Report on the Deliberation Results

June 4, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Fabhalta Capsules 200 mg
Non-proprietary Name	Iptacopan Hydrochloride Hydrate (JAN*)
Applicant	Novartis Pharma K.K.
Date of Application	August 7, 2023

Results of Deliberation

At its meeting held on May 31, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since the number of Japanese patients treated with the product in clinical studies is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a specified number of patients have been accrued. The purposes of the survey are to identify the characteristics of these patients and to collect safety and efficacy data on the product without delay, thereby taking necessary measures to facilitate the proper use of the product.
3. Prior to market launch, the applicant is required to take necessary measures to ensure that the product is used only at a suitable medical institution and only under the supervision of a physician who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks, etc. associated with the product, in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

** Japanese Accepted Name (modified INN)*

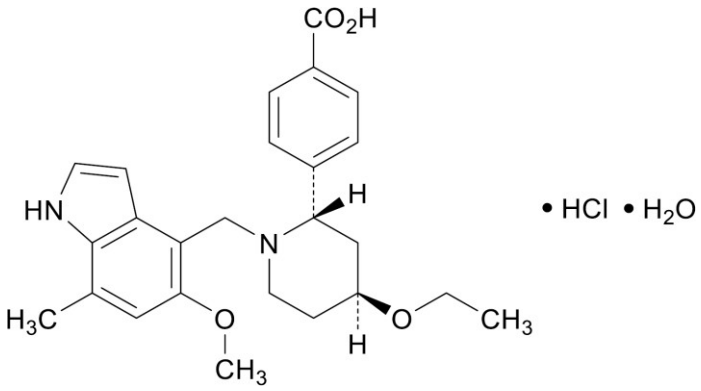
Review Report

May 20, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Fabhalta Capsules 200 mg
Non-proprietary Name	Iptacopan Hydrochloride Hydrate
Applicant	Novartis Pharma K.K.
Date of Application	August 7, 2023
Dosage Form/Strength	Each capsule contains 225.8 mg of iptacopan hydrochloride hydrate (equivalent to 200 mg of iptacopan).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{25}H_{30}N_2O_4 \cdot HCl \cdot H_2O$
Molecular weight: 476.99
Chemical name: 4-{(2*S*,4*S*)-4-Ethoxy-1-[(5-methoxy-7-methyl-1*H*-indol-4-yl)methyl]piperidin-2-yl}benzoic acid monohydrochloride monohydrate

Items Warranting Special Mention None
Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of paroxysmal nocturnal hemoglobinuria, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication

Paroxysmal nocturnal hemoglobinuria

Dosage and Administration

The usual adult dosage is 200 mg of iptacopan administered orally twice daily.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since the number of Japanese patients treated with the product in clinical studies is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a specified number of patients have been accrued. The purposes of the survey are to identify the characteristics of these patients and to collect safety and efficacy data on the product without delay, thereby taking the necessary measures to facilitate the proper use of the product.
3. Prior to market launch, the applicant is required to take necessary measures to ensure that the product is used only at a suitable medical institution and only under the supervision of a physician who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks, etc. associated with the product, in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

Attachment

Review Report (1)

April 5, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Fabhalta Capsules 200 mg
Non-proprietary Name	Iptacopan Hydrochloride Hydrate
Applicant	Novartis Pharma K.K.
Date of Application	August 7, 2023
Dosage Form/Strength	Each capsule contains 225.8 mg of iptacopan hydrochloride hydrate (equivalent to 200 mg of iptacopan).
Proposed Indication	Paroxysmal nocturnal hemoglobinuria
Proposed Dosage and Administration	The usual adult dosage is 200 mg of iptacopan administered orally twice daily.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Paroxysmal nocturnal hemoglobinuria (PNH) is a hematopoietic stem cell disease characterized by chronic intravascular hemolysis as the main symptom. In PNH, acquired mutations in the *phosphatidylinositol glycan class A* (*PIGA*) gene cause deficiency of terminal complement regulators CD55 and CD59 on the red blood cell surface (which regulate C3 convertase and membrane attack complex [MAC] formation, respectively); this activates the alternative complement pathway (AP), resulting in chronic intravascular hemolysis (*Nat Rev Dis Primers*. 2017;3:17028. *Blood*. 2014;124:2804-2811). In Japan, PNH is classified as a designated intractable disease by the Ministry of Health, Labour and Welfare (MHLW Public Notice No. 62, dated January 1, 2015). The currently approved drugs for PNH in Japan are complement C5 inhibitors that inhibit intravascular hemolysis by preventing MAC formation (eculizumab [genetical recombination], ravulizumab [genetical recombination], and crovalimab [genetical recombination]). However, some patients treated with complement C5 inhibitors develop extravascular hemolysis due to deposition of C3 fragments in PNH red blood cells (*Front Immunol*. 2019;10:1157). The approved drugs for the treatment of PNH in patients who have an inadequate response to complement C5 inhibitors are the complement C3 inhibitor pegcetacoplan and the complement factor D inhibitor danicopan.

Iptacopan hydrochloride hydrate (hereinafter referred to as iptacopan) is a compound that inhibits complement factor B (FB), which was discovered by the applicant. It binds to the active site of FB to inhibit the activation of C3 convertase, thereby preventing AP activation and MAC formation. By this mechanism of action, iptacopan is expected to inhibit both intravascular and extravascular hemolysis by preventing the deposition of C3 fragments on PNH red blood cells in patients with PNH.

The applicant has recently filed an application for the approval of iptacopan, stating that a global phase III study has demonstrated its efficacy and safety in patients with PNH.

Outside Japan, iptacopan was approved as a drug for the treatment of PNH in the US in December 2023, and an application for iptacopan was filed in the EU in April 2023. As of January 2024, the application in the EU is under review.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale purplish-pink powder. The determined general properties include description, solubility, hygroscopicity, melting point, thermal analysis (differential scanning calorimetry and thermogravimetric analysis), pH, acid dissociation constant, partition coefficient, isomerism, and polymorphism. The drug substance is present in 2 types of crystal forms (Forms [redacted] and [redacted]) and 2 types of [redacted] ([redacted] and [redacted]) and [redacted]. The drug substance was found to be produced as the monohydrate only through the manufacturing process on a commercial scale, and it was confirmed to be stable at room temperature.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry (MS), ultraviolet-visible spectroscopy (UV/VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR), X-ray powder diffraction, and single-crystal X-ray crystallography. The drug substance has 2 asymmetric carbon atoms, and the configuration is *S* for both atoms.

2.1.2 Manufacturing process

The drug substance is synthesized using the following starting materials: [redacted], [redacted], and [redacted].

The quality control strategy has been designed based on the following investigations (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on experience obtained in a process development and manufacturing transfer

Table 1. Summary of control strategy for the drug substance

CQA	Control methods
Description (appearance)	[redacted]
[redacted]	[redacted]
Identification	[redacted]
Related substances	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Residual solvents	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Content	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] of [redacted] has been defined as a critical step.

2.1.3 Control of the drug substance

The proposed specifications for the drug substance consist of content, description (appearance), identification (IR and X-ray powder diffraction), purity (related substances [high performance liquid chromatography (HPLC)], Impurity A [liquid chromatography/mass spectrometry (LC-MS)], [redacted] [Impurity CC] [HPLC], residual solvents [gas chromatography (GC)], [redacted] [GC]), water content (coulometric titration), residue on ignition, microbial limit, [redacted] ([redacted]), [redacted] ([redacted]), and assay (HPLC).

2.1.4 Stability of the drug substance

Table 2 shows the main stability studies performed on the drug substance. The results demonstrated the stability of the drug substance. Photostability testing showed that the drug substance was photostable.

Table 2. Main stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 [redacted] batches	25°C ± 2°C	60% ± 5% RH	[redacted] polyethylene bag + aluminum-laminated bag	36 months
Accelerated	3 [redacted] batches	40°C ± 2°C	75% ± 5% RH		6 months

In view of the above, a retest period of [redacted] months was proposed for the drug substance placed in a [redacted] polyethylene bag, which was then stored in an aluminum-laminated bag ([redacted]) at [redacted]. The long-term testing will be continued for [redacted] months.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is an immediate-release hard capsule. Each capsule contains 225.800 mg of iptacopan hydrochloride hydrate. The drug product contains no excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: sieving, capsule filling, primary packaging, final packaging/labeling, storage/testing, and storage. In-process control parameters and control values have been established for the following steps: [redacted] and [redacted].

The quality control strategy has been designed based on the following investigations (Table 3):

- Identification of CQAs
- Identification of CPPs based on quality risk assessment and the design of the experiments

Table 3. Summary of control strategy for the drug product

CQA	Control methods
Appearance	[redacted]
Strength	[redacted]
Degradation products	[redacted]
Content uniformity	[redacted]
Dissolution rate	[redacted]

[redacted] has been defined as a critical step.

2.2.3 Control of the drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (HPLC and UV/VIS), purity (related substances [HPLC] and Impurity A [LC-MS]), water content (coulometric titration), uniformity of dosage units (strength uniformity test [HPLC]), microbial limit test, dissolution (UV/VIS), and assay (HPLC).

2.2.4 Stability of the drug product

Table 4 shows the main stability studies performed on the drug product. The results demonstrated the stability of the drug product. Photostability testing showed that the drug product was photostable.

Table 4. Main stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 commercial-scale batches	25 ± 2°C	60% ± 5% RH	Blister pack	24 months
Accelerated	3 commercial-scale batches	40 ± 2°C	75% ± 5% RH		6 months

In view of the above, a shelf life of 36 months was proposed for the drug product stored in a blister pack (polyvinyl chloride/polyethylene/polyvinylidene chloride film and aluminum foil) at room temperature according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E guideline ("Guideline on Evaluation of Stability Data," the PFSB/ELD Notification No. 0603004 dated June 3, 2003, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare). The long-term testing will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of the drug substance and the drug product was controlled in an appropriate manner.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Studies on primary pharmacodynamics were conducted to investigate the *in vitro* binding affinity of iptacopan to FB, inhibition of AP and hemolysis, and *in vivo* effects on AP activation and nephritis models, and *ex vivo* inhibition of AP. Studies on secondary pharmacodynamics were conducted to investigate the effects of iptacopan on various proteases, receptors, kinases, etc., and on T cell-dependent B cell response. Safety pharmacology studies were conducted to investigate effects on the cardiovascular, central nervous, and respiratory systems. In *in vivo* studies, 0.5% methylcellulose/0.5% Tween 80 solution was used as the vehicle. The doses and concentrations of iptacopan are expressed as the salt form (iptacopan hydrochloride hydrate).

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity to FB and inhibition of complement pathway activation (CTD 4.2.1.1-1, 4.2.1.1-6, and 4.2.1.1-7; reference data 4.2.1.1-2 to 4.2.1.1-5, 4.2.1.1-8, and 4.2.1.1-9)

The binding affinity of iptacopan to human FB was investigated using time-resolved fluorescence resonance energy transfer (TR-FRET) assay. Iptacopan inhibited the binding of a labeled ligand to FB with a 50% inhibitory concentration (IC_{50}) of 9.6 nmol/L.

Inhibition of AP activation by iptacopan, iptacopan free base, or iptacopan trifluoroacetic acid was investigated using the serum or blood of humans and other animal species. Iptacopan, iptacopan free base, or iptacopan trifluoroacetic acid inhibited Zymosan A-stimulated AP activation with an IC_{50} of 0.11 μmol/L in 50% mouse serum, 0.56 μmol/L in 50% rat serum, 0.11 μmol/L in 50% rabbit serum, 0.41 μmol/L in 50% dog serum, 0.08 to 0.40 μmol/L in 50% cynomolgus monkey serum, 0.12 or 0.13 μmol/L in 50% human serum, and 0.22 μmol/L in 50% human whole blood. The 90% inhibitory concentration (IC_{90}) of iptacopan or iptacopan free base in 50% rat serum and 50% human serum was 1.23 and 0.45 μmol/L, respectively.

The effects of iptacopan on the activation of the classical complement pathway in human serum were investigated.[1)] Iptacopan showed no effects on the activation of the classical complement pathway up to the highest concentration (100 μmol/L) studied.

3.1.1.2 Inhibition of hemolysis (CTD reference data 4.2.1.1-10)

The effects of iptacopan free base on the hemolysis of PNH red blood cells[2)] were investigated using 100% human serum. Iptacopan free base inhibited the hemolysis of PNH red blood cells with IC_{50} and IC_{90} of 0.11 and 0.74 μmol/L, respectively.

3.1.1.3 Inhibition of hemolysis or AP by iptacopan in C3G, MPGN, and aHUS[3)] (CTD 4.2.1.1-11 and 4.2.1.1-12)

Inhibition of the hemolysis of sheep red blood cells (SRBCs) by iptacopan was investigated using serum samples derived from patients with C3 glomerulopathy (C3G) (7 patients), membranoproliferative glomerulonephritis (MPGN) (1 patient), and atypical hemolytic uremic syndrome (aHUS) (3 patients). Iptacopan completely inhibited the hemolysis of SRBCs by almost all patient-derived serum samples.

The binding affinity of iptacopan to FB variants,[4)] which have been reported in patients with aHUS, was investigated. The binding affinity of iptacopan to all FB variants was similar to that to wild-type FB. Inhibition of AP activation by iptacopan was also investigated based on C3a formation by cobra venom factor (complement C3 homolog) and FB variants, and MAC formation by FB variants in the presence of Zymosan A stimulation. Iptacopan inhibited C3a and MAC formation by AP activation with all FB variants that could be assessed.[5)]

3.1.2 *In vivo* studies

3.1.2.1 Effects in a mouse LPS-induced AP activation model (CTD reference data 4.2.1.1-13)

Inhibition of AP by iptacopan free base (3, 10, 20, and 30 mg/kg, as a single oral dose) was investigated using mice with AP activation by intraperitoneal administration of lipopolysaccharide (LPS) (50 μg). Iptacopan inhibited increases in serum C3d and iC3b levels dose-dependently at ≥10 mg/kg, and the maximum inhibition was observed at 4 hours post-dose. The IC_{50} and IC_{90} of iptacopan calculated based on plasma iptacopan concentrations were 0.560 μmol/L and 1.120 μmol/L, respectively.

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1) Activation of the classical complement pathway was measured as follows: Only the classical complement pathway was activated using an activator for the classical complement pathway and inhibitors for other complement pathways, and C5b-9 was then detected using antibodies specific to new antigens produced by complement activation.
2) PNH red blood cells were prepared as follows: Red blood cells derived from healthy subjects were incubated with blocking antibodies against CD55 and CD59, and then spiked with ethylene glycol-bis(β-aminoethyl ether)-*N*,*N*,*N*',*N*'-tetraacetic acid (EGTA) to inhibit the classical complement pathway and the lectin complement pathway.
3) Dysregulation of AP is considered to be involved in the pathogenesis of all these diseases (*Immunol Rev*. 2023;313: 339-357. *Nat Rev Nephrol*. 2010;6:494-499).
4) Of 18 variants reported in patients with aHUS, 8 were investigated, excluding those with a mutation in other domains than Bb, the binding site of iptacopan, which are reported to have lower activity than that of wild-type FB.
5) Due to no or very low AP activation, evaluation was not performed for 1 variant in the investigation of inhibition of C3a formation and 2 variants in the investigation of inhibition of MAC formation.

3.1.2.2 Effects in a rat passive Heymann nephritis model[6] (CTD 4.2.1.1-14 and 4.2.1.1-15)

The prophylactic effect of iptacopan (20 and 60 mg/kg bis in die [BID] as repeated oral doses from before nephritis onset) and the therapeutic effect of iptacopan (60 mg/kg BID as repeated oral doses after nephritis onset) were investigated using rats that had received intravenous sheep anti-rat fraction 1A (Fx1A) serum (5 mL/kg). Prophylactic administration of iptacopan at ≥20 mg/kg inhibited increases in the urinary total protein/urinary creatinine (UTP/UCREA) ratio and glomerular injury and tubular degeneration scores. Therapeutic administration of iptacopan at 60 mg/kg inhibited an increase in the UTP/UCREA ratio, decreased the glomerular injury score, and reduced the deposition of C3 in the glomeruli.

3.1.3 *Ex vivo* studies (CTD reference data 4.2.1.1-16 to 4.2.1.1-18)

Inhibition of Zymosan A-stimulated AP activation by iptacopan was investigated using the serum collected in the 26-week repeated-dose toxicity study in rats [see Section 5.2], the 39-week repeated-dose toxicity study in mature dogs [see Section 5.2], and the 52-week repeated-dose toxicity study in juvenile dogs [see Section 5.6]. Iptacopan at ≥30 mg/kg/day inhibited AP activation completely in mature dogs and by ≥80% in juvenile dogs, whereas iptacopan at 5 mg/kg/day inhibited AP activation only by 18% to 35% in both mature and juvenile dogs. In rats, the effects of iptacopan could not be evaluated because AP was not activated in the vehicle group.

3.2 Secondary pharmacodynamics

3.2.1 Effects on proteases, G-protein coupled receptors, transporters, ion channels, nuclear receptors, enzymes, and kinases (CTD 4.2.1.1-1; reference data 4.2.1.2-1 to 4.2.1.2-4)

Inhibition of 43 proteases, excluding FB, by iptacopan was investigated. Iptacopan did not inhibit any of these protases up to the highest concentration (100 μmol/L) studied.

The effects of iptacopan and iptacopan free base on a total of ≥100 G-protein coupled receptors, transporters, ion channels, nuclear receptors, and enzymes were investigated. Iptacopan or iptacopan free base showed no effects on any of the molecules up to the highest concentration (30 or 100 μmol/L) studied.

The effects of iptacopan free base on 31 kinases were investigated. Iptacopan free base inhibited the mammalian target of rapamycin (mTOR), with an IC_{50} of 9.9 μmol/L (4,178 ng/mL), but showed no effects on other kinases up to the highest concentration (10 μmol/L) studied. The IC_{50} for mTOR was approximately 5-fold the unbound maximum plasma concentration (C_{max}) (763 ng/mL)[7] at the clinical dose in humans.

3.2.2 Effects on T cell-dependent B cell response (CTD reference data 4.2.1.2-5 to 4.2.1.2-8)

Upon activation of complement pathways, C3b is cleaved into iC3b and C3d, and iC3b and C3d then bind to the complement receptor 2 (CD21) that potentiates T cell-dependent B cell response (*Front Immunol*.

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[6] A pathological model in which membranous nephropathy and glomerular nephritis are induced by administering the pathogenic antibody (anti-Fx1A [tubular epithelial fraction collected from the renal cortex] antibody) to rats. In this model, complement activation is essential for the onset of nephritis (*J Clin Invest*. 1986;77:1096-1107).

[7] The unbound C_{max} was calculated based on the steady-state C_{max} (4,120 ng/mL) following multiple oral doses of iptacopan 200 mg BID in non-Japanese healthy subjects under fasted conditions in Study X2101 and the fraction unbound in plasma (fu,p) estimated from the sigmoid maximum effect (E_{max}) model using plasma iptacopan concentration data of Study A2105 (CTD 4.2.2.3-4).

2015;6:262). Since iptacopan decreases the levels of C3b and its fragments, the effect of iptacopan on T cell-dependent B cell response was investigated using 2 animal models.

