 and 168 Change from baseline Hb, FACIT-Fatigue scores, reticulocyte count, lactate dehydrogenase (LDH) levels between day 126 – 168

	Occurrences of breakthrough haemolysis and major adverse vascular events (MAVEs) between day 1 – 168 Safety evaluations

Participant flow and baseline characteristics

125 patients were screened, 97 were randomised, 62 to the iptacopan group and 35 to the anti-C5 group. 61 (98.4%) in the iptacopan group and 35 (100%) in the anti-C5 group completed the treatment period on treatment. One patient in the iptacopan group discontinued study treatment due to pregnancy (later had a healthy baby after a normal full-term pregnancy).

Of the 96 patients who completed the 24-week treatment period, 95 entered the extension study with assignment to iptacopan, and 94 completed the extension period on iptacopan. 1 patient (1.1%) discontinued the initial study due to investigator's decision (patient clinical condition) and 1 patient (1.1%) discontinued iptacopan due to pregnancy and continued all study assessment until the end of the extension period.

Results (DCO 26 September 2022)

After the initial submission, which included data from the interim 24-week database lock for APPLY-PNH, it was discovered that an additional red blood cell transfusion had been administered to a patient in the iptacopan arm during the 24-week randomized period. Subsequently, the database was updated, the efficacy analyses were repeated and minor numerical updates were made to the efficacy results.

For the primary endpoint of ≥ 2g/dL in Hb from baseline in the absence of RBC transfusions, 51 of 60 (82.3%) patients in the iptacopan group compared to 0 of 35 (0%) in the control group achieved this. The model based difference was 80.2% (95% CI 71.3 – 87.6, p<0.0001) in favour of iptacopan. For the other primary endpoint of Hb levels ≥12g/dL, 42 (68.8%) patients in the iptacopan group achieved this compared to 0 (0%) in the control group. The model based difference was 67.0% (95% CI 56.4-76.9, p<0.0001). In terms of marginal proportions, the values for iptacopan were 82.3% (73.4, 90.2) and for anti-C5 was 2.0% (95% CI: 1.1, 4.1) in terms of increase in the haemoglobin levels from baseline of >2g/dL and for sustained haemoglobin levels of >12g/dL these values were 68.8% (95% CI: 58.3, 78.9) and 1.8% (95% CI: 0.9, 4.0) for the iptacopan and anti-C5 groups, respectively. These results are shown in Tables 3 and 4:

Table 3: APPLY-PNH Study, Results for primary and secondary endpoints – randomised treatment period

Endpoints	FABHALTA (N=62)	Anti-C5 (N=35)	Difference (95% CI) p-value
Primary endpoints			
Number of patients achieving haemoglobin improvement (sustained increase of haemoglobin 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 haemoglobin 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
Haemoglobin 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 haemolysis [h,i], % (n/N)	3.2 (2/62)	17.1 (6/35)	
Annualized rate of clinical breakthrough haemolysis	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 (in 2 patients with partially missing central haemoglobin data between days 126 and 168, the haematological response could not be established unequivocally). The haematological response was derived using multiple imputation. These patients did not discontinue).
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 haemolysis defined as meeting clinical criteria (either decrease of Haemoglobin level ≥ 2 g/dL compared to the last assessment or within 15 days; or signs or symptoms of gross haemoglobinuria, 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).

Table 4: APPLY-PNH Study, Responder analysis results

Responder Criterion Treatment	n/M	Marginal proportion (95% CI)[1]	Diff. in marginal proportion (95% CI)[1]	Ratio of marginal proportion (95% CI)[1]	Unadjusted for multiplicity	
					OR (95% CI)[2]	Two-sided p-value[2]
Increase in hemoglobin levels ≥ 2 g/dL from baseline ($) without requiring RBC transfusions (#)						
LNP023 200mg b.i.d. N=62	51/60	82.3 (73.4, 90.2)	80.3 (71.3, 87.6)	40.20 (20.73, 74.80)	338.74 (25.12, 4567.99)	<0.0001
Anti-C5 antibody N=35	0/35	2.0 (1.1, 4.1)				
Hemoglobin levels ≥ 12 g/dL ($) without requiring RBC transfusions (#)						
LNP023 200mg b.i.d. N=62	42/60	68.8 (58.3, 78.9)	67.0 (56.3, 76.9)	38.17 (16.83, 78.81)	496.80 (24.44, 10096.85)	<0.0001
Anti-C5 antibody N=35	0/35	1.8 (0.9, 4.0)				

N = The total number of patients in the treatment group included in the model (without missing covariates).
n = The number of patients who responded based on non-missing data
M = The number of patients in the treatment group with response variable defined based on non-missing data (evaluable patients).
1 Logistic regression model using Firth correction with common intercept and randomization strata, sex, indicator variable of age >= 45 years, indicator variable of baseline haemoglobin >= 9 g/dL as factors. The 95% CI is computed using bootstrap.
2 Logistic regression model using Firth correction with randomization strata, sex, indicator variable of age ?.. 45 years, indicator variable of baseline haemoglobin >= 9 g/dL as factors.
$ between Day 126 and 168 (at least 3 out of 4 scheduled measurements).
# between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria.

Consistency of the 2 primary analyses was confirmed by the results of 2 sensitivity analyses, 2 post hoc analyses and a supportive analysis using a Cochran-Mantel-Haenszel test. Pre-specified sub-group analyses for the 2 primary haematological endpoints were consistent across subgroups including the groups having transfusion history in the 6 months prior to randomisation (Yes/No), number of transfusions in the last 6 months prior to randomisation (<2/>2) and baseline haemoglobin value (<9g/dL/>9g/dL).