T cell-dependent B cell response was induced in mice by intraperitoneal administration of dinitrophenyl-keyhole limpet hemocyanin (DNP-KLH) adsorbed to aluminum hydroxide gel 1 hour after the initial dose and on Day 8 of repeated oral treatment with iptacopan (30 and 100 mg/kg BID). Although decreases in the amount of C3 fragments in plasma in the iptacopan 30 mg/kg and 100 mg/kg groups and a decrease in the amount of FB fragments in plasma in the iptacopan 100 mg/kg group were observed, the DNP-specific antibody titer and the results of population analysis of spleen cells by flow cytometry showed no differences between the iptacopan and vehicle groups. In spleen sections, there were no differences in the presence of Ki67 (a marker for proliferating cells)-stained cells or staining intensity between the iptacopan and vehicle groups.

T cell-dependent B cell response was induced in rats by intravenous administration of SRBCs at 2 hours after the initial dose of repeated oral treatment with iptacopan (6, 20, 60, and 120 mg/kg BID). The SRBC-specific IgM titer was measured as an indicator of T cell-dependent B cell response. Although the trough concentrations in the iptacopan 20 mg/kg and higher dose groups exceeded the IC_{90} (1.23 μmol/L) for AP inhibition by iptacopan in 50% rat serum, all iptacopan dose groups showed a similar time course of the SRBC-specific IgM titer to that in the vehicle group.

3.3 Safety pharmacology

Table 5 shows a summary of safety pharmacology studies.

Table 5. Summary of safety pharmacology studies

Organ system evaluated	Test system	Evaluation items/ methods, etc.	Iptacopan dose	Administration method	Findings	Attached data CTD
Cardiovascular system	HEK293 cells (≥3 specimens/group)	Inhibition of hERG current	Iptacopan free base: 3 and 10 μmol/L Iptacopan: 30, 100, 300, 600, and 1,000 μmol/L	-	IC_{50}: 414.9 μmol/L	4.2.1.3-3 Non-GLP 4.2.1.3-1 4.2.1.3-2
	HEK293 cells (≥3 specimens/group)	hERG channel trafficking to cell membrane	Iptacopan free base: 0.1 to 100 μmol/L Iptacopan: 0.1 to 300 μmol/L	-	None	Non-GLP 4.2.1.3-4 4.2.1.3-5
	HEK293 cells, HEK cells, CHO cells (≥3 specimens/group)	Inhibition of cardiac ion channels (hKvLQT1/hminK, hKir2.1, hKv4.3, and hCav1.2)	Iptacopan free base: 3 and 10 μmol/L Iptacopan: 100 and 300 μmol/, or 100, 180, and 300 μmol/L	-	IC_{50}: >300 μmol/L	Non-GLP 4.2.1.3-6 4.2.1.3-7
	Primary cultured human cardiac cells 2 or 3 adult donors 1 or 2 young donors (≥5 specimens/group)	Myocardial contractile force	3, 10, 30, and 100 μmol/L	-	Adult donors: EC_{50}: >100 μmol/L Young donors: A maximum of 150% increase in 1 donor and a maximum of 35% increase in the other donor	Non-GLP 4.2.1.3-8

Organ system evaluated	Test system	Evaluation items/ methods, etc.	Iptacopan dose	Administration method	Findings	Attached data CTD
		Ca transient	Adult donors: 10, 30, and 100 μmol/L Young donors: 3 and 10 μmol/L	-	Adult donors: None Young donors: 10: Slight increase in 50% peak width	Non-GLP 4.2.1.3-9
	Rat and dog arterial ring preparations (≥3 specimens/group)	Vasodilatation	1, 3, 10, 30, and 100 μmol/L	-	None	Non-GLP 4.2.1.3-10
	Rats (8 males/group)	Blood pressure, heart rate, body temperature	1,000 mg/kg	Single dose p.o.	None	Non-GLP 4.2.1.3-11
	Dogs (3 males/group)	Blood pressure, heart rate, body temperature	600 mg/kg	Single dose p.o.	Decreased blood pressure, increased heart rate	Non-GLP 4.2.1.3-12
	Dogs (4 males/group)	Blood pressure, heart rate, pulmonary arterial flow, total peripheral vascular resistance	600, 200, 100, and 50 mg/kg (tapering dose)	Single dose p.o.	Dose-dependent decrease in blood pressure, increase in heart rate, and decrease in total peripheral vascular resistance	Non-GLP 4.2.1.3-13
	Dogs (4 males/group)	ECG, blood pressure, heart rate, body temperature	15, 50, and 300 mg/kg	Single dose p.o.	300: Decreased blood pressure, increased heart rate, shortened RR and PR	4.2.1.3-14
	Juvenile and young adult dogs (3 or 4 dogs/group, consisting of only females or males and females)	ECG, echocardiography, hormones, biomarkers, histopathology, gene expression analysis of cardiac and aortic tissues	30 and 150 mg/kg/day 14 days	Repeated dose p.o.	Juvenile dogs: ≥30: Increased renin activity, changes in gene expression 150: Increased heart rate, increased contractile force, decreased blood pressure, mild changes in cardiac function,[a)] increased NT-proBNP concentration Young mature dogs: ≥30: Increased NT-proBNP concentration 150: Increased heart rate, increased contractile force, decreased blood pressure, mild changes in cardiac function,[a)] increased renin activity, changes in gene expression	Non-GLP 4.2.1.3-15
	Cynomolgus monkeys (3 males/group)	ECG, heart rate	10, 50, 100, 300, and 600 mg/kg (escalating dose)	Single dose p.o.	≥300: Dose-dependent QTc prolongation	Non-GLP 4.2.3.1-1
Respiratory system	Rats (6 males/group)	Whole-body plethysmography (respiratory rate, tidal volume, and minute volume)	100 and 1,000 mg/kg	Single dose p.o.	None	4.2.1.3-16
Central nervous system	Rats (6 males/group)	Modified Irwin battery, body temperature	112 and 770 mg/kg	Single dose p.o.	None	4.2.1.3-16

-, not applicable

a) Decreases in systolic left ventricular internal diameter, left ventricular end-systole area, and left ventricular end-systole volume, and increases in left ventricular fractional shortening, ejection fraction, percent left ventricular area reduction, cardiac output, and heart rate on echocardiography

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological action

The applicant's explanation about the pharmacological action of iptacopan:

PNH develops due to a lack of complement regulators CD55 and CD59 on the red blood cell surface caused by mutations in the *PIGA* gene (Reference Guide to Treatment of Paroxysmal Nocturnal Hemoglobinuria, Revised in 2022 (in Japanese); Study Group on Idiopathic Hematopoietic Disorder for Research Project on Rare and Intractable Diseases subsidized by the Health, Labour and Welfare Sciences Research Grant, Ministry of Health, Labour and Welfare). Since CD55 and CD59 regulate C3 convertase and MAC formation, respectively, the lack of these regulators causes the red blood cells of patients with PNH to be very prone to complement-mediated hemolysis (intravascular hemolysis). This can cause thrombosis. While complement C5 inhibitors for the treatment of PNH inhibit intravascular hemolysis by preventing MAC formation, these drugs do not inhibit complement activation upstream of C5. Therefore, C3 convertase is active and the amplification loop for C3 is activated to amplify the formation of C3 fragments, leading to opsonization of PNH red blood cells. Consequently, PNH red blood cells in which C3 fragments have accumulated due to inhibition of C5 are phagocytized in the liver and spleen, resulting in extravascular hemolysis.

Iptacopan is a small-molecule complement inhibitor that selectively inhibits FB. By inhibiting FB, it reduces the activity of C3 convertase, thereby preventing the activation of the C3 amplification loop, opsonization of cells by C3 fragments, formation of C5 convertase and MAC, and formation of C3a and C5a (*Proc Natl Acad Sci U S A.* 2019;116:7926-7931). Based on these effects, iptacopan is expected to inhibit intravascular and extravascular hemolysis in patients with PNH.

In the studies on primary pharmacodynamics, iptacopan inhibited the binding of FB to its ligand, and thereby preventing AP activation and hemolysis. Iptacopan inhibited AP activation in a mouse LPS-induced AP activation model, and showed prophylactic and therapeutic effects in a rat passive Heymann nephritis model. It has also been reported that iptacopan inhibited hemolysis in red blood cells derived from patients with PNH, and prevented complement activation and disease progression in a mouse K/BxN serum transfer arthritis model in which the primary pathogenic factor was complement activation (*Proc Natl Acad Sci U S A.* 2019;116:7926-7931). In view of the above, iptacopan is expected to be effective for the treatment of PNH by inhibiting FB.

PMDA's view:

The applicant's explanation based on the results of the primary pharmacodynamics studies submitted and the information from published articles, is reasonable. Iptacopan can therefore be expected to be effective for PNH in clinical practice.

3.R.2 Safety pharmacology

The applicant's explanation about the results of safety pharmacology studies of iptacopan:

In the safety pharmacology studies of iptacopan, no effects on the respiratory or central nervous system were observed. In *in vitro* studies of effects on the cardiovascular system, iptacopan did not affect human cardiac ion channels at concentrations of up to ≥28-fold the unbound C_{max} (763 ng/mL)[7)] at the clinical dose in humans,

and the IC_{50} for the human ether-à-go-go-related gene (hERG) channel was approximately 230-fold the unbound C_{max} in humans. In *in vivo* studies, prolonged corrected QT (QTc) interval in monkeys and increased heart rate and decreased blood pressure in dogs were observed at exposure levels exceeding the clinical dose (200 mg BID). The no observed effect level (NOEL) for prolonged QTc interval in monkeys was 100 mg/kg, with an approximately 9-fold safety margin, when compared to the C_{max} (4,120 ng/mL) at the clinical dose in humans [see Section 6.2.2]. Concerning increased heart rate and decreased blood pressure observed in dogs, the effects were observed at the lowest dose studied in some studies; however, the NOEL ranged from 30 to 100 mg/kg (increased heart rate) and from 30 to 50 mg/kg (decreased blood pressure) in studies with NOEL values, with approximately 4- to 17-fold and approximately 4- to 8-fold safety margins, respectively, relative to the C_{max} at the clinical dose in humans.

In clinical studies of effects on the cardiovascular system, when iptacopan at a dose of 1,200 mg was administered as a single oral dose in a foreign phase I study in healthy adults (Study A2107), the C_{max} was approximately 4-fold the C_{max} (4,120 ng/mL) at the clinical dose [see Section 6.2.2], but no cases of prolonged QTc interval, increased heart rate, or decreased blood pressure were observed. In the primary evaluation period of the global phase III study in patients with PNH (Study C12302), adverse events classified as Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) System Organ Class (SOC) “vascular disorders” were observed in 8.1% (5 of 62) of subjects in the iptacopan group and 2.9% (1 of 35) of subjects in the complement C5 inhibitor group; adverse drug reactions were observed in 2 subjects only in the iptacopan group (hot flush in 2 subjects and hypertension in 1 subject; 1 subject developed ≥1 event). Adverse events classified as MedDRA/J SOC “cardiac disorders” were observed in 6.5% (4 of 62) of subjects in the iptacopan group and 2.9% (1 of 35) of subjects in the complement C5 inhibitor group; an adverse drug reaction (sinus bradycardia) was observed in 1 subject only in the iptacopan group. The severity was mild or moderate in all subjects, except for 1 subject (sinus node dysfunction) who was assessed as “severe” in the iptacopan group. An event (sinus node dysfunction) in 1 subject in the iptacopan group was assessed as serious, but was not an adverse drug reaction, and the event resolved after cardiac pacemaker implantation and amiodarone administration. On electrocardiography (ECG), transiently prolonged Fridericia-corrected QT (QTcF) interval was observed in 1 subject in the iptacopan group. This subject developed sinus node dysfunction, and the event occurred during amiodarone administration. The QRS interval exceeded 120 ms in 8.1% (5 of 62) of subjects in the iptacopan group and 2.9% (1 of 35) of subjects in the complement C5 inhibitor group; the QRS interval was >120 ms at baseline in 4 of the 5 subjects in the iptacopan group, and the remaining 1 subject was complicated by cardiovascular disorder. The QRS interval was prolonged by >25% from baseline in 3.2% (2 of 62) of subjects only in the iptacopan group; the baseline value was low in both subjects (38 and 66 ms), and the QRS interval was <120 ms, even when prolonged by >25%, in both.

In view of the above, the effects of iptacopan on the cardiovascular system observed in non-clinical studies are unlikely to cause any safety concerns during its clinical use. Since no effects on the respiratory or central nervous system were observed, the results of the safety pharmacology studies suggest that iptacopan poses no particular safety concerns in humans.

PMDA's view:

The investigation of NOEL cannot determine whether the effects on the cardiovascular system observed in non-clinical studies is relevant to humans because increased heart rate and decreased blood pressure were observed at the lowest dose studied in some studies. On the other hand, no effects of iptacopan on the cardiovascular system were observed in Study A2107 in which iptacopan was administered at 1,200 mg, a higher dose than the clinical dose. In Study C12302, the incidence of adverse events and adverse drug reactions of "vascular disorders" and "cardiac disorders" tended to be slightly higher in the iptacopan group than the complement C5 inhibitor group. However, the severity of all events was mild or moderate, except for sinus node dysfunction in 1 subject, and serious sinus node dysfunction observed in 1 subject was not assessed as an adverse drug reaction and resolved. Concerning abnormal ECG findings, taking the concomitant drugs used, baseline values, and complications into account, the use of iptacopan would not cause clinically significant concerns compared with existing complement C5 inhibitors. In view of the above, the effects of iptacopan on the cardiovascular system are unlikely to cause any safety concerns in humans. Since no effects of iptacopan on the respiratory or central nervous system were also observed, there are no particular safety concerns about iptacopan in humans from the viewpoint of safety pharmacology.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The pharmacokinetics of iptacopan was investigated in rats, dogs, and monkeys that received iptacopan or [^{14}C]-labeled iptacopan. Plasma concentrations of iptacopan were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS), with the lower limit of quantitation (LLOQ) of 1, 5, or 100 ng/mL. The radioactivity of [^{14}C]-labeled iptacopan was measured using liquid scintillation counting and quantitative whole-body autoradiography. The doses of iptacopan administered and the concentrations of iptacopan in biomaterials are expressed as the salt form.

4.1 Absorption

4.1.1 Single-dose studies

4.1.1.1 Single-dose study of iptacopan in rats (CTD reference data 4.2.2.2-5)

Table 6 shows pharmacokinetic parameters in male rats that received a single intravenous or oral dose of iptacopan.

Table 6. Plasma pharmacokinetic parameters of iptacopan following a single dose of iptacopan in rats

Route of administration	Dose (mg/kg)	C_{max} (ng/mL)	t_{max}[a)] (h)	$AUC_{0\text{-inf}}$ (ng·h/mL)	$t_{1/2}$ (h)	Bioavailability[b)] (%)
i.v.	2	-	-	2,670 ± 486	2.91 ± 0.960	-
p.o.	10	1,410 ± 185	0.5 (0.5, 0.5)	9,070 ± 1,380	4.46 ± 1.16	68.3 ± 10.6

Mean ± standard deviation for 3 rats; -, not calculated.

a) Median (minimum, maximum)

b) ($AUC_{0\text{-inf}}$ of iptacopan following an oral dose/orally administered dose)/($AUC_{0\text{-inf}}$ of iptacopan following an intravenous dose/intravenously administered dose) × 100

4.1.1.2 Single-dose study of iptacopan in dogs (CTD reference data 4.2.2.2-7)

Table 7 shows pharmacokinetic parameters in male dogs that received intravenous infusion of iptacopan over 1 hour.

Table 7. Plasma pharmacokinetic parameters of iptacopan following a single intravenous dose of iptacopan in dogs

Dose (mg/kg)	C_{max} (ng/mL)	t_{max} [a)] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
3.5	6,350 ± 715	0.95 (0.95, 1.1)	42,100 ± 11,600	7.12 ± 3.19
10	21,500 ± 971	0.95 (0.95, 1.1)	125,000 ± 12,100	7.48 ± 0.284

Mean ± standard deviation for 3 dogs
a) Median (minimum, maximum)

4.1.1.3 Single-dose study of iptacopan in monkeys (CTD reference data 4.2.3.1-1)

Toxicokinetics was investigated in male monkeys that received a single oral dose of iptacopan.[8)] Table 8 shows the plasma pharmacokinetic parameters of iptacopan. Exposure to iptacopan (C_{max} and $AUC_{0\text{-}24h}$) increased in a generally dose-proportional manner over the dose range studied.

Table 8. Plasma pharmacokinetic parameters of iptacopan following a single oral dose of iptacopan in monkeys

Dose (mg/kg)	C_{max} (ng/mL)	t_{max} [a)] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
10	2,490 ± 593	1.00	25,700 ± 1,930
50	18,600 ± 8,260	0.667	127,000 ± 29,500
100	35,600 ± 5,880	3.00	326,000 ± 64,800
300	88,800 ± 9,820	6.00	1,270,000 ± 105,000
600	138,000 ± 28,700	5.00	1,680,000 ± 346,000

Mean ± standard deviation for 3 monkeys
a) Mean

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study of iptacopan in rats (CTD 4.2.3.2-4)

Toxicokinetics was investigated in male and female rats that received repeated oral doses of iptacopan for 26 weeks. Table 9 shows the plasma pharmacokinetic parameters of iptacopan. Exposure to iptacopan (C_{max} and $AUC_{0\text{-}24h}$) increased in a generally dose-proportional manner over the dose range studied, and repeated doses were not associated with a clear increase in exposure. The pharmacokinetics of iptacopan did not clearly differ between the sexes.

Table 9. Plasma pharmacokinetic parameters of iptacopan following repeated oral doses of iptacopan in rats

Dose (mg/kg/day)	Sex	Measurement time point (Day)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
50	Male	1	4,180	0.5	24,400
		152	7,210	0.542	45,700
	Female	1	4,550	0.5	24,400
		152	5,870	0.575	30,900
150	Male	1	13,600	0.5	99,900
		152	35,500	0.542	101,000
	Female	1	22,700	0.5	69,000
		152	26,500	1	99,300
750	Male	1	47,900	3	461,000
		152	63,900	3	295,000
	Female	1	55,000	0.5	534,000
		152	65,200	3	369,000

Calculated from the mean plasma iptacopan concentration at each measurement time point (2 rats/time point).

8) Iptacopan 10, 50, 100, 300, and 600 mg/kg were administered as a single oral dose on Days 1, 8, 12, 15, and 20, respectively (dose escalation).

4.1.2.2 Repeated-dose study of iptacopan in dogs (CTD 4.2.3.2-8)

Toxicokinetics was investigated in male and female dogs that received repeated oral doses of iptacopan for 39 days. Table 10 shows the plasma pharmacokinetic parameters of iptacopan. Exposure to iptacopan (C_{max} and $AUC_{0\text{-}24h}$) increased in a generally dose-proportional manner over the dose range studied, and repeated doses were not associated with a clear increase in exposure. The pharmacokinetics of iptacopan did not clearly differ between the sexes.

Table 10. Plasma pharmacokinetic parameters of iptacopan following repeated oral doses of iptacopan in dogs

Dose (mg/kg/day)	Sex	Measurement time point (Day)	N	C_{max} (ng/mL)	t_{max} [a)] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
5	Male	1	4	3,960 ± 357	0.5 (0.5, 0.5)	29,100 ± 3,950
		273	3	4,580 ± 141	1 (1, 1)	39,300 ± 1,190
	Female	1	4	4,020 ± 560	1 (0.5, 1)	29,500 ± 6,600
		273	4	4,710 ± 372	0.5 (0.5, 1)	37,900 ± 6,660
30	Male	1	6	20,300 ± 2,660	0.75 (0.5, 1)	139,000 ± 28,500
		273	6	25,000 ± 1,920	1 (0.5, 1)	183,000 ± 29,400
	Female	1	6	19,300 ± 3,500	1 (0.5, 1)	132,000 ± 16,800
		273	6	21,000 ± 4,010	0.75 (0.5, 1)	155,000 ± 24,600
150	Male	1	6	71,400 ± 24,100	3 (1, 3)	794,000 ± 249,000
		273	6	88,200 ± 21,500	1 (1, 3)	840,000 ± 128,000
	Female	1	6	55,100 ± 2,890	1 (1, 3)	417,000 ± 63,200
		273	6	65,900 ± 17,200	1 (1, 3)	628,000 ± 186,000

Mean ± standard deviation

a) Median (minimum, maximum)

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD reference data 4.2.2.2-3 and 4.2.2.3-1)

A single oral dose of [^{14}C]-labeled iptacopan 10 mg/kg was administered to male albino rats to investigate radioactivity in each tissue[9)] at 0.25, 2, 8, 24, 72, and 168 hours post-dose. Radioactivity in most of the tissues peaked at 0.25 to 2 hours post-dose and then decreased over time. Tissues with higher radioactivity than that in blood at 0.25 hours post-dose were the kidney (1.9-, 1.9-, and 1.1-fold in the cortico-medullary junction, cortex, and medulla, respectively), liver (6.2-fold), and stomach (1.1- and 2.6-fold in the glandular and non-glandular regions, respectively).

A single oral dose of [^{14}C]-labeled iptacopan 10 mg/kg was administered to male pigmented rats to investigate radioactivity in each tissue[10)] at 0.5, 2, 8, 24, 72, 168, and 336 hours post-dose. Radioactivity in most of the tissues peaked at 0.5 to 2 hours post-dose. Tissues with higher radioactivity than that in blood at 0.5 hours post-dose were the liver, renal cortex, kidney, renal medulla, stomach, arterial wall, adrenal gland, myocardium, intervertebral ligament, and salivary gland, with 14.8-, 3.2-, 2.6-, 1.7-, 1.5-, 1.3-, 1.2-, 1.2-, 1.2-, and 1.0-fold higher radioactivity, respectively. At 72 hours post-dose, radioactivity was below the LLOQ in all tissues

9) Blood, adrenal gland (cortex and medulla), vascular wall, bone marrow, bone, brain, cartilage, choroid plexus, epididymis, esophagus, eye (choroid, ciliary body, lens, and vitreous body), fat (brown and white), hair (follicle and tactile), Harderian gland, intestinal wall (colon and small intestine), kidney (cortico-medullary junction, cortex, and medulla), lacrimal gland, liver, lung, lymph node, meninx, muscle, myocardium, pancreas, penis, pineal body, pituitary gland, preputial gland, salivary gland, seminal vesicle wall, seminal vesicle fluid, skin, subcutaneous tissue, spinal cord, spleen, stomach (glandular and non-glandular), testis, thymus gland, thyroid gland, tongue, tongue (mucous gland), tooth

10) Adrenal gland, arterial wall, blood, bone, bone marrow, brain (whole brain, cerebellum, cerebrum, medulla, and olfactory lobe), bulbourethral gland, cecum, diaphragm, epididymis, esophagus, extraorbital lacrimal gland, lens, uvea, eye, fat (abdominal and white), Harderian gland, intervertebral ligament, intraorbital lacrimal gland, renal cortex, renal medulla, kidney, large intestine, liver, lung, lymph node, mammary gland, muscle, myocardium, turbinate, oral mucosa, pancreas, pituitary gland, preputial gland, prostate gland, salivary gland, seminal gland, skin (pigmented and non-pigmented), small intestine, spinal cord, spleen, stomach, testis, thymus gland, thyroid gland

excluding the uvea, eye, liver, and pigmented skin, and radioactivity was detected in the uvea and eye up to 336 hours post-dose. These findings suggested binding of iptacopan or its metabolites to melanin.

4.2.2 Protein binding (CTD 4.2.2.3-2 and reference data 4.2.2.3-3)

The protein binding of [^{14}C]-labeled iptacopan (10-10,000 ng/mL) was investigated using wild-type mouse, rat, and dog plasma. The protein binding rate was 62.4% to 93.7% (mouse), 62.7% to 96.0% (rat), and 65.0% to 90.5% (dog), and the rate decreased with increasing plasma iptacopan concentration. The protein binding rate of iptacopan in FB-knockout mouse plasma spiked with [^{14}C]-labeled iptacopan (10-10,000 ng/mL) was 59.2% to 64.2%, showing no concentration-dependence. The applicant explained that the binding of iptacopan to plasma protein may be related to binding to FB, the target molecule of iptacopan.

4.2.3 Distribution in blood cells (CTD 4.2.2.3-2)

The distribution of [^{14}C]-labeled iptacopan (10-10,000 ng/mL) in blood cells was investigated using rat and dog plasma. The blood-to-plasma concentration ratio was 0.994 to 3.59 (rat) and 0.717 to 1.38 (dog), and the ratio increased with increasing plasma iptacopan concentration. The applicant explained that the concentration-dependence of the blood-to-plasma concentration ratio may be related to the saturation of binding to FB, the target molecule of iptacopan.

4.3 Metabolism

4.3.1 Investigation of metabolites *in vitro* (CTD 4.2.2.4-4 and reference data 4.2.2.4-6)

Metabolites of iptacopan and iptacopan free base were investigated using mouse, rat, dog, and monkey hepatocytes. Metabolites detected were M1 (*N*-dealkylated form), M2 (*O*-deethylated form), M3 (*C*-oxidized form), M4 (*C*-oxidized form and hydroxylated form), M5 (*C*-oxidized form and hydroxylated form), M6 (*C*-oxidized form and hydroxylated form), M7 (*C*-oxidized form), M8 (glucuronide-conjugated form), and M9 (*O*-deethylated and glucuronide-conjugated form). The metabolites detected were generally similar across the animal species.

4.3.2 Percentage of unchanged iptacopan and metabolites in plasma, urine, feces, and bile (CTD reference data 4.2.2.2-3)

The percentage of unchanged iptacopan and its metabolites in plasma, urine, and feces was investigated in male rats that received a single oral dose of [^{14}C]-labeled iptacopan 10 mg/kg. The percentage of unchanged iptacopan and metabolites M1, M2, M4, and M8 in plasma up to 24 hours post-dose relative to the total exposure[11)] was 91.0%, 1.63%, 1.39%, 0.338%, and 1.34%, respectively. In urine, 5.02% of the administered dose was excreted up to 72 hours post-dose, and the main analytes detected were M1 (2.17% of the administered dose) and unchanged iptacopan (2.07% of the administered dose). In feces, 93.9% of the administered dose was excreted up to 72 hours post-dose, and the main analytes detected were unchanged iptacopan (36.1% of the administered dose), M2 (29.3% of the administered dose), M6 (6.67% of the administered dose), and M4 (6.59% of the administered dose).

[11)] Ratio of $AUC_{0\text{-}24h}$ of each metabolite to total $AUC_{0\text{-}24h}$

The percentage of unchanged iptacopan and its metabolites in urine, feces, and bile was investigated in bile duct-cannulated male rats that received a single oral dose of [^{14}C]-labeled iptacopan 2 mg/kg. In urine, 13.0% of the administered dose was excreted up to 48 hours post-dose, and the main analytes detected were unchanged iptacopan (8.04% of the administered dose) and M1 (1.28% of the administered dose). In feces, 4.21% of the administered dose was excreted up to 48 hours post-dose, and the main analyte detected was unchanged iptacopan (3.51% of the administered dose). In bile, 79.4% of the administered dose was excreted up to 48 hours post-dose, and the main analytes detected were M8[12)] (20.4% of the administered dose), M2 (20.2% of the administered dose), unchanged iptacopan (11.7% of the administered dose), M6 (5.85% of the administered dose), and M4 (5.42% of the administered dose).

An acyl glucuronide-conjugated metabolite (M8) was detected in the bile of bile duct-cannulated rats, but not in the feces of intact rats. The applicant explained that M8 in intact rats was probably deconjugated by enteric bacteria after it was secreted via bile into the gut.

4.4 Excretion

4.4.1 Urinary and fecal excretion in rats (CTD reference data 4.2.2.2-3)

In male rats that received a single oral dose of [^{14}C]-labeled iptacopan 10 mg/kg, the percentage of radioactivity excreted in urine and feces up to 168 hours post-dose was 5.09% and 94.4%, respectively, of the administered dose. In male rats that received a single intravenous dose of [^{14}C]-labeled iptacopan 2 mg/kg, the percentage of radioactivity excreted in urine and feces up to 168 hours post-dose was 5.68% and 84.6%, respectively, of the administered dose.

4.R Outline of the review conducted by PMDA

On the basis of the data submitted and the results of the investigations presented below, PMDA has concluded that the non-clinical pharmacokinetics of iptacopan was evaluated in an appropriate manner. From the viewpoint of non-clinical pharmacokinetics, PMDA has concluded that there are no particular concerns about the clinical use of iptacopan.

4.R.1 Affinity for melanin

The investigation by administration of [^{14}C]-labeled iptacopan in pigmented rats suggested binding of iptacopan or its metabolites to melanin [see Section 4.2.1]. PMDA asked the applicant to explain whether there would be any safety concerns due to accumulation of iptacopan or its metabolites in melanin-containing tissue during its clinical use.

The applicant's response:

Since the radioactivity in the melanin-containing tissue of pigmented rats decreased over time, the binding of iptacopan or its metabolites to melanin is considered reversible.

[12)] Including isomers.

The incidence of adverse events classified as “eye disorders” and “skin and subcutaneous tissue disorders” in the pooled data of iptacopan 200 mg BID administration in the primary evaluation period of the global phase III study in patients with PNH (Study C12302) and other clinical studies in patients with PNH (data up to the final analysis of Studies C12302, C12301, X2201, X2204, and LFG316X2201,[13)] and data from Study C12001B[14)] as of the data cut-off on [redacted], 20[redacted]) (hereinafter referred to as PNH pooled analysis), is presented below.

- In the primary evaluation period of Study C12302, adverse events classified as MedDRA/J SOC “eye disorders” were not observed in the complement C5 inhibitor group, but were observed in 6.5% (4 of 62) of subjects only in the iptacopan group; an adverse drug reaction (blepharospasm) was observed in 1 subject. All of these adverse events were mild and non-serious, and there were no adverse events leading to treatment discontinuation. In the PNH pooled analysis, the above adverse events were observed in 7.0% (12 of 171) of subjects, and adverse events that occurred in ≥2 subjects were cataract (3 subjects) and vision blurred (2 subjects); an adverse drug reaction (blepharospasm) was observed in 1 subject. All of these adverse events were mild. A serious adverse event (cataract) was observed in 1 subject, but the event was not assessed as an adverse drug reaction. There were no adverse events leading to treatment discontinuation.
- In the primary evaluation period of Study C12302, adverse events classified as MedDRA/J SOC “skin and subcutaneous tissue disorders” were observed in 4.8% (3 of 62) of subjects in the iptacopan group and 2.9% (1 of 35) of subjects in the complement C5 inhibitor group; 6 adverse drug reactions (acne, alopecia, dermatitis acneiform, hyperhidrosis, rash erythematous, and rash macular) were observed in 1 subject only in the iptacopan group. All of these adverse events were mild or moderate and non-serious, and there were no adverse events leading to treatment discontinuation. In the PNH pooled analysis, adverse events classified as “skin and subcutaneous tissue disorders” were observed in 16.4% (28 of 171) of subjects, and adverse events that occurred in ≥2 subjects were alopecia and pruritus (4 subjects each), rash, dermatitis allergic, and petechiae (3 subjects each), and rash erythematous, acne, dermatitis acneiform, eczema, and erythema (2 subjects each). Adverse drug reactions that occurred in ≥2 subjects were alopecia (3 subjects), and dermatitis acneiform and pruritus (2 subjects each). All of these adverse events were mild or moderate, and there were no serious adverse events or adverse events leading to treatment discontinuation.
- In the PNH pooled analysis, malignant melanoma was observed in 1 subject besides the above events classified as “eye disorders” and “skin and subcutaneous tissue disorders.” Although this event was serious and did not resolve, it was not assessed as an adverse drug reaction and the treatment with iptacopan was continued.

[13)] LFG316X2201 was a global phase II study of another investigational product in patients with PNH. Development of the investigational product was discontinued in the course of the study, and the treatment was then switched to iptacopan to provide the patients with a treatment opportunity.
[14)] An ongoing extension study in patients with PNH who completed Study C12302, C12301, X2201, X2204, or LFG316X2201.

As described above, the binding of iptacopan or its metabolites to melanin is considered reversible. All of the events classified as “eye disorders” and “skin and subcutaneous tissue disorders” observed in clinical studies were mild or moderate, and there were no adverse events leading to treatment discontinuation or were assessed as serious adverse drug reactions. Accumulation of iptacopan or its metabolites in melanin-containing tissue during its clinical use is therefore unlikely to cause any safety concerns.

PMDA’s view:
The applicant’s explanation is reasonable, and PMDA therefore considers it unnecessary to provide any particular precautions regarding the binding of iptacopan or its metabolites to melanin, as in the package insert (draft) presented by the applicant.

5. Toxicology and Outline of the Review Conducted by PMDA

Toxicity studies of iptacopan consisted of single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, a study in juvenile animals, and phototoxicity studies. The main study results are presented below. The doses of iptacopan administered and the concentrations of iptacopan in biomaterials are expressed as the salt form.

5.1 Single-dose toxicity

No independent single-dose toxicity studies were conducted. Instead, the acute toxicity of iptacopan was evaluated based on the results of dose-escalation in the toxicity study in dogs and the dose-escalation study in monkeys. Table 11 shows the evaluation results.

Table 11. Summary of single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached data CTD
Male dogs (Beagle)	p.o.[a)]	50, 100, 300, 600, 1,000	≥100: Increased heart rate ≥300: Vomiting ≥600: Salivation 1,000: Increased fibrinogen/AST/ALP/total bilirubin/CK	>1,000	Non-GLP 4.2.3.2-5.1
Male cynomolgus monkeys	p.o.[b)]	10, 50, 100, 300, 600	≥300: Prolonged QTc 600: Increased ALT/AST/total bilirubin	>600	Non-GLP 4.2.3.1-1

a) Solution of 0.5% w/w methylcellulose and 0.5% w/w Tween 80 was used as the vehicle.
b) Solution of 0.5% w/v methylcellulose and 0.5% v/v Tween 80 was used as the vehicle.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in rats (up to 26 weeks) and repeated oral dose toxicity studies in dogs (up to 39 weeks) were conducted (Table 12). The main target organs were the heart, bone marrow, testes, thyroid gland, and liver.

In the 26-week repeated-dose toxicity study in rats, the $AUC_{0\text{-}24h}$ in males and females at the no observed adverse effect level (NOAEL) (750 mg/kg/day) was 5.8- and 7.2-fold, respectively, the exposure at the clinical

dose.[15)] In the 39-week repeated-dose toxicity study in dogs, $AUC_{0\text{-}24h}$ in males and females at the NOAEL (5 mg/kg/day in males and 30 mg/kg/day in females) was 0.8- and 3.0-fold, respectively, the exposure at the clinical dose.[15)]

Table 12. Summary of repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Male and female rats (Wistar)	p.o.	4 weeks (QD) + 4-week recovery period	0,[a)] 100, 300, 1,000	≥100: Increased total bilirubin/direct bilirubin 1,000: Decreased food consumption; increased TSH; hypertrophy of thyroid follicular epithelial cells; degeneration/regeneration of the acini of the Harderian gland Reversibility: Reversible	300	4.2.3.2-2.1
Male and female rats (Wistar)	p.o.	13 weeks (QD) + 8-week recovery period	0,[b)] 50, 150, 500	≥50: Increased T4 500: Salivation; increased thyroid/parathyroid weight; hypertrophy of thyroid follicular epithelial cells; degeneration of the seminiferous tubule Reversibility: Reversible	150 (male) 500 (female)	4.2.3.2-3
Male and female rats (Wistar)	p.o.	26 weeks (QD) + 27-week recovery period	0,[b)] 50, 150, 750	≥50: Increased thyroid/parathyroid weight ≥150: Hypertrophy of thyroid follicular epithelial cells 750: Salivation; increased ALP/total bilirubin; increased TSH/T3/T4 Reversibility: Reversible	750	4.2.3.2-4
Male and female dogs (Beagle)	p.o.	4 weeks (QD) + 4-week recovery period	0,[a)] 15, 50, 300	≥15: Increased heart rate; increased total bilirubin; decreased T4; decreased thyroid weight; hypertrophy of thyroid follicular epithelial cells 300: Decreased body weight[c)]; decreased testis/epididymis weight; degeneration/necrosis of myocardial cells; detachment of germ cells in the testis; decreased sperm in the epididymis; cell debris in the epididymal duct; hyperplasia of the bile duct; pigment deposition in Kupffer cells in the liver Reversibility: Reversible	50	4.2.3.2-6.1
Male and female dogs (Beagle)	p.o.	13 weeks (QD) + 8-week recovery period	0,[b)] 5, 30, 150	≥5: Increased total testosterone/androstenedione; increased thyroid weight ≥30: Salivation; degeneration of the seminiferous tubule; cell debris in the epididymal duct; hypertrophy of thyroid follicular epithelial cells; depletion of lymphoid cells in mesenteric lymph nodes 150: Decreased food consumption; decreased weight gain; increased heart rate; changes in hematological tests[d)]; changes in blood chemistry tests[e)]; increased granulocyte/erythroblast ratio in the bone marrow; increased prostate/testis/epididymis weight; single cell necrosis/mixed inflammatory cell	5 (male) 30 (female)	4.2.3.2-7.1

[15)] $AUC_{0\text{-}24h}$ in humans was calculated by doubling the $AUC_{0\text{-}12h}$ (AUC_{tau}, 25,600 ng·h/mL) at the clinical dose (200 mg BID) in the foreign phase I study in healthy adults (Study X2101).