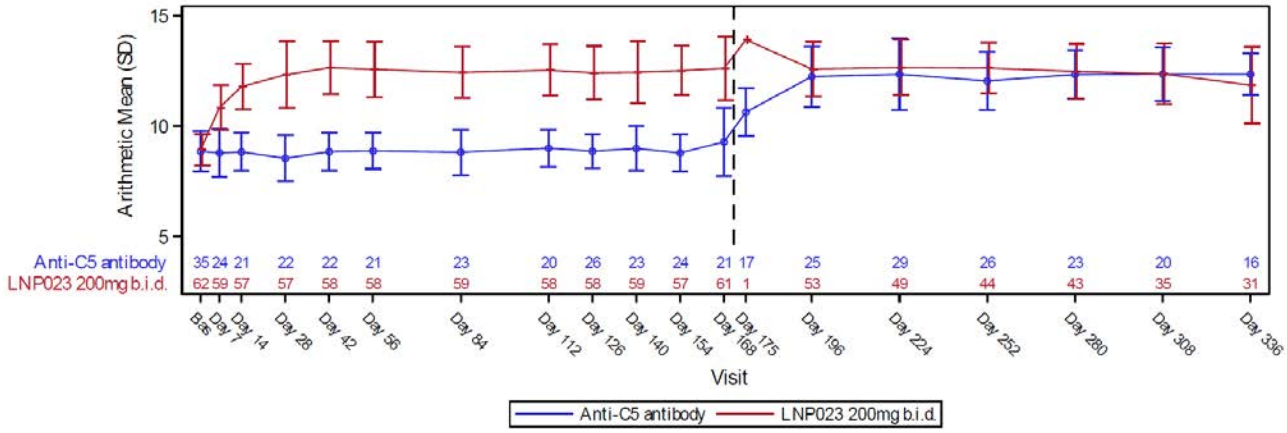
The results for secondary endpoints are included in table 2, above. Iptacopan was superior to anti-C5 therapy in terms of avoiding transfusion between day 14 – 168, change from baseline in Hb, reticulocyte count, and LDH, and the annualised adjusted rate of breakthrough haemolysis.

Iptacopan was not statistically significantly superior to anti-C5 therapy for MAVEs between day 1 and 168 of the randomised treatment period. Event rates however were small: 1 patient in the iptacopan group had a MAVE, a transient ischemic attack, translating into an annualised rate (95% CI) of 0.03% (0.00, 0.25) and there being no event in the anti-C5 group (p=0.3173).

Results (DCO 6 March 2023)

No formal statistical inference was planned for the endpoints in the extension phase of the APPLY-PNH study. Nevertheless, the 48 week efficacy results supported the durability of iptacopan at 200mg bd in terms of the increase in mean Hb levels, and transfusion independence (Figure 2). The following figure shows the arithmetic mean (SD) of haemoglobin (g/dL) by treatment group and visit. For patients initially randomised to iptacopan, increased Hb levels were maintained throughout the extension period (mean (SD) haemoglobin was 8.93 (0.70) g/dL at baseline, 12.61 (1.43) g/dL at Day 168 (24 weeks) and 12.19 (1.57) g/dL at Day 336). For patients who switched from a C5 inhibitor to iptacopan for the extension period, an increase in mean Hb was seen following the switch, and was maintained throughout the extension period (mean (SD) haemoglobin was 8.85 (0.90) g/dL at baseline, 9.15 (1.41) g/dL at Day 168 (24 weeks) (last assessment before switch) and 12.12 (1.41) g/dL at Day 336 (48 weeks). Note that the trial eligibility criteria required residual anaemia despite anti-C5 therapy, thus, is it not know how iptacopan compares to C5 inhibitors in the general PNH population.

Figure 2: Plot of haemoglobin values over time in available data up to Week 48 in APPLY-PNH (FAS)



Bas: Baseline.

SD: standard deviation.

At each visit-window, only patients with a value at both baseline and that visit-window are included.

Haemoglobin values within 30 days following the transfusion are considered missing.

The number of patients used for analysis are presented for each treatment group.

The plot shows the mean(+/- SD) based on observed central lab haemoglobin data.

In patients randomised to iptacopan, from Day 14 of treatment with iptacopan until the end of the study (Day 336), 57 of 62 (91.9%) patients remained transfusion free. In the patients randomized to anti-C5 and switching to iptacopan at Day 168, 94.1% patients remained transfusion free from Day 14 of iptacopan treatment to Day 336. LDH levels were comparable in both groups throughout the extension period.

Supportive studies

APPOINT-PNH (CLNP023C12301) (DCO 2 November 2022)

This was a multicentre, single-arm, open-label study investigating the efficacy and safety of iptacopan in patients who had not previously received a complement inhibitor. The study was conducted in China, the Czech Republic, France, Germany, Italy, Japan, South Korea, Malaysia, Singapore and the United Kingdom, from 17 July 2021 to the DCO on 2 November 2022.

The trial consisted of 3 periods: a screening period lasting up to 8 weeks; a core treatment period for 24 weeks; and an extension treatment period for 24 weeks (Table 5).

Table 5: APPOINT-PNH (CLNP023C12301) study

Population	Complement inhibitor naïve patients with PNH, and haemolysis (LDH >1.5 ULN) and anaemia (Hb <10g/dL). 40 patients were planned, 52 were screened and 40 enrolled. All 40 patients completed the core treatment period. 39 patients entered the extension period and at the DCO, 7 (17.5%) had completed the extension period.
Intervention	Iptacopan 200mg bd orally during the core and extension treatment periods
Control	N/A
Outcome	Primary endpoint: sustained increase from baseline in Hb of ≥2g/dL in the absence of red blood cell transfusion (proportion of patients reaching the status of responder). 92.2% (95% CI: 82.5-100.0) of patients achieve a sustained increase in Hb from baseline of ≥2g/dL without RBC transfusions.
	Secondary endpoints: Hb ≥12g/dL in the absence of RBC transfusion o 62.8% of patients (95% CI: 47.5-77.5) Transfusion avoidance o 97.6% of patients (95% CI: 92.5 - 100.0) Change from baseline in Hb levels (g/dL) o Adjusted mean: 4.28 (95% CI: 3.87-4.70) Change from baseline in LDH levels (%) o -83.55 (95% CI: -84.90- -82.08) Breakthrough haemolysis events No events in the treatment period MAVEs No events in the treatment period

APPOINT-PNH (CLNP023C12301) (DCO 29 April 2023)

At the end of this study, all 40 patients had completed the extension period to 48 weeks. The results from the extension period support the durability of iptacopan 200mg bd in terms of haemoglobin increase and transfusion avoidance. At baseline, patients had a mean (SD) haemoglobin level of 8.16 (1.087) g/dL, 12.56 (1.486) g/dL at Day 168 and 13.24 g/dL (1.798) at Day 336, resulting in a mean increase from baseline of 5.09 (2.010) g/dL. One patient required transfusions during the extension period (case confounded by emergence of cold agglutinins); therefore 39/40 patients (97.5%) did not require a transfusion between day 14 and 336.