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
				infiltration in the liver; hyperplasia of the bile duct; pigment deposition in hepatocytes and Kupffer cells; depletion of lymphoid cells in mandibular lymph nodes; depletion of lymphoid cells in the spleen Reversibility: Reversible		
Male and female dogs (Beagle)	p.o.	39 weeks (QD) + 27-week recovery period	0,[b] 5, 30, 150	Premature necropsy[f]: 150 (1 of 6 males) Premature necropsy: 150: Pallor of the ear and gums; sedation/slow action; cold tactile sensation; decreased body weight; decreased white blood cell count/neutrophil count/eosinophil count/lymphocyte count/monocyte count; decreased red blood cell count/Hb/hematocrit/reticulocyte count; nucleated red blood cell; increased fibrinogen; fibrosis of the femoral and sternal bone marrow; increased cancellous bone and light brown pigment deposition; degeneration of centrilobular hepatocytes; focal necrosis of hepatocytes; megakaryocytic extramedullary hematopoiesis in the liver; brown pigment deposition in hepatocytes and Kupffer cells; degeneration of the seminiferous tubule; cell debris in the epididymal duct; extramedullary hematopoiesis in the spleen Planned necropsy: ≥5: Increased thyroid/parathyroid weight; hypertrophy of thyroid follicular epithelial cells ≥30: Increased T3; degeneration of the seminiferous tubule; cell debris in the epididymal duct lumen 150: Increased heart rate; nucleated red blood cell; increased TSH; decreased testis weight; pigment deposition in Kupffer cells in the liver Reversibility: Reversible	5 (male) 30 (female)	4.2.3.2-8.1

a) Solution of 0.5% w/w methylcellulose and 0.5% v/v Tween 80
b) Solution of 0.5% w/w methylcellulose and 0.5% w/w Tween 80
c) Since decreased body weight was observed in 1 male and 2 females in the 300 mg/kg/day group on Day 8, supplementary food was given to all animals in the 300 mg/kg/day group until the body weight recovered. Iptacopan administration had no effect on body weight at the end of the administration period.
d) Increased platelet count was observed in females in the 150 mg/kg/day group, and decreased white blood cell count, neutrophil count, red blood cell parameters (red blood cell count, Hb, and hematocrit), and platelet count in 1 male in the 150 mg/kg/day group, and decreased neutrophil count, increased monocyte count, and increased fibrinogen in 1 female each in the 150 mg/kg/day group.
e) Increased globulin, increased total protein, and decreased albumin/globulin ratio were observed in 1 male and 1 female each in the 150 mg/kg/day group.
f) Euthanized 103 days after the start of the recovery period.

5.3 Genotoxicity

A bacterial reverse mutation assay, an *in vitro* micronucleus assay in human peripheral blood lymphocytes, and a rat micronucleus assay were conducted. The results of all of these assays were negative. The applicant therefore considered that iptacopan is unlikely to be genotoxic (Table 13).

Table 13. Summary of genotoxicity studies

Study		Test system	S9 (duration)	Concentration or dose	Result	Attached data CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA97a, TA98, TA100, TA102, TA1535	−/+	0,[a] 5, 16, 50, 160, 500, 1,600, 5,000 µg/plate	Negative	4.2.3.3.1-2
	Micronucleus assay	Human peripheral blood lymphocytes	− (3 and 24 hours)	0,[a] 300, 350, 400, 459 µg/mL	Negative	4.2.3.3.1-4
			+ (3 hours)	0,[a] 300, 350, 400, 459 µg/mL		
In vivo	Micronucleus assay[b]	Male and female rat (Wistar) peripheral reticulocytes		0,[c] 100, 300, and 1,000 mg/kg/day	Negative	4.2.3.2-2.1

a) DMSO
b) Conducted as part of the 4-week repeated-dose toxicity study in rats (CTD 4.2.3.2-2.1).
c) Solution of 0.5% w/w methylcellulose and 0.5% v/v Tween 80

5.4 Carcinogenicity

A 104-week repeated oral dose carcinogenicity study in rats and a 26-week repeated oral dose carcinogenicity study in Tg-rasH2 mice were conducted. The studies showed that iptacopan is non-carcinogenic (Table 14).

Table 14. Summary of carcinogenicity studies

Test system	Route of administration	Administration period	Results								Non-carcinogenic dose (mg/kg/day)	Attached data CTD
Male and female rats (Wistar)	p.o.	104 weeks (QD)	Main findings		N	Dose (mg/kg/day)					750	4.2.3.4.1-1
						0[a) c)]	0[b) c)]	150[c)]	300[c)]	750[c)]		
						Male, 52; female, 50	Male, 50; female, 51	50/sex	50/sex	Male, 51; female, 50		
			Neoplastic lesions		No particular finding							
			Non-neoplastic lesions	Hypertrophy of thyroid follicular epithelial cells[d)]	Male	11 (0)	15 (1)	14 (0)	22 (0)	17 (3)		
					Female	7 (0)	3 (0)	8 (1)	8 (0)	18 (4)		
				Hyperplasia of thyroid diffuse C cells[e)]	Male	39 (4)	35 (3)	40 (8)	38 (8)	28 (10)		
					Female	37 (2)	38 (5)	42 (8)	45 (5)	27 (10)		
				Hepatocellular vacuolation[d)]	Male	44 (3)	40 (0)	44 (4)	42 (6)	41 (6)		
					Female	26 (1)	27 (0)	34 (3)	40 (3)	35 (1)		
			Other findings		≥150: Abnormal respiration 750: Decreased survival rate,[f)] salivary hypersecretion							
Male and female mice (Tg-rasH2)	p.o.	26 weeks (QD)	Main findings		N	Dose (mg/kg/day)					1,000	4.2.3.4.2-1
						0 [a)]	0 [b)]	100	300	1,000		
						25/sex	25/sex	25/sex	25/sex	25/sex		
			Neoplastic lesions		No particular finding							
			Non-neoplastic lesions	Hepatocellular vacuolation	Male	7	4	12	13	15		
					Female	2	0	1	8	7		

a) Purified water
b) Solution of 0.5% w/w methylcellulose and 0.5% w/w Tween 80
c) Since the mortality rate increased in the 750 mg/kg/day group, the dosing volume was changed from 5 mL/kg to 7.5 mL/kg from Day 21. For males, the treatment in the 750 mg/kg/day group was discontinued at Week 94 when the number of surviving animals in the said group became 20. The treatment of the surviving animals in the 750 mg/kg/day group was suspended, and the study was then continued. At Weeks 102 to 103 when the number of surviving animals in the 750 mg/kg/day group became 15, the study in males in all treatment groups was terminated. Concerning females, the number of surviving animals in the 750 mg/kg/day group became 15 at Weeks 99 to 100, at which the study in the surviving animals in the said group was terminated. The study in females in the other treatment groups was completed at Weeks 105 to 106, as initially planned.
d) The frequency of findings with high severity (moderate or severe) is presented in parentheses.
e) The frequency of findings with high severity (moderate) is presented in parentheses.
f) No deaths possibly related to the toxicity of iptacopan were observed.

5.5 Reproductive and developmental toxicity

Studies of fertility and early embryonic development to implantation in rats, studies of embryo-fetal development in rats or rabbits, and a study of effects on pre- and postnatal development, including maternal function, in rats were conducted (Table 15).

In the study of fertility and early embryonic development to implantation in female rats, increased pre- and post-implantation loss and decreased number of living fetuses were observed at 1,000 mg/kg/day.

The $AUC_{0\text{-}24h}$ of iptacopan at the NOAEL for early embryonic development (300 mg/kg/day) in the study of fertility and early embryonic development to implantation in female rats was 2.4-fold the exposure at the clinical dose.[15)]

Table 15. Summary of reproductive and developmental toxicity studies

Study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Fertility and early embryonic development to implantation	Male rats (Wistar)	p.o.	116 days (13 weeks before mating, during the mating period, and until 1 day before necropsy) (QD)	0,[a)] 50, 150, 750	None	General toxicity: 750 Reproductive function: 750 Early embryonic development: 750	4.2.3.5.1-1
	Female rats (Wistar)	p.o.	Up to 35 days (2 weeks before mating, during the mating period, and until Gestation Day 6) (QD)	0,[a)] 100, 300, 1,000	1,000: Increased pre-implantation loss/early resorptions/post-implantation loss, decreased number of live fetuses	General toxicity: 1,000 Reproductive function: 1,000 Early embryonic development: 300	4.2.3.5.1-2
Embryo-fetal development	Female rats (Wistar)	p.o.	Gestation Days 6 to 17 (QD)	0,[a)] 100, 300, 1,000	None	General toxicity in maternal animals: 1,000 Embryo-fetal development: 1,000	4.2.3.5.2-1
	Female rabbits (NZW)	p.o.	Gestation Days 7 to 20 (QD)	0,[a)] 100, 250, 450	Maternal animals: 450: Decreased food consumption, decreased weight gain	General toxicity in maternal animals: 250 Embryo-fetal development: 450	4.2.3.5.2-3
Pre- and postnatal development, including maternal function	Female rats (Wistar)	p.o.	Gestation Day 6 to Lactation Day 21 (QD)	0,[a)] 100, 300, 1,000	None	General toxicity in maternal animals: 1,000 F_1 offspring development and growth: 1,000	4.2.3.5.3-1

a) Solution of 0.5% w/w methylcellulose and 0.5% w/w Tween 80

5.6 Study in juvenile animals

A 52-week repeated-dose toxicity study in juvenile dogs was conducted (Table 16). In this study, increased heart weight and mineralization of the aorta at the base of the heart (outflow tract of the aorta), which were not observed in the repeated-dose toxicity studies in dogs, were observed at ≥30 mg/kg/day. $AUC_{0\text{-}24h}$ at the NOAEL (5 mg/kg/day) was 0.9-fold the exposure at the clinical dose.[15)]

Table 16. Summary of the study in juvenile animals

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Male and female juvenile dogs (Beagle)	p.o.	52 weeks (started 28 days after birth) (QD) + 27-week recovery period	0,[a)] 5, 30, 150	≥5: Salivation; increased reticulocyte count; increased total bilirubin/fibrinogen ≥30: Decreased red blood cell count/Hb/hematocrit; increased phosphorus; increased NT-proBNP; increased thyroid/heart weight; mineralization of the aorta at the base of the heart; increased bone marrow hematopoiesis; decreased spermatogenesis of the testis; hypertrophy of thyroid follicular epithelial cells; pigment deposition in Kupffer cells in the liver 150: Increased heart rate; red blood cell nucleated morphology; increased urea/creatinine; increased Ca; increased androstenedione/testosterone/dihydrotestosterone; increased T3; myocardial fibrosis/degeneration/necrosis (mainly in the left ventricular wall and papillary muscle); vacuolation of the zona glomerulosa of the adrenal cortex; cell debris in the epididymal duct lumen Reversibility: Reversible (excluding mineralization of the aorta at the base of the heart, cardiac fibrosis, and pigment deposition in Kupffer cells in the liver)	5	4.2.3.5.4-2

a) Solution of 0.5% w/w methylcellulose and 0.5% w/w Tween 80

5.7 Phototoxicity

An *in vitro* phototoxicity study using a mouse 3T3 fibroblast cell line and an ultraviolet irradiation local lymph node assay using mice were conducted. On the basis of the results, the applicant considered that iptacopan is unlikely to be phototoxic (Table 17).

Table 17. Summary of phototoxicity studies

Study	Test system	Testing method	Results	Attached data CTD
In vitro phototoxicity	BALB/c mouse 3T3 fibroblast cell line	The mouse 3T3 fibroblast cell line was treated with iptacopan at up to 1,000 µmol/L for approximately 1 hour, irradiated with UVA (5.0 ± 0.3 J/cm^2) for approximately 50 minutes, and then cultured for 20 to 22 hours. The culture was then treated with neutral red (NR), and the optical density of the NR extract at 540 nm using a spectrophotometer.	Positive	Non-GLP 4.2.3.7.7-1
In vivo phototoxicity	BALB/cByJ mice (female)	Iptacopan 0,[a)] 100, 300, and 1,000 mg/kg/day was orally administered, and irradiated with UVA at 10 J/cm^2 at 60 to 90 minutes post-dose (for 3 consecutive days). During the administration period, clinical signs and local reactions in the ear and tail were observed. At necropsy, both ears, lymph nodes of both ears, and abdominal skin were collected and weighed, and a cell suspension was prepared from the lymph nodes and subjected to measurement of the total cell count.	Negative	4.2.3.7.7-2

a) Solution of 0.5% w/w methylcellulose and 0.5% w/w Tween 80

5.R Outline of the review conducted by PMDA

5.R.1 Increased heart weight and mineralization of the aorta at the base of the heart in the toxicity study in juvenile dogs

The applicant's explanation about the mechanism of onset of increased heart weight and mineralization of the aorta at the base of the heart in the 52-week repeated-dose toxicity study in juvenile dogs [see Section 5.6] and the extrapolability of these findings to patients with PNH:

In safety pharmacology studies on the cardiovascular system in juvenile and young adult dogs [see Section 3.3], hemodynamic abnormalities such as persistently increased cardiac output and heart rate were observed, but there was a difference in response (changes were more prominent in juvenile dogs). Therefore, hemodynamic abnormalities attributable to iptacopan administration in juvenile dogs, which are considered to have an incompletely matured cardiovascular system, may have induced increased heart weight and mineralization of the aorta at the base of the heart due to arterial wall disorder. In the foreign phase I study in healthy adults (Study A2107), no effects on the cardiovascular system, including heart rate and blood pressure, were observed. In the global phase III study in patients with PNH (Study C12302), the cardiovascular safety in the iptacopan group showed no clinically significant trends when compared with the complement C5 inhibitor group in the primary evaluation period [see Section 3.R.2]. In view of the above, increased heart weight and mineralization of the aorta at the base of the heart observed in juvenile dogs are unlikely to occur in adult patients with PNH.

PMDA's view:

The applicant's explanation is reasonable. On the basis of the data submitted and the above investigation, PMDA concluded that there are no particular concerns about the clinical use of iptacopan from the viewpoint of toxicity.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The global phase III studies (Studies C12302 and C12301) submitted as the pivotal data for the present application used the formulation in which only [redacted] is different from that of the proposed commercial formulation.

Both the plasma and plasma ultrafiltrate concentrations of iptacopan were measured using LC-MS/MS, with an LLOQ of 1.0 ng/mL (plasma) and 0.2 ng/mL (plasma ultrafiltrate). Serum AP activity values were evaluated by measuring the C5b-9 complex using enzyme-linked immunosorbent assay (ELISA). Plasma concentrations of the fragment Bb of Factor B (hereinafter referred to as Bb) were measured using ELISA. The doses of iptacopan administered and the concentrations of iptacopan in biomaterials are expressed as the salt form.

6.1.1 Studies using human biomaterials

6.1.1.1 Protein binding (CTD 4.2.2.3-2 and reference data 4.2.2.3-3)

The protein binding rate of iptacopan in human plasma spiked with [^{14}C]-labeled iptacopan (10-10,000 ng/mL) was 74.6% to 98.8%, and the rate tended to decrease with increasing plasma iptacopan concentration. The protein binding rates of iptacopan in human serum albumin solution, α_1-acidic glycoprotein solution, and lipoprotein solution spiked with [^{14}C]-labeled iptacopan (100-10,000 ng/mL) were 25.2% to 31.8%, 8.95% to 9.69%, and 15.0% to 16.5%, respectively, showing no concentration-dependence. The applicant explained that the binding of iptacopan to human plasma protein may be related to binding to FB, the target molecule of iptacopan.

6.1.1.2 Distribution in blood cells (CTD 4.2.2.3-2)

The distribution of [^{14}C]-labeled iptacopan (10-10,000 ng/mL) in blood cells was investigated using human blood. The blood-to-plasma concentration ratio of iptacopan was 0.600 to 2.14, and the ratio increased with increasing iptacopan concentration.

6.1.1.3 Investigation of metabolites *in vitro* (CTD 4.2.2.4-4)

Metabolites of iptacopan were investigated using human hepatocytes. The major metabolites detected were M1 (*N*-dealkylated form), M2 (*O*-deethylated form), M3 (*C*-oxidized form), M6 (hydroxylated form and *C*-oxidized form), M7 (*C*-oxidized form), M8 (glucuronide-conjugated form), and M9 (*O*-deethylated form and glucuronide-conjugated form). No human-specific metabolites were identified [see Section 4.3.1].

6.1.1.4 Investigation of metabolizing enzymes involved in the metabolism of iptacopan (CTD 4.2.2.4-9 and reference data 4.2.2.4-8)

Using human hepatic microsomes spiked with [^{14}C]-labeled iptacopan (20 μmol/L) and each CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4), and flavin-containing monooxygenase (FMO) inhibitors,[16)] the contribution of each CYP isoform and FMO to the metabolism of iptacopan was investigated. The CYP2C8 inhibitor montelukast decreased the metabolic activity of iptacopan. Inhibitors of other CYP isoforms did not clearly inhibit the metabolism of iptacopan.

Human enzyme expression systems (CYP1A1, CYP1A2, CYP2A6, CYP3A4, CYP3A5, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP4F2, CYP4F3A, CYP4F3B, CYP4F12, and CYP2J2, FMO3, and MAO-A/B) were spiked with [14C]-labeled iptacopan (5 μmol/L). As a result, iptacopan was metabolized by CYP2C8 (metabolic ratio, 5.4%; M1, M2, and M6 were formed), CYP1A1 (metabolic ratio, 2.4%; M6 was formed), CYP2D6 (metabolic ratio, 1.8%; M1 and M6 were formed), CYP2C9 (metabolic ratio, 1.0%; M2 and M6 were formed), and CYP3A4 (metabolic ratio, 0.8%; M1, M2, and M6 were formed).

[16)] Inhibitors used: CYP1A2, furafylline; CYP2B6, ticlopidine; CYP2C8, montelukast; CYP2C9, sulfaphenazole; CYP2C19, loratadine and ticlopidine; CYP2D6, quinidine; CYP2E1, sodium diethyldithiocarbamate; CYP3A4, azamulin and ketoconazole; FMO, methimazole.

Evaluation of the percent contribution to oxidative metabolism in the liver[17] suggested that the percent contribution of CYP2C8 and CYP2D6 was 98% and 2%, respectively. Therefore, the applicant explained that the major enzyme involved in the oxidative metabolism of iptacopan in the liver may be CYP2C8.

6.1.1.5 Investigation of UGT isoforms involved in the metabolism of iptacopan (CTD reference data 4.2.2.4-10 and 4.2.2.4-11)

Human enzyme expression systems (uridine diphosphate-glucuronosyltransferase [UGT] 1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15, and UGT2B17) were spiked with [14C]-labeled iptacopan (5 μmol/L). As a result, the acyl glucuronide-conjugated metabolite M8 was formed by UGT1A1 (metabolic ratio, approximately 2%), UGT1A8 (metabolic ratio, approximately 2%), and UGT1A3 (metabolic ratio, approximately 0.5%).

Correlation between the rate of metabolism to acyl glucuronide-conjugated metabolites (M8 and M8c[18]) and the metabolic activity of UGT substrates[19] (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was investigated using human hepatic microsomes spiked with [^{14}C]-labeled iptacopan free base (10 μmol/L). The results showed a positive correlation between the metabolic rate of iptacopan and the metabolic activity of UGT1A1 (correlation coefficient R, 0.83).

Taking the expression of each UGT isoform in the liver into account, UGT1A1 may be mainly involved in the direct glucuronide conjugation metabolism of iptacopan. However, given the percentage of iptacopan and its metabolites excreted in urine and feces in the mass balance study (Study A2101) [see Section 6.2.3], the applicant explained that the percent contribution of UGT isoforms to the elimination of iptacopan is considered to be <25%.

6.1.1.6 Inhibition of human drug-metabolizing enzymes by iptacopan (CTD 4.2.2.4-14, reference data 4.2.2.4-13, 4.2.2.4-15, and 4.2.2.4-17)

The reversible inhibitory effect of iptacopan (0.39-100 μmol/L) on CYP isoforms[20] (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) was investigated using human hepatic microsomes. Iptacopan did not show a clear reversible inhibitory effect on any CYP isoforms over the concentration range studied.