Study CLNP023X2204 (study X2204)

This is a phase II randomised, open-label, multicentre study of iptacopan in PNH patients who had not previously received a complement inhibitor. The study was conducted between 5 April 2019-9 February 2022 in the Republic of Korea, Malaysia, Singapore and Taiwan.

The study consisted of an 8 week screening period, a 4 week treatment period at the first dose (period 1), an 8 week period at the second dose (period 2), then a 2 year extension period (period 3) for patients who responded. Patients were enrolled in one of two cohorts (Table 6).

Table 6: Study CLNP023X2204

Population	Complement inhibitor naïve patients with PNH, LDH values ≥ 1.5 × ULN and Hemoglobin level < 10.5 g/dL 13 patients were enrolled, 7 were randomized to Cohort 1 and 6 to cohort 2. 11 patients completed the study.
Cohort 1	Sequence 1: 4 weeks of treatment with iptacopan 25mg bd in period 1 followed by iptacopan 100mg bd for 8 weeks (period 2) and during the extension period (period 3). If during period 1, LDH was not reduced by ≥40% for the mean of pre-treatment values by week 2, the iptacopan dose was to be up-titrated to 100mg bd from study day 17. If the LDH was not reduced by ≥40% from the mean of pre-treatment values at week 4, the iptacopan dose was to be up-titrated to 200mg bd in period 2 and 3 starting from day 30. In the approximate 2-year extension period (extension period 3), patients maintained the same treatment regimen as used in period 2.
Cohort 2	Sequence 2: 4 weeks of treatment with iptacopan 50mg bd in period 1 followed by iptacopan 200mg bd for 8 weeks (period 2) and during the extension period (period 3) If during period 1, LDH was not reduced by ≥40% for the mean of pre-treatment values by week 2, the dose was up-titrated to 200mg bd from study day 17. In the approximate 2-year extension period 3, patients remained on 200mg bd.

Outcome	Primary endpoint: Proportion of patients with 60% reduction in LDH or LDH below ULN, after up to 12 weeks of treatment Of the 13 patients enrolled, 12 were assessed for efficacy and all 12 (100%) achieved the primary endpoint by week 12 No patients required up titration of iptacopan dose Cohort 1: mean reduction in LDH from baseline was 86.2% at week 12 Cohort 2: mean reduction in LDH from baseline was 85.9% at week 12 Long-term persistence of LDH reduction (into treatment extension period 3) of over 80% was seen in both cohorts with all patients who continued treatment up to week 108 (5 patients in cohort 1 and 4 in cohort 2). Secondary endpoints: Dose-response effect of iptacopan on reduction of PNH-associated haemolysis Markers of intravascular and extravascular haemolysis In cohort 1, there was improvement in haemoglobin levels with levels ≥120g/dL in 3 patients and between ≥100g/l and <120g/l in the remaining 3 patients at week 12. In cohort 2, 2 of 3 patients at week 12 showed improvement in haemoglobin concentrations with levels ≥120g/dL. A total of 3 patients achieved haemoglobin normalisation by week 12

Study CLNP023X2201 (X2201)

This was an open-label, multiple dose phase II study of iptacopan given in addition to an anti-C5 antibody in patients with PNH and active haemolysis. The study was conducted in France, Germany and Italy over 13 weeks, and patients were enrolled in one of two cohorts, as shown below (Table 7).

Table 7: Study CLNP023X2201

Population	Patients with PNH who had signs of active haemolysis were enrolled. Patients were required to be on a stable regimen of standard of care (anti-C5 monoclonal antibody) for at least 3 months prior to the first iptacopan dose. 15 patients were planned, 16 were enrolled, 10 patients in cohort 1 and 6 in cohort 2. All patients completed part 1 of the study (13 weeks) and 13 (81.3%) completed part 2. There were 3 deaths in cohort 1, further discussed in the safety section of this overview. In summary: Two patients in cohort 1 died due to TEAEs, 1 due to general physical health deterioration following *Escherichia coli* sepsis after surgery for aortic repair and 1 from squamous cell carcinoma of the oral cavity. there was 1 death due to sepsis following salvage chemotherapy for a lymphoproliferative disorder.

Cohort 1	Iptacopan 200mg bd for 13 weeks (part 1) and ongoing for 2-3 years (part 2) + 'standard of care' treatment with an anti-C5 antibody
Cohort 2	Iptacopan 50mg bd for at least 2 weeks, then increased to 200mg bd + 'standard of care' treatment with an anti-C5 antibody
Outcome	Primary endpoint: Reduction in chronic haemolysis, as assessed by LDH levels at week 13 6/10 in cohort 1 and 1/6 in cohort 2 achieved complete normalisation of LDH (<250 U/L) LS means of LDH (95% CI) for cohort 1 was 189 (-15.8, 394.7) U/L compared to 391 (106.4, 674.8) U/L in cohort 2 Secondary endpoints: Markers of intra and extravascular haemolysis mean haemoglobin increased by 32.04 g/dL from baseline, to 126.60 g/dL at day 92 with sustained increase in haemoglobin of 33.08 from baseline to day 1233 9 patients achieved normal haemoglobin levels at day 92 and in addition 9 patients at day 393 and 8 at day 729 The majority of patients were transfusion independent although 1 patient required red blood cell transfusion on day 1 in cohort 1 and 1 patient on day 2 in cohort 2

Study CLFG316X2201

This was an open-label proof of concept study to assess the use of LFG316 intravenous anti-C5 monoclonal antibody in patients with PNH. Patients received LFG316 IV every 14 days for 4 weeks and entered an optional 48 week treatment period continuing LFG316 infusions every 14 days. An additional extension period up to 260 weeks was allowed following which patients were switched to LNP023 (iptacopan) for approximately 21 weeks.

For those patients who continued into the iptacopan treatment period 4, the minimum exposure was 134 days and maximum exposure 169 days at a dosage of 200mg bd. The primary objective of the study was to assess the IV LFG316 treatment and thus was not directly relevant to the proposed indication. However, it was found that complement inhibition with iptacopan controlled intravascular and extravascular haemolysis.

Safety

Safety data from APPLY-PNH, APPOINT-PNH, and other studies of iptacopan in C3 glomerulopathy and IgA nephropathy have been reviewed by the clinical Evaluator. Details can be found in the clinical evaluation report, p55. This overview focuses on the safety data from the randomised period of APPLY-PNH, as this is the key comparative safety data supporting the submission.

Safety in APPLY-PNH (DCO 26 September 2022)

The pivotal study, APPLY-PNH provides comparative safety data between iptacopan and anti-C5 antibodies. Data from the 26 September 2022 data cut (the end of the randomised study period) is presented here, as it allows comparison with C5 inhibitors and therefore provides meaningful safety data. Additional safety data from the extension period of this study, in which all patients received iptacopan, as well as other studies including APPOINT-PNH, are also presented in separate sections of this overview.

Median duration of exposure in APPLY-PNH was 24.1 weeks in both groups in the randomised period. 51/62 patients (82.3%) in the iptacopan group compared to 28/35 (80.0%) in the anti-C5 group experienced at least one treatment-emergent adverse event (TEAE). Most adverse events (AEs) were tolerable, with no TEAEs leading to dose interruption or discontinuation during the treatment period. Serious adverse events (SAEs) occurred more frequently in the anti-C5 arm (14.3%) compared to the iptacopan arm (9.7%).

In addition, there were no deaths during the study. A summary of TEAEs is presented in Table 8.

Table 8: APPLY-PNH, summary of TEAEs

Category	LNP023 200 mg b.i.d. N=62 n (%)	Anti-C5 N=35 n (%)
Adverse events	51 (82.3)	28 (80.0)
Suspected to be related to study medication	16 (25.8)	3 (8.6)
Severe AEs	3 (4.8)	3 (8.6)
Suspected to be related to study medication	0	0
SAEs	6 (9.7)	5 (14.3)
Suspected to be related to study medication	1 (1.6)	0
Fatal SAEs (Deaths)	0	0
Treatment-related	0	0
AEs leading to treatment discontinuation	0	0
Treatment-related	0	0
AEs leading to interruption	0	0
AEs requiring additional therapy	40 (64.5)	18 (51.4)

- A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
- Data collected on AE CRF pages is summarized.
- Serious events are those marked Yes for SAE.
- AEs causing study drug discontinuations refer to those with 'Action taken with study treatment' answered as 'Drug withdrawn'.
- AEs causing study drug interruptions refer to those with 'Action taken with study treatment' answered as 'Drug interrupted'.
- Treatment Emergent Adverse Event (TEAE) is defined as event started during on-treatment period.
- On-treatment period for LNP023 is from first dose date until 7 days after the date of last dose administered.
- On-treatment period for Anti-05 is from the first dose date until one day before the next planned dose.

The most common TEAEs occurring in ≥ 5 patients in either group were headache, diarrhoea, nasopharyngitis, nausea and arthralgia, all occurring more frequently in the iptacopan group compared to the anti-C5 group, as shown below. This may explain the higher numbers of AEs suspected to be due to medication in the iptacopan group (16, 25.8%) compared to the anti-C5 group (3, 8.6%). Breakthrough haemolysis was more frequent in the anti-C5 group (Table 9).

Table 9: APPLY-PNH, most common TEAEs (≥ 5 patients in either group) by preferred term in randomised treatment period

Preferred term	LNP023 200 mg b.i.d. N=62 n (%)	Anti-C5 N=35 n (%)	Risk Difference (95% CI)
Number of patients with at least one event	**51 (82.3)**	**28 (80.0)**	**2.26 (-14.05, 18.57)**
Headache	10 (16.1)	1 (2.9)	13.27 (2.58, 23.96)
Diarrhoea	9 (14.5)	2 (5.7)	8.80 (-2.86, 20.46)
Nasopharyngitis	7 (11.3)	2 (5.7)	5.58 (-5.43, 16.58)
Nausea	6 (9.7)	1 (2.9)	6.82 (-2.38, 16.02)
Arthralgia	5 (8.1)	1 (2.9)	5.21 (-3.53, 13.95)
COVID-19	5 (8.1)	9 (25.7)	-17.65 (-33.64, -1.66)
Urinary tract infection	5 (8.1)	1 (2.9)	5.21 (-3.53, 13.95)
Abdominal pain	4 (6.5)	1 (2.9)	3.59 (-4.64, 11.83)
Blood lactate dehydrogenase increased	4 (6.5)	3 (8.6)	-2.12 (-13.23, 8.99)
Dizziness	4 (6.5)	0	6.45 (0.34, 12.57)
Back pain	3 (4.8)	2 (5.7)	-0.88 (-10.24, 8.49)
Breakthrough haemolysis	2 (3.2)	6 (17.1)	-13.92 (-27.15, -0.68)
Pyrexia	2 (3.2)	3 (8.6)	-5.35 (-15.61, 4.92)
Sinusitis	2 (3.2)	3 (8.6)	-5.35 (-15.61, 4.92)
Upper respiratory tract infection	2 (3.2)	3 (8.6)	-5.35 (-15.61, 4.92)
Extravascular haemolysis	0	2 (5.7)	-5.71 (-13.40, 1.98)

- A patient with multiple adverse events (preferred terms) is counted only once in the total row. - A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
- Preferred terms are sorted in descending frequency of AEs in the LNP023 column.
- MedDRA Version 25.0 has been used for the reporting of adverse events.
- Treatment Emergent Adverse Event (TEAE) is defined as event started during on-treatment period.
- On-treatment period for LNP023 is from first dose date until 7 days after the date of last dose administered.
- On-treatment period for Anti-05 is from the first dose date until one day before the next planned dose.