[17] The metabolic rate of iptacopan when [14C]-labeled iptacopan (2-400 μmol/L) was incubated with the human CYP2C8 expression system was expressed using the Michaelis–Menten equation as follows: Km,app, 31.93 μmol/L; Vmax, 2.64 pmol/min/pmol CYP; CLint,app, 0.083 μL/min/pmol CYP. For CYP2D6, since the metabolic rate was not sufficient because the metabolic ratio was low, the metabolic rate with iptacopan 2 μmol/L was used. Using the obtained parameter values, unbound fraction with the test system, and the expression of CYP isoforms in hepatic microsomes (*Br J Clinical Pharmacology*. 2004;57: 687-688), the percent contribution of each isoform to oxidative metabolism in the liver was calculated by extrapolating the intrinsic clearance (Clint) of unbound iptacopan with the isoform (0.78 μL/min/mg protein for CYP2C8 and 0.02 μL/min/mg protein for CYP2D6).

[18] Isomer of M8

[19] Substrates used: UGT1A1, estradiol; UGT1A4, trifluoperazine; UGT1A6, naphthol; UGT1A9, propofol; UGT2B7, morphine.

[20] Substrates used: CYP1A2, phenacetin; CYP2A6, coumarin; CYP2B6, bupropion; CYP2C8, amodiaquine; CYP2C9, diclofenac; CYP2C19, S-mephenytoin; CYP2D6, bufuralol; CYP2E1, chlorzoxazone; CYP3A4/5, midazolam and testosterone.

The time-dependent inhibitory effect of iptacopan or iptacopan free base (15.63-500 μmol/L for CYP2C8 and 3.13-100 μmol/L for other CYP isoforms) on CYP isoforms[21)] (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) was investigated using human hepatic microsomes. Iptacopan inhibited CYP2C8 in a time-dependent manner (K_I, 179 μmol/L; k_{inact}, 0.0702 min^{-1}).

The inhibitory effect of iptacopan (0.39-100 μmol/L) on UGT1A1[22)] was investigated using human hepatic microsomes and the human UGT1A1 expression system. Iptacopan did not show a clear inhibitory effect on UGT1A1 over the concentration range studied.

6.1.1.7 Induction of human drug-metabolizing enzymes by iptacopan (CTD 4.2.2.4-16)

Human hepatocytes were incubated with iptacopan (0.1-100 μmol/L) to investigate changes in the mRNA expression of CYP1A2, CYP2B6, CYP2C9, and CYP3A4. The mRNA expression of CYP3A4 increased in an almost concentration-dependent manner, with a maximum fold induction (fold induction of iptacopan 100 μmol/L) of 2.49- to 2.75-fold (5.76% to 19.07% of the positive control).

6.1.1.8 Investigation of transporter-mediated transport (CTD reference data 4.2.2.7-11 and 4.2.2.7-12)

Using Madin-Darby canine kidney (MDCK) II cells engineered to express P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), transport of [^{14}C]-labeled iptacopan (0.5-800 μmol/L) mediated by P-gp or BCRP was investigated. The results suggested that iptacopan is a substrate of P-gp and BCRP. Using vesicles engineered to express multidrug resistance protein 2 (MRP2), transport of [^{14}C]-labeled iptacopan (0.5-400 μmol/L) mediated by MRP2 was investigated. The results suggested that iptacopan is a substrate of MRP2.

Using HEK293 cells engineered to express organic anion transporting polypeptide (OATP)1B1 or OATP1B3, transport of [^{14}C]-labeled iptacopan (0.25-400 μmol/L) mediated by OATP1B1 and OATP1B3 was investigated. The results suggested that iptacopan is a substrate of OATP1B1 and OATP1B3.

Using cell lines engineered to express organic anion transporter (OAT)1 (HEK293 and CHO-K1 cells), OAT2 (HEK293 cells), OAT3 (HEK293 and MDCKII cells) or organic cation transporter (OCT)2 (CHO-K1 cells), transport of iptacopan (0.1-400 μmol/L for OAT1 and OAT3, and 0.1-300 μmol/L for OAT2 and OCT2) mediated by OAT1, OAT2, OAT3, and OCT2 was investigated. The results suggested that iptacopan is not a substrate of OAT1, OAT2, OAT3, or OCT2.

In view of the point described below, the applicant explained that drug interactions mediated by P-gp, BCRP, and MRP2 are unlikely to affect the safety of iptacopan.

In the mass balance study (Study A2101), iptacopan was excreted unchanged in feces, and the percentage of unchanged iptacopan excreted in feces was 16.8% of the administered dose. The unchanged iptacopan is

[21)] Substrates used: CYP1A2, phenacetin; CYP2B6, bupropion; CYP2C8, amodiaquine; CYP2C9, diclofenac; CYP2C19, S-mephenytoin; CYP2D6, bufuralol; CYP3A4/5, midazolam.
[22)] Substrate used: β-estradiol.

derived from [1] iptacopan excreted in bile, [2] the aglycone of the acyl glucuronide-conjugated metabolite (M8) excreted in bile, and [3] iptacopan not absorbed in the gastrointestinal tract, and the efflux transporters are considered to be involved in [1] and [3]. The increase in the AUC of iptacopan in case the efflux transporters are completely inhibited in the gastrointestinal tract and liver was estimated using the formula (*Drug Metab Dispos*. 2008;36:1698-1708) based on the amount of unchanged iptacopan excreted in feces. The AUC of iptacopan was estimated to show not more than a 1.19-fold increase, suggesting that the increase in exposure due to transporter inhibition would be within the range of variation in plasma iptacopan concentrations when iptacopan is administered at the clinical dose to patients with PNH [see Sections 6.2.4 to 6.2.7].

6.1.1.9 Investigation of transporter inhibition (CTD 4.2.2.7-6; reference data 4.2.2.7-2 to 4.2.2.7-5, 4.2.2.7-8, and 4.2.2.7-9)

Using cell lines engineered to express P-gp (LLC-PK1 cells) or BCRP (MDCKII cells) and vesicles engineered to express P-gp or BCRP, the effect of iptacopan (0.1-400 μmol/L) on the transport of reference materials[23)] was investigated. In the study using cell lines, iptacopan did not show a clear inhibitory effect on either P-gp or BCRP over the concentration range studied. In the study using vesicles, iptacopan did not inhibit BCRP-mediated transport over the concentration range studied. On the other hand, iptacopan inhibited P-gp-mediated transport concentration-dependently, with an IC_{50} of 37.0 μmol/L.

Using vesicles engineered to express MRP2 or bile salt export pump (BSEP), the effect of iptacopan (0.1-260 μmol/L for MRP2 and 0.1-400 μmol/L for BSEP) on the transport of reference materials[24)] was investigated. Iptacopan did not show a clear inhibitory effect on MRP2 or BSEP over the concentration range studied.

Using HEK293 cells engineered to express OATP1B1 or OATP1B3, the effect of iptacopan (0.1-400 μmol/L) on the transport of the reference material[25)] was investigated. Iptacopan inhibited OATP1B1 and OATP1B3 with an IC_{50} of 25.6 μmol/L and >400 μmol/L, respectively.

Using HEK293 cells expressing OAT1 or OAT3 and MDCKII cells expressing multidrug and toxin extrusion (MATE)1 or MATE2-K, the effect of iptacopan (0.1-400 μmol/L) on the transport of reference materials[26)] was investigated. Iptacopan inhibited OAT3- and MATE1-mediated transport concentration-dependently, with an IC_{50} of 178 μmol/L and 424 μmol/L, respectively.

Using HEK293 cells expressing OCT1 or OCT2, the effect of iptacopan (0.1-400 μmol/L) on the transport of the reference material[27)] was investigated. Iptacopan inhibited OCT1- and OCT2-mediated transport concentration-dependently, with an IC_{50} of 322 μmol/L and 361 μmol/L, respectively.

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23) Substrates evaluated in the study using cell lines: P-gp, [^{3}H]digoxin; BCRP, [^{14}C]2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine. Substrates evaluated in the study using cell vesicles: P-gp, [^{3}H] N-methyl-quinidine; BCRP, [^{3}H]estrone-3-sulfate.
24) Substrates evaluated: MRP2, [^{3}H]estradiol-17β-D-glucuronide; BSEP, [^{3}H]taurocholic acid.
25) Substrate evaluated: [^{3}H]estradiol-17β-D-glucuronide.
26) Substrates evaluated: OAT1, [^{3}H]para-aminohippuric acid; OAT3, [^{3}H]estrone-3-sulfate; MATE1 and MATE2-K, [^{14}C]metformin.
27) Substrate evaluated: [^{14}C]metformin.

Using HEK293 cells expressing OAT1, OAT3, OCT1, or OCT2 and MDCKII cells expressing MATE1 or MATE2-K, the effect of 30-minute pre-incubation with iptacopan (0.1-400 μmol/L) on the transport of reference materials[28)] was investigated. Iptacopan inhibited OAT3-, OCT1-, and MATE1-mediated transport concentration-dependently, with an IC_{50} of 188.2 μmol/L, 398.9 μmol/L, and 347.2 μmol/L, respectively.

According to the applicant, investigation based on the "Guideline on drug interaction for drug development and appropriate provision of information" (PSEHB/PED Notification No. 0723-4 dated July 23, 2018, issued by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)" (hereinafter referred to as the drug interaction guideline) suggested that iptacopan was unlikely to induce drug interactions by inhibiting OAT3, MATE1, OCT1, and OCT2. The effect of iptacopan on P-gp, OATP1B1, and OATP1B3 is discussed in Section 6.2.9.

6.2 Clinical pharmacology

6.2.1 Japanese phase I single-dose study (CTD 5.3.3.1-1: Study X1102 [[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, single-blind study was conducted at 1 Japanese study site to investigate pharmacokinetics and safety following a single oral dose of iptacopan in Japanese healthy adults (target sample size, 30 subjects [2 subjects in each placebo group and 8 subjects in each iptacopan group]).

Placebo or iptacopan 25, 100, or 400 mg was administered as a single oral dose under fasted conditions.

All 30 subjects who received the study drug were included in the safety set, and all 24 subjects who received iptacopan were included in the pharmacokinetic analysis population.

Table 18 shows the plasma pharmacokinetic parameters of iptacopan following a single oral dose of iptacopan. The C_{max} and $AUC_{0\text{-}inf}$ of iptacopan showed less than dose-proportional increases. According to the applicant's explanation, the less than dose-proportional increase occurred because iptacopan was more rapidly cleared from the systemic circulation and distributed broadly with an increase in the unbound fraction of iptacopan, which was caused by the saturation of iptacopan binding to plasma FB resulting from the increasing plasma concentration of iptacopan due to high affinity of iptacopan for plasma FB.

Table 18. Plasma pharmacokinetic parameters of iptacopan following a single oral dose of iptacopan in Japanese healthy adults

Iptacopan dose	N	C_{max} (ng/mL)	t_{max} [a)] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
25 mg	8	1,160 ± 254	1.5 (1.0, 3.0)	12,500 ± 3,300	13 ± 2.2
100 mg	8	2,460 ± 735	1.8 (1.0, 2.5)	28,700 ± 9,170	15 ± 3.6
400 mg	8	7,990 ± 1,360	2.3 (1.0, 3.0)	73,500 ± 14,300 [b)]	25 ± 16

Mean ± standard deviation
a) Median (minimum, maximum)
b) N = 7

[28)] Substrates evaluated: OAT1, [^{3}H]tenofovir; OAT3, [^{3}H]estrone-3-sulfate; OCT1, OCT2, MATE1, and MATE2-K, [^{14}C]metformin.

Concerning safety, adverse events were observed in 12.5% (1 of 8) of subjects in the iptacopan 100 mg group and 25.0% (2 of 8) of subjects in the iptacopan 400 mg group, and adverse drug reactions were observed in 12.5% (1 of 8) of subjects in the iptacopan 100 mg group and 12.5% (1 of 8) of subjects in the iptacopan 400 mg group. There were no adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.2 Foreign phase I single-dose and multiple-dose study and food effect study (CTD 5.3.3.1-2: Study X2101 [[redacted] to [redacted]])

A placebo-controlled, randomized, single-blind study (Part 1 and Part 2) and a randomized, open-label, 2-group 2-period crossover study (Part 3) were conducted at 1 foreign study site to investigate the pharmacokinetics and safety of iptacopan administered as a single dose or as multiple oral doses (Part 1 and Part 2) and the effect of food on the pharmacokinetics and the safety of iptacopan administered as a single oral dose (Part 3) in non-Japanese healthy adults (target sample size, 100 subjects [2 subjects in each placebo group and 6 subjects in each iptacopan group for Part 1 and Part 2, 12 subjects in the iptacopan group for Part 3]).

Part 1: Single oral dose

Placebo or iptacopan 5, 10, 25, 50, 100, 200, or 400 mg was administered as a single oral dose under fasted conditions.

All 56 subjects who received the study drug were included in the safety set, and all 42 subjects who received iptacopan were included in the pharmacokinetic analysis population.

Table 19 shows the plasma pharmacokinetic parameters of iptacopan following a single oral dose of iptacopan under fasted conditions. The C_{max} and $AUC_{0\text{-}inf}$ of iptacopan increased in a less than dose-proportional manner.

Table 19. Plasma pharmacokinetic parameters of iptacopan following a single oral dose of iptacopan under fasted conditions in non-Japanese healthy adults

Iptacopan dose	N	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
5 mg	6	466 ± 70.3	1.0 (0.77, 2.5)	5,300 ± 1,280	14 ± 2.4
10 mg	6	714 ± 136	1.0 (0.75, 1.5)	8,440 ± 2,080	15 ± 2.2
25 mg	6	994 ± 211	1.1 (0.75, 2.5)	12,700 ± 2,910	16 ± 5.2
50 mg	6	1,370 ± 155	1.3 (0.73, 3.0)	17,500 ± 3,730	18 ± 5.1
100 mg	6	1,980 ± 459	1.0 (0.75, 2.0)	25,600 ± 8,050	14 ± 2.6
200 mg	6	3,230 ± 844	1.1 (0.50, 2.5)	36,500 ± 12,100	18 ± 10
400 mg	6	5,070 ± 1,310	1.3 (0.75, 2.5)	61,200 ± 15,800	17 ± 3.1

Mean ± standard deviation

a) Median (minimum, maximum)

Concerning safety, adverse events were observed in 14.3% (2 of 14) of subjects in the placebo group, 16.7% (1 of 6) of subjects in the iptacopan 25 mg group, 16.7% (1 of 6) of subjects in the 50 mg group, 33.3% (2 of 6) of subjects in the 100 mg group, and 33.3% (2 of 6) of subjects in the 200 mg group. None of the adverse events were assessed as adverse drug reactions. There were no adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation in any of the treatment groups.

Part 2: Multiple oral doses

Placebo or iptacopan 25, 50, 100, or 200 mg was administered as multiple oral doses BID under fasted conditions.

All 32 subjects who received the study drug were included in the safety set, and all 24 subjects who received iptacopan were included in the pharmacokinetic analysis population.

Table 20 shows the plasma pharmacokinetic parameters of iptacopan following multiple oral doses of iptacopan under fasted conditions. While the C_{max} and AUC_{tau} of iptacopan increased in a less than dose-proportional manner over the iptacopan dose range of 25 to 100 mg, increases in the C_{max} and AUC_{tau} of iptacopan were generally dose-proportional between the iptacopan doses of 100 mg and 200 mg. The applicant explained that the apparent pharmacokinetics of iptacopan becomes close to linear with the increase in target occupancy associated with dose increase due to the involvement of target-mediated drug disposition (*Drug Discov Today*. 2018;23:2023-2030) in the pharmacokinetics of iptacopan. The C_{max} and AUC_{tau} of iptacopan tended to be higher on Day 14 than on Day 1 over the dose range studied.

Table 20. Plasma pharmacokinetic parameters of iptacopan following multiple oral doses of iptacopan under fasted conditions in non-Japanese healthy adults

Iptacopan dose	Measurement time point	N	C_{max} (ng/mL)	t_{max} a) (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
25 mg	Day 1	6	894 ± 162	1.2 (0.98, 2.9)	6,140 ± 967	6.9 ± 1.1
	Day 14	6	1,100 ± 167	1.5 (0.98, 2.0)	9,150 ± 1,330	18 ± 5.5
50 mg	Day 1	6	1,400 ± 261	1.0 (0.73, 1.5)	8,060 ± 942	6.9 ± 1.6
	Day 14	6	1,530 ± 267	1.5 (1.0, 3.0)	11,500 ± 1,350	24 ± 9.8
100 mg	Day 1	6	1,510 ± 280	1.8 (1.5, 2.5)	8,970 ± 1,100	6.0 ± 1.3
	Day 14	6	2,250 ± 421	1.5 (0.75, 2.5)	14,400 ± 1,870	22 ± 3.0
200 mg	Day 1	6	3,750 ± 1,010	0.88 (0.50, 2.5)	19,000 ± 3,490	5.7 ± 2.3
	Day 14	6	4,120 ± 1,090	2.0 (0.75, 3.0)	25,600 ± 4,300	25 ± 11

Mean ± standard deviation

a) Median (minimum, maximum)

Concerning safety, adverse events were observed in 62.5% (5 of 8) of subjects in the placebo group, 16.7% (1 of 6) of subjects in the iptacopan 25 mg group, 83.3% (5 of 6) of subjects in the 50 mg group, 83.3% (5 of 6) of subjects in the 100 mg group, and 66.7% (4 of 6) of subjects in the 200 mg group, and adverse drug reactions were observed in 12.5% (1 of 8) of subjects in the placebo group and 33.3% (2 of 6) of subjects in the iptacopan 100 mg group. There were no adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation in any of the treatment groups.

Part 3: Food effect

Iptacopan 100 mg was administered as a single oral dose after intake of a high-fat diet and under fasted conditions. A 5-day washout period was required after each period.

All 12 subjects who received iptacopan were included in the safety set and the pharmacokinetic analysis population.

Table 21 shows the plasma pharmacokinetic parameters of iptacopan following a single oral dose of iptacopan under fed and fasted conditions. The ratio (fed/fasted) of the geometric means of C_{max} and $AUC_{0\text{-}inf}$ [90% confidence interval (CI)] was 0.97 [0.82, 1.14] and 0.89 [0.82, 0.96], respectively,[29] showing no clear effect of food.

Table 21. Plasma pharmacokinetic parameters of iptacopan following a single oral dose of iptacopan under fed and fasted conditions in non-Japanese healthy adults

Iptacopan dose	Administration condition	N	C_{max} (ng/mL)	t_{max} a) (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
100 mg	Fed	12	1,820 ± 670	1.3 (0.75, 4.0)	23,600 ± 5,430	16 ± 4.6
	Fasted	12	1,850 ± 501	1.8 (0.75, 4.0)	26,900 ± 7,720	18 ± 7.1

Mean ± standard deviation
a) Median (minimum, maximum)

Concerning safety, adverse events were observed in 25.0% (3 of 12) of subjects treated with iptacopan under fed conditions and 16.7% (2 of 12) of subjects treated with iptacopan under fasted conditions, and adverse drug reactions were observed in 8.3% (1 of 12) of subjects treated with iptacopan under fasted conditions. There were no adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.3 Foreign phase I study (mass balance study) (CTD reference data 5.3.3.1-3: Study A2101 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at 1 foreign study site to investigate mass balance, etc. following a single oral dose of [^{14}C]-labeled iptacopan in non-Japanese healthy adults (target sample size, 6 subjects).

Subjects received [^{14}C]-labeled iptacopan 100 mg as a single oral dose under fasted conditions.

All 6 subjects who received iptacopan were included in the pharmacokinetic analysis population.

Table 22 shows the plasma pharmacokinetic parameters of unchanged iptacopan. The percentage of $AUC_{0\text{-}48h}$ of unchanged iptacopan and metabolites M8 (acyl glucuronide-conjugated form) and M9 (*O*-deethylated and acyl glucuronide-conjugated form) to the total plasma radioactivity up to 48 hours post-dose was 83.0%, 8.05%, and 5.17%, respectively, showing that unchanged iptacopan was mainly detected in plasma.

Table 22. Plasma pharmacokinetic parameters of unchanged iptacopan following a single oral dose of [^{14}C]-labeled iptacopan in non-Japanese healthy adults

Iptacopan dose	N	C_{max} (ng/mL)	t_{max} a) (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
100 mg	6	2,150 ± 247	1.5 (0.77, 1.6)	23,300 ± 4,280	13 ± 2.7

Mean ± standard deviation
a) Median (minimum, maximum)

The percentage of radioactivity of [^{14}C]-labeled iptacopan excreted in urine and feces up to 216 hours post-dose was 24.8% and 71.5%, respectively, of the administered radioactivity. In urine up to 96 hours post-dose,

[29] Log-transformed plasma pharmacokinetic parameters were analyzed using a linear fixed-effect model.

unchanged iptacopan was mainly detected, accounting for 17.9% of the administered radioactivity. In feces up to 96 hours post-dose, M2 (*O*-deethylated form), unchanged iptacopan, and M7 (*C*-oxidized form) were mainly detected, accounting for 26.7%, 16.8%, and 8.32%, respectively, of the administered radioactivity.

6.2.4 Foreign phase II study (CTD reference data 5.3.5.2-2: Study X2201 [April 2018 to February 2022])

An open-label study was conducted at 4 foreign study sites to investigate pharmacokinetics and pharmacodynamics following multiple oral doses of iptacopan in patients with PNH who had an inadequate response to eculizumab (target sample size, 15 subjects [10 in Cohort 1 and 5 in Cohort 2]).

This study consisted of a primary evaluation period of 13 weeks and a treatment extension period of approximately 2 to 3 years. Subjects orally received iptacopan 200 mg BID (Cohort 1), or iptacopan 50 mg BID as the starting dose, with an option for dose increase to 200 mg BID which was allowed on or after Day 15 of treatment[30)] (Cohort 2). In both cohorts, eculizumab was continuously administered.[31)]

All 16 subjects who received iptacopan (10 in Cohort 1 and 6 in Cohort 2) were included in the safety set and the pharmacokinetic analysis population.

Table 23 shows plasma pharmacokinetic parameters of iptacopan following multiple oral doses of iptacopan. Exposure to iptacopan increased in a less than dose-proportional manner.

Table 23. Plasma pharmacokinetic parameters of iptacopan following multiple oral doses of iptacopan in non-Japanese patients with PNH

Iptacopan dose	Measurement time point	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{trough} (ng/mL)
50 mg (Cohort 2[a)])	Day 1	5	1,570 ± 366	8,620 ± 1,310	-
	Day 29	6	1,770 ± 469	14,800 ± 4,100	903 ± 195
200 mg (Cohort 1)	Day 1	10	3,400 ± 1,060	18,200 ± 6,700	-
	Day 29	10	3,500 ± 1,340	24,400 ± 8,720	1,190 ± 433

Mean ± standard deviation; -, not applicable.

a) The dose of iptacopan was not increased to 200 mg BID by Day 29 in any patients.

Concerning pharmacodynamics, Table 24 shows AP activity values and plasma Bb concentrations following multiple oral doses of iptacopan. The values and concentrations tended to decrease after the start of iptacopan treatment, compared to baseline.

30) Dose increase to 200 mg BID p.o. was allowed if the lactate dehydrogenase (LDH) level was outside the reference range or had not decreased by ≥60% from baseline after Day 15.

31) Change of the dosage regimen of eculizumab was not allowed from 3 months before to 6 months after the start of iptacopan treatment. From 6 months after the start of iptacopan treatment, dose reduction or discontinuation of eculizumab was allowed in subjects in a stable condition without active hemolysis.

Table 24. AP activity values and plasma Bb concentrations following multiple oral doses of iptacopan in non-Japanese patients with PNH

	AP activity (%)		Plasma Bb concentration (ng/mL)	
	Iptacopan 200 mg (Cohort 1)	Iptacopan 50 mg (Cohort 2[a)])	Iptacopan 200 mg (Cohort 1)	Iptacopan 50 mg (Cohort 2[a)])
Baseline	32.1 ± 25.2 (10)	20.7 ± 15.5 (6)	4,871 ± 4,752 (10)	3,154 ± 3,922 (6)
Day 8	7.6 ± 0.0 (10)	13.2 ± 0.7 (6)	1,138 ± 244.1 (10)	1,031 ± 256.9 (6)
Day 15	7.6 ± 0.0 (10)	14.1 ± 1.3 (6)	1,252 ± 319.7 (10)	1,077 ± 237.4 (6)
Day 22	7.6 ± 0.0 (10)	12.9 ± 0.9 (6)	1,212 ± 400.2 (10)	1,101 ± 231.2 (6)
Day 29	10.9 ± 7.4 (10)	12.9 ± 0.8 (6)	1,230 ± 275.0 (10)	1,110 ± 203.7 (6)
Day 57	7.6 ± 0.00 (8)	14.3 ± 7.5 (6)	1,304 ± 409.7 (9)	1,232 ± 201.2 (6)
Day 92	7.6 ± 0.00 (9)	11.1 ± 3.1 (5)	1,198 ± 208.5 (10)	1,530 ± 640.7 (5)

Mean ± standard deviation (No. of subjects)

a) The dose of iptacopan was not increased to 200 mg BID by Day 92 in any patients.

Concerning safety, adverse events were observed in all subjects in both Cohort 1 and Cohort 2, and adverse drug reactions were observed in 30.0% (3 of 10) of subjects in Cohort 1 and 50.0% (3 of 6) of subjects in Cohort 2. Deaths were observed in 3 subjects only in Cohort 1 (septic shock/lymphoproliferative disorder,[32)] general physical health deterioration,[33)] and squamous cell carcinoma of the oral cavity[34)] in 1 subject each). Lymphoproliferative disorder was assessed as an adverse drug reaction. Serious adverse events were observed in 40.0% (4 of 10) of subjects (basal cell carcinoma, lymphoproliferative disorder, squamous cell carcinoma of the oral cavity, squamous cell carcinoma of the tongue, haemorrhage intracranial, and penetrating aortic ulcer in 1 subject each; some subjects developed ≥1 event) in Cohort 1, and 33.3% (2 of 6) of subjects (urinary tract infection, bladder transitional cell carcinoma, and urinary bladder polyp in 1 subject each; 1 subject developed ≥1 event) in Cohort 2. Only lymphoproliferative disorder (fatal case) was assessed as an adverse drug reaction. Adverse events leading to treatment discontinuation were reported in 2 subjects only in Cohort 1 (lymphoproliferative disorder and squamous cell carcinoma of the oral cavity in 1 subject each). Lymphoproliferative disorder was assessed as an adverse drug reaction.

6.2.5 Foreign Phase II study (CTD reference data 5.3.5.2-3: Study X2204 [April 2019 to February 2022])

A randomized, open-label study was conducted at 5 foreign study sites to investigate pharmacokinetics and pharmacodynamics following multiple oral doses of iptacopan in complement inhibitor (complement C5 inhibitor, etc.) treatment-naïve patients with PNH (target sample size, 10 subjects [5 subjects in the iptacopan 25/100 mg group and 5 subjects in the 50/200 mg group]).

Subjects orally received iptacopan 25 or 50 mg BID in the low dose period (4 weeks), and iptacopan 100 or 200 mg BID in the high dose period (8 weeks) and the treatment extension period (2 years).

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32) A 45-year-old white female. The subject developed extensive lymphadenopathy and multiple extranodal masses approximately 11 months after the start of iptacopan treatment. A diagnosis of B-cell lymphoproliferative disease was made, and iptacopan was discontinued on Day 356. After receiving rescue chemotherapy, the subject developed febrile neutropenia, cholangitis, and septic shock on Day 698, and died on Day 699.

33) A 78-year-old white male. The subject developed basal cell carcinoma on Day 628 and penetrating aortic ulcer on Day 765, and underwent surgery. The subject developed Escherichia coli bacteremia on Day 792, general physical health deterioration on Day 812, and Escherichia coli bacteremia again on Day 826, was referred to the palliative care department on Day 841, and died of general physical health deterioration on Day 867. The last dose of iptacopan was administered on Day 779.

34) A 52-year-old white male. The subject developed an ulcer at an existing tongue lesion on Day 44. The ulcer was histologically confirmed as squamous cell carcinoma of the tongue (severe) on Day 100. The subject underwent hemiglossectomy and lateral cervical lymph node dissection, and recovered (with sequelae) on Day 116. The subject developed squamous cell carcinoma of the oral cavity on Day 350, and underwent local tumor surgery on Day 353. On Day 402, the subject was hospitalized again due to severely painful swallowing. On Day 427, new oral cavity/cervical lesions were confirmed on CT scan. Recurrence of known squamous cell carcinoma was confirmed on histological evaluation on Day 441, and the treatment with iptacopan was suspended on Day 452. On Day 504, the subject died of squamous cell carcinoma of the oral cavity.

All 13 subjects who received iptacopan (7 subjects in the iptacopan 25/100 mg group and 6 subjects in the 50/200 mg group) were included in the safety set and the pharmacokinetic analysis population.

Table 25 shows the plasma pharmacokinetic parameters of iptacopan at steady state (Day 29 for 25 and 50 mg, and Day 57 for 100 and 200 mg) following multiple oral doses of iptacopan. Exposure to iptacopan increased in a less than dose-proportional manner.

Table 25. Plasma pharmacokinetic parameters of iptacopan at steady state following multiple oral doses of iptacopan in non-Japanese patients with PNH

Iptacopan dose	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{trough} (ng/mL)
25 mg	6	1,240 ± 372	9,630 ± 3,870	520 ± 299
50 mg	5	1,800 ± 368	15,200 ± 2,390	809 ± 239
100 mg	6	2,640 ± 590	19,800 ± 4,900	931 ± 460
200 mg	5	4,520 ± 1,520	33,300 ± 8,830	1,510 ± 416

Mean ± standard deviation

Concerning pharmacodynamics, Table 26 shows AP activity values and plasma Bb concentrations following multiple oral doses of iptacopan. The values and concentrations tended to decrease after the start of iptacopan treatment, compared to baseline.

Table 26. AP activity values and plasma Bb concentrations[a)] following multiple oral doses of iptacopan in non-Japanese patients with PNH

		AP activity (%)		Plasma Bb concentration (ng/mL)	
		Iptacopan 25 mg/100 mg	Iptacopan 50 mg/200 mg	Iptacopan 25 mg/100 mg	Iptacopan 50 mg/200 mg
Baseline		57.4 ± 12.9 (7)	68.7 ± 14.2 (6)	4,154 ± 2,237 (7)	4,920 ± 5,174 (6)
Low dose period	Week 2	44.9 ± 14.9 (7)	34.1 ± 14.8 (5)	1,421 ± 666.9 (7)	1,081 ± 294.9 (5)
	Week 4	41.5 ± 16.2 (7)	40.4 ± 15.0 (5)	2,013 ± 1,744 (7)	1,088 ± 228.5 (5)
High dose period	Week 8	33.8 ± 23.6 (7)	15.0 ± 4.9 (5)	2,110 ± 1,992 (7)	1,582 ± 1,085 (5)
	Week 12	16.0 ± 10.4 (6)	12.6 ± 8.0 (5)	1,242 ± 491.8 (6)	1,273 ± 328.9 (5)

Mean ± standard deviation (No. of subjects)

a) AP activity values or plasma Bb concentrations before the start of the study treatment

Concerning safety, adverse events were observed in 57.1% (4 of 7) of subjects in the iptacopan 25/100 mg group and 83.3% (5 of 6) of subjects in the 50/200 mg group, and adverse drug reactions were observed in 28.6% (2 of 7) of subjects in the iptacopan 25/100 mg group and 50.0% (3 of 6) of subjects in the 50/200 mg group. There were no adverse events resulting in death or serious adverse events. An adverse event leading to treatment discontinuation was reported in 1 subject (headache) only in the iptacopan 50/200 mg group. Headache occurred on Day 2 of treatment with iptacopan 50 mg BID and was assessed as an adverse drug reaction. The event resolved after discontinuation of iptacopan and medical treatment.

6.2.6 Global phase III study (CTD 5.3.5.1-1 and 5.3.5.1-5: Study C12302 [January 2021 to March 2023])

The study investigated pharmacokinetics following multiple oral doses of iptacopan in patients with PNH who had an inadequate response to complement C5 inhibitors (ravulizumab or eculizumab).

This study consisted of a primary evaluation period of 24 weeks and a treatment extension period of 24 weeks. Subjects received iptacopan 200 mg BID as multiple oral doses or a complement C5 inhibitor (ravulizumab or eculizumab) intravenously in the primary evaluation period, and then received iptacopan 200 mg BID as multiple oral doses in the treatment extension period.

For a study outline and the efficacy and safety results, see Section 7.1.

All 96 subjects who received iptacopan (62 in the iptacopan group and 34 in the complement C5 inhibitor group) were included in the pharmacokinetic analysis population.

For pharmacokinetics, Table 27 shows changes in trough plasma iptacopan concentration during the study period.

Table 27. Trough plasma iptacopan concentrations (ng/mL) in patients with PNH

Treatment group	Day 7 of iptacopan treatment	Day 28 of iptacopan treatment	Day 168 of iptacopan treatment	Day 196 of iptacopan treatment	Day 336 of iptacopan treatment
Iptacopan	1,590 ± 949 (58)	1,470 ± 510 (59)	1,740 ± 802 (56)	1,730 ± 757 (58)	1,690 ± 714 (53)
Complement C5 inhibitor[a)]	1,520 ± 831 (28)	1,780 ± 892 (28)	1,800 ± 919 (25)	-	-

Mean ± standard deviation (No. of subjects); -, not applicable.
a) Patients assigned to the anti-C5 group in the primary evaluation period and treated with iptacopan in the treatment extension period

6.2.7 Global phase III study (CTD 5.3.5.2-1 and 5.3.5.2-5: Study C12301 [July 2021 to April 2023])

The study investigated pharmacokinetics following multiple oral doses of iptacopan in complement inhibitor (complement C5 inhibitor, etc.) treatment-naïve patients with PNH.

Subjects received iptacopan 200 mg BID as multiple oral doses.

For a study outline and the efficacy and safety results, see Section 7.2.

All 40 subjects who received iptacopan were included in the pharmacokinetic analysis population.

Concerning pharmacokinetics, Table 28 shows changes in the trough plasma iptacopan concentration.

Table 28. Trough plasma iptacopan concentrations (ng/mL) in patients with PNH

Day 7	Day 28	Day 84	Day 168
2,310 ± 1,460 (39)	2,060 ± 856 (37)	1,960 ± 826 (35)	1,870 ± 738 (39)

Mean ± standard deviation (No. of subjects)

6.2.8 Foreign phase I study (effect of hepatic impairment) (CTD 5.3.3.3-1: Study A2105 [November 2021 to June 2022])

An open-label study was conducted at 1 foreign study site to investigate the effect of hepatic impairment on the pharmacokinetics of iptacopan in non-Japanese subjects with normal hepatic function and non-Japanese subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C)

hepatic impairment (target sample size, 44 subjects; 6 to 18 subjects in the normal hepatic function group, and ≥6 subjects in each hepatic impairment group).

Subjects received iptacopan 200 mg as a single oral dose under fasted conditions.

All 38 subjects who were enrolled in the study and received the study drug (16 with normal hepatic function, 8 each with mild and moderate hepatic impairment, and 6 with severe hepatic impairment) were included in the safety set and the pharmacokinetic analysis population.

Table 29 shows the geometric mean ratios (subjects with hepatic impairment/subjects with normal hepatic function) of plasma pharmacokinetic parameters of iptacopan.

Table 29. Geometric mean ratios (subjects with hepatic impairment/subjects with normal hepatic function) of plasma pharmacokinetic parameters of iptacopan

Analyte	Hepatic impairment	C_{max}	$AUC_{0\text{-}inf}$
Iptacopan concentration	Mild	1.04 [0.893, 1.22]	1.03 [0.880, 1.22]
	Moderate	0.952 [0.816, 1.11]	1.01 [0.861, 1.19]
	Severe	0.919 [0.765, 1.10]	1.03 [0.853, 1.25]
Unbound iptacopan concentration[a)]	Mild	1.38 [1.11, 1.71]	1.48 [1.27, 1.73]
	Moderate	1.67 [1.35, 2.08]	1.58 [1.35, 1.85]
	Severe	2.11 [1.63, 2.73]	3.71 [3.08, 4.47]

Geometric mean ratio [90% CI]
a) Concentration in plasma ultrafiltrate

Concerning safety, 2 adverse events were observed only in 12.5% (1 of 8) of subjects with moderate hepatic impairment. One of these events was assessed as a serious adverse event (basal ganglia haemorrhage), but neither was assessed as an adverse drug reaction. There were no adverse events resulting in death or leading to treatment discontinuation.

6.2.9 Foreign phase I study (drug interactions with clopidogrel, cyclosporine, digoxin, and rosuvastatin) (CTD reference data 5.3.3.4-1: Study A2104 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at 1 foreign study site to investigate the effect of clopidogrel (CYP2C8 inhibitor) and cyclosporine (inhibitor of OATP1B1 and OATP1B3) on the pharmacokinetics of iptacopan, and the effect of iptacopan on the pharmacokinetics of digoxin (a substrate of P-gp) and rosuvastatin (a substrate of OATP1B1 and OATP1B3) in non-Japanese healthy adults (target sample size, 18 subjects in each cohort).

Table 30 shows the geometric mean ratios of the C_{max} and $AUC_{0\text{-}inf}$ of iptacopan when coadministered with clopidogrel or cyclosporine to its C_{max} and $AUC_{0\text{-}inf}$ when iptacopan was administered alone.

Table 30. Geometric mean ratios (coadministration with clopidogrel or cyclosporine/without these drugs) of plasma pharmacokinetic parameters of iptacopan

Iptacopan	Concomitant drug	N	C_{max}	$AUC_{0\text{-}inf}$
100 mg, single dose	Clopidogrel 300 mg/75 mg QD[a)]	18	1.05 [0.97, 1.14]	1.36 [1.28, 1.45][c)]
	Cyclosporine 175 mg BID[b)]	15	1.41 [1.35, 1.47]	1.50 [1.42, 1.59][d)]

Geometric mean ratio [90% CI]

a) Subjects received iptacopan 100 mg as a single oral dose under fasted conditions on Day 1, clopidogrel 300 mg (Day 6) and clopidogrel 75 mg QD (Days 7 to 10) orally under fasted conditions, and iptacopan 100 mg in combination with clopidogrel 75 mg orally on Day 7 under fasted conditions.
b) Subjects received iptacopan 100 mg as a single oral dose under fasted conditions on Day 1, iptacopan 100 mg as a single oral dose on Day 6, and cyclosporine 175 mg BID as multiple oral doses under fasted conditions on Days 6 to 9.
c) 17 subjects
d) 13 subjects

Table 31 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of digoxin and rosuvastatin when coadministered with iptacopan to their C_{max} and $AUC_{0\text{-}inf}$ when these drugs were administered without iptacopan.