Adverse events of special interest

Adverse events of special interest (AESIs) for iptacopan included serious or severe infections, infection caused by encapsulated bacteria, haemolysis and thrombosis events, testicular effects, thyroid changes and decreased platelets, with frequencies shown in Table 10:

Table 10: APPLY-PNH, AESI in the randomised treatment period

Risk Name Preferred term	LNP023 200 mg b.i.d. N=62	Anti-C5 N=35	Risk Difference (95% CI)
Number of patients with at least one event	**16 (25.8)**	**11 (31.4)**	**-5.62 (-24.47, 13.22)**
Serious or severe infections	2 (3.2)	3 (8.6)	-5.35 (-15.61, 4.92)
COVID-19	1 (1.6)	2 (5.7)	-4.10 (-12.41, 4.20)
Pyelonephritis	1 (1.6)	0	1.61 (-1.52, 4.75)
Urinary tract infection	1 (1.6)	0	1.61 (-1.52, 4.75)
Arthritis bacterial	0	1 (2.9)	-2.86 (-8.38, 2.66)
Intervertebral discitis	0	1 (2.9)	-2.86 (-8.38, 2.66)
Sepsis	0	1 (2.9)	-2.86 (-8.38, 2.66)
Infections caused by encapsulated bacteria	1 (1.6)	0	1.61 (-1.52, 4.75)
Bronchitis haemophilus	1 (1.6)	0	1.61 (-1.52, 4.75)
PNH Haemolysis and Thrombosis	10 (16.1)	10 (28.6)	-12.44 (-29.99, 5.10)
Blood lactate dehydrogenase increased	4 (6.5)	3 (8.6)	-2.12 (-13.23, 8.99)
Breakthrough haemolysis	2 (3.2)	6 (17.1)	-13.92 (-27.15, -0.68)
Blood creatinine increased	1 (1.6)	0	1.61 (-1.52, 4.75)
Haemoglobinuria	1 (1.6)	0	1.61 (-1.52, 4.75)
Hemiparesis	1 (1.6)	0	1.61 (-1.52, 4.75)
Ocular icterus	1 (1.6)	0	1.61 (-1.52, 4.75)
Transient ischaemic attack	1 (1.6)	0	1.61 (-1.52, 4.75)
Extravascular haemolysis	0	2 (5.7)	-5.71 (-13.40, 1.98)
Jaundice	0	1 (2.9)	-2.86 (-8.38, 2.66)
Testicular effects	1 (1.6)	0	1.61 (-1.52, 4.75)
Dihydrotestosterone decreased	1 (1.6)	0	1.61 (-1.52, 4.75)
Thyroid changes	1 (1.6)	0	1.61 (-1.52, 4.75)
Hypothyroidism	1 (1.6)	0	1.61 (-1.52, 4.75)
Decreased platelets	4 (6.5)	0	6.45 (0.34, 12.57)
Thrombocytopenia	3 (4.8)	0	4.84 (-0.50, 10.18)
Platelet count decreased	1 (1.6)	0	1.61 (-1.52, 4.75)

- A patient with multiple adverse events within risk is counted only once in the total row.
- A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
- Preferred terms are sorted within risk in descending frequency of AEs in the LNP023 column.
- MedDRA Version 25.0 has been used for the reporting of adverse events.
- Treatment Emergent Adverse Event (TEAE) is defined as event started during on-treatment period.
- On-treatment period for LNP023 is from first dose date until 7 days after the date of last dose administered.
- On-treatment period for Anti-CS is from the first dose date until one day before the next planned dose.
- A patient with multiple occurrences of a risk under one treatment is counted only once for the same risk for that treatment.

Infections

Iptacopan carries a risk of infections, particularly with encapsulated bacteria, due to its mechanism of action inhibiting the alternative complement pathway. In APPLY-PNH, 2 patients (5.0%) randomised to iptacopan experienced infections caused by encapsulated bacteria during the initial 24 week study period. One was a case of bronchitis caused by haemophilus influenzae, and the other was pyelonephritis.

Haemolysis

Breakthrough haemolysis occurs in PNH, can be triggered by infection, and can also occur on treatment discontinuation. In APPLY-PNH, the rate of breakthrough haemolysis was lower in the iptacopan group (2 patients, 3.2%) compared to the anti-C5 group (6 patients, 17.1%).

Appropriate information about monitoring patients after discontinuation is included in the PI, however a box warning regarding the risk of infection is also needed.

Dyslipidaemia

In APPLY-PNH, 6.5% of patients in the iptacopan arm had a TEAE of lipid disorder compared to 0% in the anti-C5 arm. Elevated total cholesterol, LDL-cholesterol, and triglycerides occurred in more patients in the iptacopan arm compared to the anti-C5-arm.

Safety in APPLY-PNH (6 March 2023 DCO)

At the end of the extension period, for the 62 patients initially randomised to iptacopan, the median duration of exposure was 47.9 weeks, with 31 subjects having at least 48 weeks of exposure. At the end of the 48 week extension period, no new safety signals had been detected. Overall, 6 SAEs occurred during the extension period, with only 1 (platelet count decreased in a patient initially randomised to iptacopan) deemed to be related to iptacopan treatment. The only new SAE was portal vein thrombosis, deemed unrelated to iptacopan, in a patient with a prior history of this condition.

In terms of AESI, there was an additional AE of infection (otitis media in a patient initially randomised to anti-C5) in the extension period. There were also additional cases of breakthrough haemolysis in the extension period, however none were serious or severe, and patients continued on iptacopan. There were two SAEs of thrombosis (one of portal vein thrombosis previously mentioned; the other a "non-serious"' transient ischemic attacks). There were also increases in mean total cholesterol.

There were no deaths and no TEAEs leading to discontinuation of iptacopan during the extension period. No events were reported for hypersensitivity, testicular effects, or thyroid effects.

The FDA identified a death in the Rollover Extension Study, for which the study report is not yet available. This death was due to encapsulated organism infection in a 69 year old female patient who had received iptacopan. This highlights the importance of a box warning in the PI clearly stating the risk of infections with encapsulated bacteria.

Safety in other studies:

APPOINT-PNH:

In APPOINT-PNH, median duration of exposure was 21.1 weeks for the core treatment period and 45.4 weeks including the extension period. A total of 37/40 patients (92.5%) had at least 1 TEAE and the majority of AEs were mild or moderate. 48.5% were investigator assessed as treatment related.