Table 31. Geometric mean ratios (coadministration with iptacopan/without iptacopan) of plasma pharmacokinetic parameters of digoxin and rosuvastatin

Iptacopan	Concomitant drug	N	C_{max}	$AUC_{0\text{-}inf}$
200 mg BID	Digoxin 0.25 mg, single dose[a)]	17	1.08 [0.94, 1.24]	1.02 [0.93, 1.12][b)]
	Rosuvastatin 10 mg, single dose[a)]	17	1.00 [0.87, 1.15]	1.01 [0.91, 1.12]

Geometric mean ratio [90% CI]

a) Subjects received digoxin 0.25 mg and rosuvastatin 10 mg as a single oral dose under fasted conditions on Day 1, iptacopan 200 mg BID as multiple oral doses under fed conditions on Days 12 to 26, and digoxin 0.25 mg and rosuvastatin 10 mg orally concomitantly with iptacopan under fasted conditions on Day 17.
b) 16 subjects

6.2.10 Drug concentration-response analysis of QT/QTc interval (CTD 5.3.4.1-1)

Drug concentration-response analysis was performed using data obtained in phase I studies in non-Japanese healthy adults (Studies A2107[35)] and X2101). The results did not show a clear correlation between the plasma iptacopan concentration and the change from baseline in QTcF (ΔQTcF) over the iptacopan dose range of 400 to 1,200 mg. The upper limit of the 90% CI for placebo-corrected estimated ΔQTcF at the geometric mean C_{max} (16,600 ng/mL) of iptacopan orally administered at 1,200 mg, a dose exceeding the maximum clinical dose (200 mg), was 3.22 ms, which fell below 10 ms.

In view of the above, the applicant explained that the risk of QT/QTc prolongation is considered to be low when iptacopan is administered at the proposed dosage and administration.

6.2.11 Population pharmacokinetic analysis (CTD reference data 5.3.3.5-1)

Population pharmacokinetic analysis was performed (software: MONOLIX Version 2019 R2) using the pharmacokinetic data of iptacopan (a total of 234 subjects, at 2,439 measurement time points) obtained in clinical studies in patients with PNH (Studies X2201, X2204, C12302, and C12301), Study X2202 in patients with C3G,[36)] and Study X2203 in patients with immunoglobulin A (IgA) nephropathy.[37)]

35) Placebo-controlled, randomized, single-blind study in non-Japanese healthy adults. Placebo or iptacopan 400, 800, or 1,200 mg was administered as a single oral dose under fasted conditions.
36) In this phase II study in patients with C3G, iptacopan was administered as multiple oral doses of 10, 25, 100, or 200 mg BID.
37) In this phase II study in patients with IgA nephropathy, iptacopan was administered as multiple oral doses of 10, 50, 100, or 200 mg BID.

The pharmacokinetics of oral iptacopan in patients with PNH was described by a 1-compartment model with first-order absorption and elimination plus lag time. As a result of investigation of the covariates,[38] body weight, ethnicity (Chinese), and estimated glomerular filtration rate (eGFR) at baseline were selected for the CL/F of iptacopan. Population pharmacokinetic parameters estimated from the final model[39] were as follows: 138 L/day for CL/F, 1.59 L for Vc/F, 1.53 day^{-1} for ka.

6.R Outline of the review conducted by PMDA

On the basis of the data submitted and the results of the investigations in Sections 6.R.1 to 6.R.5, PMDA considers that the pharmacokinetics of iptacopan was evaluated in an appropriate manner, except for administration in patients with severe renal impairment and patients with hepatic impairment, coadministration with drugs that inhibit CYP2C8 or OATP1B1 and OATP1B3, and coadministration with substrates of CYP3A4 and CYP2C8. Regarding administration of iptacopan in patients with severe renal impairment and patients with hepatic impairment, coadministration of iptacopan with drugs that inhibit CYP2C8 or OATP1B1 and OATP1B3, and coadministration of iptacopan with substrates of CYP3A4 and CYP2C8, PMDA considers it appropriate to include precautionary statements in the package insert.

6.R.1 Differences in the pharmacokinetics of iptacopan in the Japanese and non-Japanese populations

The applicant's explanation about the pharmacokinetics of iptacopan in the Japanese and non-Japanese populations:

Concerning pharmacokinetic parameters of iptacopan administered as a single oral dose of 25, 100, and 400 mg in healthy adults, C_{max} and $AUC_{0\text{-}inf}$ in Japanese subjects (Study X1102) were approximately 1.6- and 1.2-fold, respectively, those in non-Japanese subjects (Study X2101) [see Sections 6.2.1 and 6.2.2]. Table 32 shows changes in the trough plasma iptacopan concentration in the global phase III study (Study C12302). Exposure to iptacopan tended to be slightly higher in Japanese subjects than in non-Japanese subjects. A possible factor for this difference in exposure between the Japanese and non-Japanese populations is the differences in body weight and baseline eGFR between the populations, because body weight and baseline eGFR have been shown to be statistically significant covariates for the CL/F of iptacopan in the population pharmacokinetic analysis [see Section 6.2.11] and the difference in plasma iptacopan concentration between Japanese and non-Japanese subjects corrected for these covariates became smaller.

Table 32. Trough plasma iptacopan concentrations (ng/mL) in Japanese and non-Japanese patients with PNH

		Day 7	Day 28	Day 168	Day 196	Day 336
Japanese	Iptacopan	1,890 ± 970 (6)	1,570 ± 654 (6)	2,350 ± 1,170 (6)	2,260 ± 1,170 (6)	2,100 ± 1,090 (5)
	Complement C5 inhibitor[a)]	1,400 ± 412 (3)	1,490 ± 165 (3)	1,770 ± 214 (3)	-	-
Non-Japanese	Iptacopan	1,550 ± 950 (52)	1,460 ± 498 (53)	1,670 ± 729 (50)	1,670 ± 686 (52)	1,640 ± 666 (48)
	Complement C5 inhibitor[a)]	1,540 ± 872 (25)	1,820 ± 939 (25)	1,800 ± 980 (22)	-	-

Mean ± standard deviation (No. of subjects); -, not applicable.

a) Patients assigned to the complement C5 inhibitor group in the primary evaluation period and treated with iptacopan in the treatment extension period

[38] The following covariates were investigated: body weight, age, sex, ethnicity (Japanese, Chinese, other Asian, and non-Asian), baseline eGFR, disease (PNH, C3G, and IgA nephropathy), and type of PNH patient (complement C5 inhibitor-treated PNH, complement inhibitor treatment-naïve PNH, and non-PNH).

[39] A non-Asian subject weighing 70 kg and with baseline eGFR of 66 mL/min/1.73 m^2 was considered as the reference subject for the covariate effects.

PMDA's view:

Concerning the pharmacokinetics of iptacopan in the Japanese and non-Japanese populations, exposure tended to be slightly higher in Japanese subjects than in non-Japanese subjects both in studies in healthy adults and in patients with PNH. However, the applicant's explanation that the difference in exposure between the Japanese and non-Japanese populations is attributable to differences in body weight and baseline eGFR between the populations, is reasonable, and the efficacy and safety in the Japanese population in Study C12302 did not tend to differ from those in the entire population [see Sections 7.R.1.1 and 7.R.2.1]. The pharmacokinetics of iptacopan therefore show no clear clinically relevant differences between the Japanese and non-Japanese populations.

6.R.2 Effect of renal impairment

The applicant's explanation about the effect of renal impairment on the pharmacokinetics of iptacopan:

No clinical pharmacology studies were conducted to evaluate the effect of renal impairment on the pharmacokinetics of iptacopan. In the population pharmacokinetic analysis [see Section 6.2.11], the steady-state pharmacokinetic parameters of iptacopan following multiple oral doses of 200 BID were estimated in PNH patients with normal renal function and those with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2), moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), and severe renal impairment (eGFR <30 mL/min/1.73 m^2) enrolled in clinical studies. Table 33 shows the results.

Table 33. Pharmacokinetic parameters (estimates) following multiple oral doses of iptacopan in patients with PNH by severity of renal impairment

Severity of renal impairment	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{trough} (ng/mL)
Normal	98	3,940 ± 950	32,100 ± 8,080	1,640 ± 530
Mild impairment	45	4,480 ± 1,510	37,500 ± 13,800	1,970 ± 790
Moderate impairment	17	5,170 ± 1,450	43,800 ± 12,100	2,310 ± 680
Severe impairment[a)]	1	5,610	47,000	2,440

Mean ± standard deviation

a) Individual estimate of 1 subject

Exposure to iptacopan tended to increase with decreasing renal function. However, taking variability in pharmacokinetics into account, renal function is unlikely to have clinically significant effects on the pharmacokinetics of iptacopan. On the other hand, there are limitations to the evaluation of the effect of severe renal impairment on the pharmacokinetics of iptacopan because the subjects enrolled in clinical studies included only 1 patient with PNH and severe renal impairment.

Safety was evaluated based on the pooled data of patients who received iptacopan as multiple oral doses of 200 mg BID from the data up to the final analysis of Studies C12302, C12301, X2201, and X2204, and the data from Study C12001B as of the data cut-off on [redacted], 20[redacted]. Table 34 shows the summary of adverse events by severity of renal impairment. The incidence of adverse events did not tend to clearly increase with decreasing renal function.

Table 34. Summary of adverse events by severity of renal impairment following an oral dose of iptacopan in patients with PNH

	Normal[a)] (N = 96)	Mild impairment[b)] (N = 46)	Moderate impairment[c)] (N = 19)	Severe impairment[d)] (N = 1)
All adverse events	91.7 (88)	97.8 (45)	100.0 (19)	100.0 (1)
All adverse drug reactions	31.3 (30)	28.3 (13)	26.3 (5)	0
Deaths	2.1 (2)	0	5.3 (1)	0
Serious adverse events	15.6 (15)	26.1 (12)	42.1 (8)	100.0 (1)
Serious adverse drug reactions	1.0 (1)	2.2 (1)	10.5 (2)	0
Adverse events leading to treatment discontinuation	1.0 (1)	0	5.3 (1)	0

Incidence % (n)

a) Baseline eGFR ≥90 mL/min/1.73 m^2

b) Baseline eGFR ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2

c) Baseline eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2

d) Baseline eGFR <30 mL/min/1.73 m^2

In view of the above, although exposure to iptacopan tended to increase due to renal impairment, renal function is not considered to have clinically significant effects on its safety. The applicant therefore considers it unnecessary to include precautionary statements regarding iptacopan administration in patients with renal impairment in the package insert.

PMDA's view:

Concerning PNH patients with mild or moderate renal impairment, although exposure to iptacopan may increase compared with those with normal renal function, there were no trends toward differences in the incidence of adverse events in clinical studies that may cause safety concerns. Therefore, the applicant's explanation that increased exposure to iptacopan in patients with mild or moderate renal impairment is unlikely to cause clinical concerns, is reasonable.

Concerning PNH patients with severe renal impairment, the population pharmacokinetic analysis showed that exposure to iptacopan may increase, and there are limitations to the evaluation of its pharmacokinetics and safety because the clinical studies included only 1 patient with PNH and severe renal impairment. Precautionary statements should therefore be included in the package insert, etc. to ensure that the patient's condition is carefully monitored when iptacopan is administered to patients with severe renal impairment.

6.R.3 Effect of hepatic impairment

The applicant's explanation about the effect of hepatic impairment on the pharmacokinetics of iptacopan:

In Study A2105, the C_{max} and $AUC_{0\text{-}inf}$ of unbound iptacopan, compared to those in subjects with normal hepatic function, were 1.38- and 1.48-fold, respectively, in subjects with mild hepatic impairment, 1.67- and 1.58-fold, respectively, in subjects with moderate hepatic impairment, and 2.11- and 3.71-fold, respectively, in subjects with severe hepatic impairment [see Section 6.2.8].

In clinical studies in patients with PNH, patients with hepatic impairment were not enrolled.[40)] The C_{max} and $AUC_{0\text{-}inf}$ of iptacopan administered as a single dose of up to 1,200 mg in healthy subjects in Study A2107 were 17,200 ng/mL and 168,000 ng·h/mL, respectively. These values were 4.2- and 3.3-fold, respectively, the

[40)] In all enrolled subjects, ALT or ALP was CTCAE Grade ≤1 at baseline.

steady-state C_{max} and $AUC_{0\text{-}24h}$[41)] following administration of iptacopan 200 mg BID (Study X2101), but iptacopan administered as a single oral dose in healthy adults was well tolerated at high doses of up to 1,200 mg.

In view of the above, although iptacopan has not been administered to patients with PNH and hepatic impairment, there are no safety concerns about iptacopan administration in patients with mild, moderate, or severe hepatic impairment. The applicant therefore considers it unnecessary to include precautionary statements regarding iptacopan administration in patients with hepatic impairment in the package insert.

PMDA's view:
In the phase I study that investigated the effect of hepatic impairment on the pharmacokinetics of iptacopan (Study A2105), although the total concentration of iptacopan was similar in subjects with normal hepatic function and those with mild, moderate, and severe hepatic impairment, the unbound iptacopan concentration tended to be higher in subjects with hepatic impairment. Since patients with PNH and hepatic impairment were not enrolled in global phase III studies (Studies C12302 and C12301), the pharmacokinetics and safety of iptacopan administered as multiple oral doses at the clinical dose (200 mg BID) in patients with PNH and hepatic impairment are unknown. There are also limitations to the explanation of the safety of iptacopan administered as multiple oral doses at the clinical dose (200 mg BID) in patients with PNH and hepatic impairment based only on the results of Study A2107. The unbound concentration of iptacopan may therefore increase when administered to patients with PNH and hepatic impairment and cause safety concerns. However, the appropriateness of restricting iptacopan treatment in all patients with hepatic impairment only because the unbound iptacopan concentration may increase is unknown. It is therefore appropriate to provide precautions to ensure that the patient's condition is carefully monitored when iptacopan is administered to patients with hepatic impairment.

6.R.4 Coadministration with CYP3A4 or CYP2C8 substrates

The applicant's explanation about coadministration of iptacopan with CYP3A4 or CYP2C8 substrates, as iptacopan was considered to induce CYP3A4 and inhibit CYP2C8 [see Sections 6.1.2.6 and 6.1.2.7]:
No clinical drug interaction studies on the coadministration of iptacopan with CYP3A4 or CYP2C8 substrates were conducted. The effect of iptacopan on the pharmacokinetics of midazolam (a substrate of CYP3A) and repaglinide (a substrate of CYP2C8) was investigated using physiologically based pharmacokinetic (PBPK) model analysis.[42)] The $f_{u,p}$ of the PBPK model was set as 0.19 because the $f_{u,p}$ at the C_{max} (4,120 ng/mL) of iptacopan administered at the clinical dose (200 mg BID) was estimated to be 0.19.[43)]

Concerning the effect of iptacopan on the pharmacokinetics of midazolam (a substrate of CYP3A), the geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of midazolam when coadministered with iptacopan 200 mg BID to its C_{max} and $AUC_{0\text{-}inf}$ when midazolam was administered without iptacopan were estimated to be 0.92 and 0.91, respectively. Of note, the plasma iptacopan concentrations estimated using the PBPK model were lower (0.26-

41) $AUC_{0\text{-}24h}$ (51,200 ng·h/mL) was calculated as daily exposure by doubling AUC_{tau} (25,600 ng·h/mL).
42) Simcyp version 21 was used for the PBPK model analysis.
43) Estimated from the E_{max} model using the plasma iptacopan concentration data of Study A2105 (CTD 4.2.2.3-4).

fold for C_{max} and 0.15-fold for $AUC_{0\text{-}12h}$) than the plasma iptacopan concentrations in clinical studies. In the sensitivity analysis with the PBPK model, the geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of midazolam when coadministered with iptacopan 200 mg BID to its C_{max} and $AUC_{0\text{-}inf}$ when midazolam was administered without iptacopan, when the $IndC_{50}$ (4.31 μmol/L) for CYP3A4 was decreased to 1/15 (0.287 μmol/L), were 0.62 and 0.58, respectively.

Concerning the effect of iptacopan on the pharmacokinetics of repaglinide (a substrate of CYP2C8), the geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of repaglinide when coadministered with iptacopan 200 mg BID to its C_{max} and $AUC_{0\text{-}inf}$ when repaglinide was administered without iptacopan were estimated to be 1.03 and 1.05, respectively. Of note, the estimated plasma iptacopan concentrations were lower (0.26-fold for C_{max} and 0.15-fold for $AUC_{0\text{-}12h}$) than the plasma iptacopan concentrations in clinical studies. In the sensitivity analysis with the PBPK model, the geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of repaglinide when coadministered with iptacopan 200 mg BID to its C_{max} and $AUC_{0\text{-}inf}$ when repaglinide was administered without iptacopan when the $K_{I,u}$ (171 μmol/L) for CYP2C8 was decreased to 1/15 (11.4 μmol/L), were 1.18 and 1.25, respectively.

In view of the above, pharmacokinetic drug interactions of iptacopan with CYP3A4 or CYP2C8 were considered unlikely to cause any concerns in the clinical use of iptacopan.

PMDA's view:
In view of the results of *in vitro* studies [see Sections 6.1.2.6 and 6.1.2.7] and the drug interaction guideline, iptacopan at the clinical dose may show drug interactions mediated by CYP3A4 and CYP2C8. In addition, since the plasma iptacopan concentrations estimated using the PBPK model were lower than the plasma iptacopan concentrations in clinical studies, there are limitations to the prediction of the drug interactions of iptacopan based on the PBPK model. Accordingly, there still is concern about decreased exposure to CYP3A substrates and increased exposure to CYP2C8 substrates in the presence of coadministered iptacopan. It is therefore appropriate to include precautionary statements regarding possible changes in exposure to these substrates in the package insert, etc. Based on this and since information on coadministration of iptacopan with CYP3A4 or CYP2C8 substrates is important for the proper use of iptacopan, such information, including published literature, etc., should continuously be collected, and any new findings identified should immediately be provided to healthcare professionals.

6.R.5 Coadministration with drugs that inhibit CYP2C8 and drugs that inhibit OATP1B1 and OATP1B3

The applicant's explanation about coadministration of iptacopan with inhibitors of CYP2C8, OATP1B1, and OATP1B3, as iptacopan was considered to be mainly metabolized by CYP2C8 [see Section 6.1.2.4] and serve as a substrate of OATP1B1 and OATP1B3 [see Section 6.1.2.8]:
The investigation of the effect of clopidogrel (inhibitor of CYP2C8) on the pharmacokinetics of iptacopan in non-Japanese healthy adults showed that the C_{max} and $AUC_{0\text{-}inf}$ of iptacopan increased 1.05- and 1.36-fold, respectively, in the presence of coadministered clopidogrel. The C_{max} and $AUC_{0\text{-}inf}$ of iptacopan increased 1.41- and 1.50-fold, respectively, in the presence of coadministered cyclosporine (inhibitor of OATP1B1 and

OATP1B3) [see Section 6.2.9]. The C_{max} and $AUC_{0\text{-}inf}$ of iptacopan administered as a single oral dose of up to 1,200 mg in healthy adults (Study A2107) were 4.2- and 3.3-fold, respectively, the steady-state C_{max} and $AUC_{0\text{-}24h}$[41)] following administration of iptacopan 200 mg BID (Study X2101). Since iptacopan administered as a single oral dose of up to 1,200 mg was well tolerated, the safety margin for exposure to iptacopan is considered to be ≥3-fold that following multiple oral doses of 200 mg BID. The increase in exposure expected when iptacopan is coadministered with inhibitors of CYP2C8, OATP1B1, and OATP1B3 is therefore not considered to cause clinical concerns.