There was 1 (2.5%) SAE of chest pain and bacterial pneumonia in the initial 24 week period. At the 48-week data cut, SAEs were reported in 8 (20.0%) patients; 2 (5.0%) patients had SAEs assessed as treatment-related, pneumonia as described above, and COVID-19.

Two infections were reported as being caused by encapsulated bacteria, 1 patient having serious bacterial lobar pneumonia described above, and another patient with a non-serious staphylococcal skin infection of moderate severity in the extension treatment period. Iptacopan treatment was continued for both events, which resolved with treatment.

In the extension treatment period, 2 patients had one event each of breakthrough haemolysis. Iptacopan treatment was continued in both instances and the events resolved.

There were 4 patients (10%) with severe TEAEs in the extension period, one case of malignant melanoma in an 82 year old patient was not suspected to be related to iptacopan by the treating physician, and one case of pneumonia (described above) which was assessed as treatment related.

Across the 48-week study, there were no events reported for thrombosis, hypersensitivity, testicular effects or thyroid effects.

When comparing the safety profile between the APPLY-PNH and APPOINT-PNH studies, there were broadly comparable events during iptacopan therapy i.e., in patients who were either anti-C5 experienced or anti-C5-naïve.

X2204 Study

In this phase II study of the 13 patients receiving iptacopan, 9 (69.2%) had AEs and the majority of these were mild. Only 1 subject (7.7%) had an AE of moderate headache leading to treatment discontinuation, whilst on a 50mg bd dose.

X2201 Study

In this phase II study, patients received both iptacopan and an anti-C5 antibody at the same time. All 16 patients experienced at least one TEAE. Three of the 16 patients (18.6%) died during the study; as follows:

- A 78yo male patient died due to a TEAE of general physical health deterioration following Escherichia coli sepsis after surgery for aortic repair. The event was not suspected to be related to iptacopan
- A 52yo male patient died following an SAE of squamous cell carcinoma of the oral cavity. This was not suspected to be related to iptacopan
- A 45yo female patient died after developing an SAE of lymphoproliferative disorder and sepsis after chemotherapy. The involvement of iptacopan could not be excluded, however causality is difficult to determine.

Although not necessarily related to treatment, Study X2201 raises safety concerns regarding combination treatment.

Studies of other conditions: X2202 and X2203

No new safety signals were reported in studies of other conditions, and the pattern of AEs was similar to that of the pivotal trial.

Risk Management Plan (RMP) evaluation summary

An EU-RMP version 1.0 (dated 06 April 2023; DLP 02 November 2022) and ASA version 1.0 (dated 20 June 2023) were submitted and evaluated by the TGA.

The summary of safety concerns are outlined in Table 11.

Table 11: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infections caused by encapsulated bacteria	✓	✓*§	✓	✓†‡

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	Serious haemolysis following discontinuation of iptacopan		✓*§	✓	✓‡
	Malignancies		✓*§	-	–
Missing information	Use in pregnant patients		✓§	✓	–
	Long-term safety (>2 years)		✓*§	-	–

* Study CLNP023C12001 B
§ PASS in Iptacopan-treated patients using registry data
‡ HCP guide, Patient/caregiver guide
† Patient Safety card, System for controlled access; annual reminder of mandatory vaccinations

The clinical Evaluator did not identify any new safety concerns. Malignancy has been added as an Important Potential Risk in EU-RMP and ASA (both version 1.1). The summary of safety concerns in the ASA aligns with the EU-RMP and is satisfactory.

Routine and additional pharmacovigilance activities are proposed. Additional pharmacovigilance activities include ongoing Study CLNP023C12001B and a planned PASS which will utilise data from the international PNH registry. The pharmacovigilance plan in the ASA aligns with the EU-RMP and is acceptable.

Routine and additional risk minimisation activities are proposed. Additional risk minimisation activities include a Health Care Practitioner Guide, a Patient/Carer Guide and a Patient safety card. In addition to these measures, there will also be a system for controlled access and an annual reminder to physicians or pharmacists of mandatory revaccinations as additional risk minimisation activities to mitigate the Important Identified Risk “Infections caused by encapsulated bacteria”. This is similar to other products with the same safety risk.

Risk-benefit analysis

PNH is a rare and life-threatening chronic disease. Iptacopan presents an opportunity for oral treatment for patients who will need to be on life-long therapy. This represents a substantial benefit in terms of quality of life.

Efficacy

The efficacy of iptacopan has been demonstrated in the pivotal study, APPLY-PNH, and the supportive study APPOINT-PNH. APPLY-PNH is a well designed randomised controlled trial comparing iptacopan to the currently registered anti-C5 inhibitors eculizumab or ravulizumab. Efficacy has been demonstrated at 24 weeks, in terms of increases in Hb and transfusion avoidance, with 82% of the iptacopan group having a ≥ 2g/dL increase in Hb from baseline (without RBC transfusions) compared to 0% in the anti-C5 group. Transfusion avoidance occurred in 95% of the iptacopan group compared to 46% of anti-C5 treated subjects. This study enrolled patients with residual anaemia despite treatment with an anti-C5 antibody and therefore, there is robust comparative evidence of efficacy in this patient group.

APPOINT-PNH was a single arm study in patients with PNH and anaemia in patients who had not previously received a complement inhibitor. 77.5% of patients achieved a sustained increase in Hb of ≥ 2g/dL from baseline without RBC transfusions. Although this was a single arm study, it is unlikely than an effect of this magnitude would occur spontaneously. The Delegate is therefore of the view that in the context of this rare disease, this is sufficient evidence to support the use of iptacopan in patients who have not previously received a C5 inhibitor.

Proposed indication

The clinical Evaluator recommended restricting the indication to patients who have received an anti-C5 antibody. However, the Delegate is of the view that the indication should not be restricted. Although the evidence for iptacopan in anti-C5 naïve patients is limited to the single arm study APPOINT-PNH, it is reasonably likely that the magnitude of benefit seen in this study can be attributed to iptacopan. Given the rarity of PNH, the feasibility of another randomised controlled trial is uncertain. Iptacopan will only be prescribed by experienced clinicians in Australia, and an unrestricted indication will allow clinicians to choose the best treatment option for each individual patient. Although there is more uncertainty in the C5-inhibitor naïve population, there are clear benefits of having an oral treatment available, plus the benefits demonstrated in the APPOINT-PNH which are reasonably likely to be due to iptacopan. The Delegate is of the view that the risk-benefit balance is favourable in both C5-naïve and C5-experienced patients. Expert advice is requested on the optimal indication for Australia.

Safety

In general, the risks of iptacopan were similar to other complement inhibitors used in PNH.

Common AEs associated with iptacopan seen it the trials were headache, nasopharyngitis, diarrhoea, abdominal pain, infection, and nausea. The risk of serious infections, particularly with encapsulated bacteria, is an important AESI which occurred in the trials. The PI must contain a box warning with vaccination information in order for this risk to be appropriately mitigated. This would bring iptacopan into line with other complement inhibitors registered in Australia, which all have box warnings for this risk. Dyslipidaemia was another AESI emerging from the trials, and further details in the PI have been requested.

The Risk Management Plan for iptacopan includes a patient card, and patient/carer guide and a health practitioner guide. The Sponsor is also planning a system for controlled access and an annual reminder to clinicians regarding mandatory vaccinations. These are important risk mitigation measures that would be enhanced by a box warning. A box warning is essential communication to GPs, emergency physicians and other primary care health practitioners that may see a patient who presents with infection. These clinicians would not have received the health practitioner guide or be included in the vaccination reminders; therefore, the PI is an essential means of communication for these practitioners, who require this vital information if seeing the patient in a primary care or emergency situation.

The risk of haemolysis when stopping treatment or switching to another treatment is mitigated by appropriate information in the PI including monitoring for PNH manifestations after discontinuation of iptacopan.

The long term safety of iptacopan is an important consideration, as patients may be on treatment for their lifetime. The proposed conditions of registration will provide longer term safety data to further characterise the risks of iptacopan.

Study X2201: Combination treatment with iptacopan and anti-C5 antibody

Study X2201 was a small phase II study of 16 patients treated with both iptacopan and an anti-C5 antibody. There were 3 deaths in this study, two of which involved sepsis. Although causality is difficult to determine, this raises concerns that the safety of combination treatment is unacceptable. Furthermore, there is very little evidence of efficacy for combination treatment. Expert advice is requested on whether a contraindication or specific wording should be added to the PI advising against the use of Iptacopan with anti-C5 antibodies.

Conditions of registration

The FDA have imposed the following post-market requirements, and the Delegate intends to impose similar conditions of registration in Australia:

- Participate in a registry to characterize the long-term safety of iptacopan in adults with paroxysmal nocturnal hemoglobinuria, with up to 5 years of follow-up. Submit yearly safety follow-up data and a summary of the major safety findings for all patients and all serious infections with encapsulated bacteria. The final study report should include an integrated safety dataset and patient-level data, including data on iptacopan dosing, meningococcal, pneumococcal, and H. influenza vaccination status, and concomitant medications. Draft Protocol: 04/2024 Final Protocol: 08/2024 Interim Report #1: 12/2025 Interim Report #2: 12/2026 Interim Report #3: 12/2027 Interim Report #4: 12/2028

  Final Report Submission: 7/2030

- Complete study APPLY-PNH (CLNP023C12302): “A randomized, multicenter, active comparator controlled, open-label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult patients with PNH and residual anaemia, despite treatment with an intravenous anti-C5 antibody”. Include an updated summary of safety and efficacy analyses and datasets at the time of final clinical study report submission.

  Final Report Submission: 7/2024

- Complete study APPOINT-PNH (CLNP023C12301): “A multicenter, single-arm, open- label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who are naive to complement inhibitor therapy.” Include an updated summary of safety and efficacy analyses and datasets at the time of final clinical study report submission.

  Final Report Submission: 7/2024

- Complete study CLNP023C12001B PNH REP: “An open label, multicenter roll-over extension program to characterize the long-term safety and tolerability of iptacopan in patients with paroxysmal nocturnal hemoglobinuria (PNH) who have completed PNH phase 2 and phase 3 studies with iptacopan.” Include an updated summary of safety and efficacy analyses and datasets at the time of final clinical study report submission.

  Final Report Submission: 5/2029

Overall, provided the Sponsor agrees to the requested PI changes and box warning, the Delegate is of the view that the risk benefit balance of iptacopan in the proposed indication is favourable. The Delegate is requesting expert advice on the indication and PI/CMI to ensure the most appropriate wording for Australia.

Independent expert advice

The Delegate received the following independent expert advice.

19 July 2024: written expert advice was requested from two independent Australian clinical experts in the field of haematology.

The first expert provided the following responses to the Delegate's questions:

1. Uncertainty in anti-C5 antibody naïve patients

The evidence presented in the C5 antibody naïve patients relies on the small, single arm, open label APPOINT-PNH clinical trial. There is no randomised controlled comparison to standard of care – the anti-C5 monoclonal antibody therapy. However, the data suggests that the response to iptacopan is clinically significant and that this is of the same magnitude that has been seen in prior clinical trials of anti-C5 monoclonal antibody therapy when used in treatment naïve patients. I would agree with the Delegate that the evidence would support an unrestricted indication and allow treatment of PNH by iptacopan in the treatment naïve context.

Preferred wording for an unrestricted listing would be: Iptacopan is approved to treat adult patients with paroxysmal nocturnal haemoglobinuria (PNH).

2. Format of safety data in the PI

The Sponsor has proposed to include non-comparative pooled safety data in the PI. I agree with the Delegate and Evaluators that this is not appropriate as the clinical trials presented are in different patient populations with differences in study design. It is not appropriate due to the confounding differences seen. The Delegate has requested the comparative safety data from the APPLY-PNH study with percentages of AEs which would be more consistent with the standard of safety data in a PI in Australia.

3. Box Warning

This is essential and should be the same as the anti-C5 monoclonal antibodies and C3 inhibitors, stipulating the need for vaccination and prophylactic antibiotics. I appreciate that the prescribers will likely be familiar with the risks of these pharmaceuticals due to the specialised nature of this disorder however other medical, nursing, and allied health staff are not, and pharmacists dispensing may also not be as familiar with the risks.

4. Combination iptacopan with other complement inhibitors

The clinical data on combination therapy of iptacopan with eculizumab or ravulizumab is limited and there are clear safety concerns with 3 of 16 patients dying on clinical trial, which whilst not clearly related to the study drug do outweigh the clinical benefit seen. Additionally, there is no evidence of the combination of iptacopan with the C3 inhibitor pegcetacoplan. At this time, I would agree that the safety concerns outweigh any potential benefit of combination therapy with iptacopan and would recommend that the PI does contain a contraindication for use with other medicines for PNH.

The second expert provided the following responses

5. Please comment on your preferred wording for the indication of Iptacopan in Australia.

FABHALTA is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. (this is the EMA indication, FDA doesn't state haemolytic anaemia).

6. Please provide your opinion on the optimal format of safety data in the PI.

I am in favour with the way the data is demonstrated as per FDA. Agree with RMP plan with patient card, patient/carer guide and health practitioner guide. It should be available through restricted access; can we also have a REMS plan in Australia? Note the common AEs listed in

particular headache, risk of serious infections (see boxed warning example in Q3), and dyslipidaemia which will need following. I also agree with additional conditions of registration as per Delegate as longer follow up is needed to assess treatment effects as well as effects of this therapy on the known PNH complications such as thrombosis and infection.

7. ***Would you support a box warning in the PI regarding the risk of infection with encapsulated organisms and the need for vaccination?***

Yes, this is the FDA warning:

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

See full prescribing information for complete boxed warning.

FABHALTA increases the risk of serious and life-threatening infections caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B.

- **Complete or update vaccination for encapsulated bacteria at least 2 weeks prior to the first dose of FABHALTA, unless the risks of delaying 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. (5.1)**
- **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. (5.1)**

FABHALTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called FABHALTA REMS. (5.2)

8. ***Should the PI contain a contraindication or particular wording stating that iptacopan should not be used in combination with other medicines for PNH such as anti-C5 inhibitors?***

Yes. The studies used this as monotherapy only, but did allow cross over if the patients were on an anti-C5 previously with persisting anaemia and transfusion requirements. So, we need to ensure that new diagnoses and changeover from an anti-C5 to this new therapy is possible with the wording of the indication.

The Delegate reviewed the expert advice outlined above, and the Sponsor's response to the Delegate's Overview. The Delegate proposes to approve iptacopan for the indication:

"FABHALTA is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH)."

Although one of the two experts recommended inclusion of the words 'who have haemolytic anaemia,' the Delegate did not consider this to be necessary given that iptacopan will be used by specialist haematologists in Australia who will be best placed to make individual risk-benefit assessments, and determine whether iptacopan is appropriate for each individual patient.

The Delegate proposes to impose the following conditions of registration, in addition to standard conditions and the conditions recommended by the RMP Evaluator:

- Participate in a registry to characterise the long-term safety of iptacopan in adults with paroxysmal nocturnal hemoglobinuria, with up to 5 years of follow-up. Submit annual safety reports from the registry to the TGA with the Periodic Safety Update Reports (PSURs).
- Complete the roll-over extension program (study CLNP023C12001B PNH REP) and submit all study reports to the TGA as soon as available.

Delegate's review of the PI and CMI:

The following changes to the PI, and equivalent changes to the CMI, are required before a favourable decision can be considered:

Boxed warning

As per the expert advice received, a boxed warning is essential and must be added to the Australian PI and CMI to mitigate the serious risk of infection associated with iptacopan. A boxed warning will alert primary care and emergency department staff to the risk of infection in patients taking iptacopan, which may result in more timely and appropriate treatment. A boxed warning is required to ensure a favourable risk-benefit balance for iptacopan. It is suggested that wording similar to the box warning in the pegcetacoplan Australian PI should be used.

Dosage regimen

Include words to the effect of 'no information is available regarding switching from PNH therapies other than eculizumab and ravulizumab'

Hepatic Impairment

Given that the FDA and EMA PIs both state that iptacopan is not recommended in severe hepatic impairment (Child-Pugh class C), please amend the new statement in the Australian PI to the following (or words to the same effect):

> *"the use of iptacopan 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."*

Contraindications

Addition of *Haemophilus influenzae* type B to the second contraindication i.e. 'in patients who are not currently vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Haemophilus influenzae* type B…'

In accordance with the expert advice received, a contraindication should be added to the PI to clearly state that iptacopan must not be used in combination with other therapies for PNH. The risk-benefit balance of combination treatment is unfavourable due to the safety concerns and thus, should be contraindicated. Please ensure that the wording allows for changeover from an anti-C5 therapy to iptacopan.

Special warnings and precautions

Addition of a subheading 'PNH laboratory monitoring' and text recommending regular monitoring for signs of haemolysis, similar to the EU EmPC.

Addition of information about the educational materials that will be available in Australia for physicians and patients.

Addition of a statement that co-administration with other medicinal products has not been studied and is therefore not recommended.

Interactions with other medicines and other forms of interactions

Addition of the following wording (from the EU SmPC):

> *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 (see section 4.4).*

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.

Consumer medicines information

Update the CMI in line with the PI changes requested above, particularly the boxed warning.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register FABHALTA (iptacopan) for the following indication:

> *FABHALTA is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH)*

Specific conditions of registration

- FABHALTA (iptacopan) is to be included in the Black Triangle Scheme. The PI and CMI for FABHALTA must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The FABHALTA EU-Risk Management Plan (RMP) (version 1.1, dated 6 December 2023, data lock point 2 November 2022), with Australian Specific Annex (version 1.1, dated 22 February 2024, included with submission PM-2023-02564-1-6 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently

than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the Sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

- Participate in a registry to characterize the long-term safety of iptacopan in adults with paroxysmal nocturnal hemoglobinuria, with up to 5 years of follow-up. Submit annual safety reports from the registry to the TGA with the Periodic Safety Update Reports (PSURs).
- Complete the roll-over extension program (study CLNP023C12001B PNH REP) and submit all study reports to the TGA as soon as available.

Product Information and Consumer Medicines Information

For the most recent Product Information (PI) and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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