PMDA's view:

The results of the pharmacokinetic drug interaction study of iptacopan coadministered with clopidogrel or cyclosporine showed that coadministration of iptacopan with drugs that inhibit CYP2C8, OATP1B1, and OATP1B3 may increase the exposure to iptacopan. There are also limitations to the explanation of the safety at the exposure following multiple doses of iptacopan at the clinical dose (200 mg BID) coadministered with clopidogrel or cyclosporine based only on the results of Study A2107 in which iptacopan was administered as a single oral dose in healthy adults. It is therefore appropriate to include precautionary statements regarding drugs that inhibit CYP2C8, OATP1B1, and OATP1B3 by listing them under "Precautions for Concomitant Use" in the package insert of iptacopan.

7. Clinical Efficacy and Safety, and Outline of the Review Conducted by PMDA

The applicant submitted results from 2 global phase III studies as the pivotal data for efficacy and safety (Table 35).

Table 35. Outline of the main clinical studies on efficacy and safety

Phase	Study identifier	Population	Study design	Group, No. of subjects, dose, administration period	Primary efficacy endpoint
Global phase III	C12302	Patients with PNH who have an inadequate response to complement C5 inhibitors	Randomized Open-label Active-controlled Parallel-group	• Primary evaluation period (24 weeks) Iptacopan (200 mg BID, p.o.) group: 62 subjects (including 6 Japanese subjects) Complement C5 inhibitor group: 35 subjects (including 3 Japanese subjects) • Treatment extension period (24 weeks): 95 subjects (including 9 Japanese subjects) Subjects in the iptacopan group continued to receive iptacopan. Subjects in the complement C5 inhibitor group were switched to iptacopan (200 mg BID, p.o.).	• Increase in Hb level by ≥2 g/dL from baseline without blood transfusion • Hb level ≥12 g/dL without blood transfusion
Global phase III	C12301	Complement inhibitor treatment-naïve patients with PNH	Open-label Uncontrolled	• Primary evaluation period (24 weeks), treatment extension period (24 weeks) Iptacopan (200 mg BID, p.o.): 40 subjects (no Japanese subject)	Increase in Hb level by ≥2 g/dL from baseline without blood transfusion

7.1 Global phase III study (CTD 5.3.5.1-1 and 5.3.5.1-5: Study C12302 [January 2021 to March 2023])

A multicenter, randomized, open-label, active-controlled, parallel-group study was conducted at 39 study sites in 12 countries, including Japan, to investigate the efficacy and safety of iptacopan in patients with PNH who had an inadequate response to complement C5 inhibitors (ravulizumab or eculizumab) (Table 36) (target

sample size, 91 subjects[44]; 56 subjects in the iptacopan group and 35 subjects in the complement C5 inhibitor group).

Table 36. Main inclusion criteria

Main inclusion criteria • Patients aged ≥18 years. • Patients diagnosed with PNH confirmed by high-sensitivity flow cytometry. • Patients who have been on a stable regimen with a complement C5 inhibitor (ravulizumab or eculizumab) for ≥6 months before randomization. • Patients with Hb <10.0 g/dL. • Patients who received meningococcal vaccination before the start of the study treatment. • Patients who had previously been vaccinated against *Pneumococcus* and *Haemophilus influenzae*, if available in the study country or region, before the start of the study treatment. Main exclusion criteria • Patients who received eculizumab at intervals of ≤11 days or ravulizumab at intervals of <8 weeks. • Patients with confirmed or suspected hereditary complement deficiency. • Patients with past history of hematopoietic stem cell transplantation. • Patients with any of the following laboratory test findings of bone marrow failure: Reticulocyte count $<100 \times 10^9$/L, platelet count $<30 \times 10^9$/L, neutrophil count $<0.5 \times 10^9$/L. • Patients who had active and systemic infection within 14 days before the start of the study treatment. • Patients with past history of recurring invasive infections with encapsulated bacteria such as *Meningococcus* and *Pneumococcus*. • Patients who received immunosuppressants on a non-stable regimen for 8 weeks, or systemic corticosteroids (<1 mg/kg) used for hematological conditions on a non-stable regimen for 4 weeks, before screening.

This study consisted of a primary evaluation period of 24 weeks (treatment with iptacopan or a complement C5 inhibitor) and a treatment extension period of 24 weeks (continued treatment with iptacopan in the iptacopan group, and treatment switched to iptacopan in the complement C5 inhibitor group). Subjects who completed the treatment extension period were allowed to enter the roll-over extension program (Study C12001B).

In the primary evaluation period, subjects received iptacopan 200 mg BID as multiple oral doses in the iptacopan group, and a complement C5 inhibitor (ravulizumab or eculizumab) intravenously at the same dosage regimen as that prior to enrollment in this study in the complement C5 inhibitor group. In the iptacopan group, subjects on prior eculizumab regimen (at 2-week intervals) started to receive iptacopan 7 to 8 days after the last dose of eculizumab, and subjects on prior ravulizumab regimen (at 8-week intervals) started to receive iptacopan 41 to 43 days after the last dose of ravulizumab. In the treatment extension period, all subjects received multiple oral doses of iptacopan 200 mg BID.

All 97 randomized subjects (62 subjects [including 6 Japanese] in the iptacopan group and 35 subjects [including 3 Japanese] in the complement C5 inhibitor group) were included in the Full Analysis Set (FAS) and the safety set (SAF). The FAS of the primary evaluation period was the primary efficacy analysis population. In the primary evaluation period, 1 subject (pregnancy) in the iptacopan group discontinued the study. Excluding this discontinued subject and 1 subject in the complement C5 inhibitor group who did not enter the treatment extension period at the discretion of the investigator, 95 subjects (61 subjects [including 6 Japanese] in the iptacopan group and 34 subjects [including 3 Japanese] in the complement C5 inhibitor group)

[44] The proportion of subjects with "increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168 without blood transfusion" was assumed to be 50% in the iptacopan group and 16% in the complement C5 inhibitor group. The proportion of subjects with "Hb level ≥12 g/dL between Day 126 and Day168 without blood transfusion" was assumed to be 35% in the iptacopan group and 5% in the complement C5 inhibitor group. Based on these assumptions, with a sample size of 56 subjects in the iptacopan group and 35 subjects in the complement C5 inhibitor group, and a 1-sided significance level of 0.0125, the power based on Fisher's exact test was calculated to be 83.2% and 89.1% for these endpoints, respectively.

entered the treatment extension period. Of the 97 subjects included in the FAS and SAF, 1 subject in the complement C5 inhibitor group who did not enter the treatment extension period was excluded, and the remaining 96 subjects were included in the long-term FAS and the long-term SAF. In the treatment extension period, 1 subject (pregnancy) in the iptacopan group discontinued the study.

Concerning efficacy, the primary endpoints were the response defined as "increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168[45)] without blood transfusion" and the response defined as "Hb level ≥12 g/dL between Day 126 and Day 168[45)] without blood transfusion." Iptacopan was considered effective if either of these endpoints demonstrated its superiority. "Without blood transfusion" was defined as a case where the subject did not receive blood transfusion between Day 126 and Day 168 and did not meet the blood transfusion criteria[46)] specified in the protocol. Table 37 shows the results of the primary endpoints. Both endpoints demonstrated the superiority of iptacopan over the complement C5 inhibitor.

Table 37. Results of primary endpoints (FAS)

	Treatment group	No. of responders/ No. of subjects evaluated	Adjusted odds ratio [95% CI][b)]	*P* value[b) c)]
Increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day168[a)] without blood transfusion	Iptacopan (N = 62)	51/60	338.25 [25.07, 4,564.14]	<0.0001
	Complement C5 inhibitor (N = 35)	0/35		
Hb level ≥12 g/dL between Day 126 and Day 168[a)] without blood transfusion	Iptacopan (N = 62)	42/60	495.74 [24.41, 10,066.53]	<0.0001
	Complement C5 inhibitor (N = 35)	0/35		

a) At ≥3 of 4 specified measurement time points
b) Calculated using a logistic regression model using Firth's correction, with treatment group as the independent variable, and type of the complement C5 inhibitor used for prior treatment, prior blood transfusion for 6 months before randomization, sex, age (≥45 years, <45 years), and baseline Hb level (≥9 g/dL, <9 g/dL) as covariates. Missing data not related to blood transfusion were imputed by multiple imputation.
c) The type I error rate of the entire study was controlled by graphical approach. The significance level originally assigned to each primary endpoint was 1-sided 0.0125. If the null hypothesis for one primary endpoint alone was rejected, the original plan specified to assign 10% of the significance level of the rejected hypothesis to the hypothesis of the other endpoint, and then perform the test at a 1-sided significance level of 0.01375. If the null hypothesis was not rejected despite the above procedure, the original plan specified to perform the test at a 1-sided significance level of 0.025 only when part of the secondary endpoints (transfusion avoidance, change in Hb level, change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score, and change in reticulocyte count) all showed statistical significance. As a result, the null hypothesis was rejected for both primary endpoints at the originally assigned 1-sided significance level of 0.0125.

Concerning safety in the primary evaluation period, adverse events were observed in 82.3% (51 of 62) of subjects in the iptacopan group and 80.0% (28 of 35) of subjects in the complement C5 inhibitor group, and adverse drug reactions were observed in 25.8% (16 of 62) of subjects in the iptacopan group and 8.6% (3 of 35) of subjects in the complement C5 inhibitor group. Table 38 shows adverse events observed in ≥5% of subjects in either group.

In the primary evaluation period, there were no deaths, and serious adverse events were observed in 9.7% (6 of 62) of subjects (transient ischaemic attack, sinus node dysfunction, pyelonephritis, urinary tract infection, COVID-19, blood creatine phosphokinase increased, myelodysplastic syndrome, and basal cell carcinoma in 1 subject each; some subjects developed ≥1 event) in the iptacopan group, and 14.3% (5 of 35) of subjects

[45)] At ≥3 of 4 measurement time points between Day 126 and Day 168
[46)] Red blood cells were transfused if either of the following was met:
- Hb level ≤9 g/dL, with clinical signs or symptoms that justify blood transfusion.
- Hb level ≤7 g/dL, with or without clinical signs or symptoms.

(COVID-19 in 2 subjects, and arthritis bacterial, intervertebral discitis, sepsis, influenza A virus test positive, breakthrough haemolysis, extravascular haemolysis, acute kidney injury, bilirubinuria, and jaundice in 1 subject each; some subjects developed ≥1 event) in the complement C5 inhibitor group. Of these, the event (blood creatine phosphokinase increased) in 1.6% (1 of 62) of subjects in the iptacopan group was the only serious adverse drug reaction, but the treatment with iptacopan was continued, and the event resolved after medical treatment. There were no adverse events leading to treatment discontinuation.

Table 38. Adverse events observed in ≥5% of subjects in either group (primary evaluation period; SAF)

	Primary evaluation period (24 weeks)	
	Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)
All adverse events	82.3 (51)	80.0 (28)
Headache	16.1 (10)	2.9 (1)
Diarrhoea	14.5 (9)	5.7 (2)
Nasopharyngitis	11.3 (7)	5.7 (2)
Nausea	9.7 (6)	2.9 (1)
COVID-19	8.1 (5)	25.7 (9)
Arthralgia	8.1 (5)	2.9 (1)
Urinary tract infection	8.1 (5)	2.9 (1)
Blood lactate dehydrogenase increased	6.5 (4)	8.6 (3)
Abdominal pain	6.5 (4)	2.9 (1)
Dizziness	6.5 (4)	0
Back pain	4.8 (3)	5.7 (2)
Breakthrough haemolysis	3.2 (2)	17.1 (6)
Pyrexia	3.2 (2)	8.6 (3)
Upper respiratory tract infection	3.2 (2)	8.6 (3)
Sinusitis	3.2 (2)	8.6 (3)
Extravascular haemolysis	0	5.7 (2)

MedDRA/J ver 25.0, incidence % (n)

Safety in the entire treatment period (primary evaluation period and treatment extension period) was evaluated from the start of iptacopan treatment (from the entry in the treatment extension period, for subjects who were on complement C5 inhibitor in the primary evaluation period and switched to iptacopan in the treatment extension period) to the end of the study. Adverse events were observed in 93.5% (58 of 62) of subjects who entered the treatment extension period from the iptacopan group (hereinafter referred to as the iptacopan-continued population) and 88.5% (85 of 96) of subjects who were treated with iptacopan (hereinafter referred to as the iptacopan-treated population), and adverse drug reactions were observed in 27.4% (17 of 62) of subjects in the iptacopan-continued population and 21.9% (21 of 96) of subjects in the iptacopan-treated population. Table 39 shows the adverse events observed in ≥5% of subjects in either population.

In the entire treatment period, there were no deaths, and serious adverse events were observed in 14.5% (9 of 62) of subjects (transient ischaemic attack, sinus node dysfunction, pyelonephritis, urinary tract infection pseudomonal, COVID-19, rhabdomyolysis, myelodysplastic syndrome, basal cell carcinoma, cellulitis, septic shock, and ovarian cyst in 1 subject each; 1 subject developed ≥1 event) in the iptacopan-continued population, and 13.5% (13 of 96) of subjects (transient ischaemic attack, sinus node dysfunction, pyelonephritis, urinary tract infection pseudomonal, COVID-19, rhabdomyolysis, myelodysplastic syndrome, basal cell carcinoma, cellulitis, septic shock, ovarian cyst, platelet count decreased, pancreatolithiasis, portal vein thrombosis, and systemic infection in 1 subject each; 1 subject developed ≥1 event) in the iptacopan-treated population. Of

these, the event (platelet count decreased) in 1.0% (1 of 96) of subjects in the iptacopan-treated population was the only serious adverse drug reaction, but the treatment with iptacopan was continued, and the event did not resolve despite treatment with eltrombopag. There were no adverse events leading to treatment discontinuation.

Table 39. Adverse events observed in ≥5% of subjects in either population (entire treatment period; long-term FAS)

	Entire treatment period	
	Iptacopan-continued population (N = 62)	Iptacopan-treated population (N = 96)
All adverse events	93.5 (58)	88.5 (85)
COVID-19	29.0 (18)	27.1 (26)
Headache	19.4 (12)	14.6 (14)
Diarrhoea	16.1 (10)	12.5 (12)
Nasopharyngitis	14.5 (9)	12.5 (12)
Nausea	12.9 (8)	11.5 (11)
Arthralgia	11.3 (7)	7.3 (7)
Urinary tract infection	11.3 (7)	7.3 (7)
Breakthrough haemolysis	9.7 (6)	7.3 (7)
Blood lactate dehydrogenase increased	9.7 (6)	6.3 (6)
Abdominal pain	8.1 (5)	5.2 (5)
Hypertension	6.5 (4)	6.3 (6)
Pyrexia	6.5 (4)	5.2 (5)
Dizziness	6.5 (4)	4.2 (4)
Insomnia	6.5 (4)	4.2 (4)
Thrombocytopenia	4.8 (3)	5.2 (5)
Vomiting	3.2 (2)	5.2 (5)

MedDRA/J ver. 25.1, incidence % (n)

Concerning safety in the Japanese population, adverse events in the primary evaluation period (6 subjects in the iptacopan group and 3 subjects in the complement C5 inhibitor group) were observed in 100% (6 of 6) of subjects in the iptacopan group and 66.7% (2 of 3) of subjects in the complement C5 inhibitor group, with no adverse drug reactions reported. There were no adverse events observed in ≥2 subjects. Adverse events in the entire treatment period (6 subjects in the iptacopan-continued population and 9 subjects in the iptacopan-treated population) were observed in 100% (6 of 6) of subjects in the iptacopan-continued population and 100% (9 of 9) of subjects in the iptacopan-treated population, and no adverse drug reactions were reported. Nasopharyngitis in the iptacopan-treated population was observed in ≥2 subjects (2 of 9 subjects). There were no deaths, and a serious adverse event was observed in 1 subject (basal cell carcinoma) in the iptacopan group in the primary evaluation period, and no serious adverse drug reactions were reported. There were no adverse events leading to treatment discontinuation.

7.2 Global phase III study (CTD 5.3.5.2-1 and 5.3.5.2-5: Study C12301 [July 2021 to April 2023])

A multicenter, open-label, single-group study was conducted at 16 study sites in 10 countries, including Japan, to investigate the efficacy and safety of iptacopan in complement inhibitor (complement C5 inhibitor, etc.) treatment-naïve patients with PNH (Table 40) (target sample size, 40 subjects[47)]).

[47)] Assuming a sample size of 40 subjects, the half-width of the 95% CI (the proportion of responders – the lower limit of 95% CI) for the proportion of subjects with the response defined as "increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day168 without blood transfusion," assessed as a primary endpoint, was calculated to be not more than an acceptable error of 0.155, even when the proportion is 50% at which the standard deviation is maximal. With the sample size of 40 subjects, and assuming the proportion of responders to be 40%, the probability of the lower limit of the 2-sided 95% CI being equal to or higher than the threshold value of 15% was calculated to be 96.4%.

Table 40. Main inclusion criteria

Main inclusion criteria • Patients aged ≥18 years. • Patients diagnosed with PNH that was confirmed by high-sensitivity flow cytometry. • Patients with LDH >1.5 × upper limit of normal (ULN) (>2 times at an interval of 2 to 8 weeks in the screening period). • Patients with Hb <10.0 g/dL. • Patients who received meningococcal vaccination before the start of the study treatment. • Patients who had previously been vaccinated against *Pneumococcus* and *Haemophilus influenzae*, if available in the study country or region, before the start of the study treatment. Main exclusion criteria • Patients with prior treatment with complement inhibitors (complement C5 inhibitor, etc.). • Patients with confirmed or suspected hereditary complement deficiency. • Patients with past history of hematopoietic stem cell transplantation. • Patients with any of the following laboratory test findings of bone marrow failure: Reticulocyte count <100 × 10^9/L, platelet count <30 × 10^9/L, neutrophil count <0.5 × 10^9/L. • Patients who had active and systemic infection within 14 days before the start of the study treatment. • Patients with past history of recurring invasive infections with encapsulated bacteria such as *Meningococcus* and *Pneumococcus*. • Patients who had received immunosuppressants, or systemic corticosteroids (<0.25 mg/kg/day) used for hematological conditions, at a non-stable regimen within 8 and 4 weeks, respectively, before screening.

This study consisted of a primary evaluation period of 24 weeks and a treatment extension period of 24 weeks. Subjects who completed the treatment extension period were allowed to enter the roll-over extension program (Study C12001B).

Subjects received iptacopan 200 mg BID as repeated oral doses.

All 40 subjects (including no Japanese) who received the study drug were included in the FAS and the SAF. There were no discontinuations in the primary evaluation period, and all 40 subjects entered the treatment extension period. There were no discontinuations in the treatment extension period.

Concerning efficacy, the primary endpoints was the status of response defined as "increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168[45)] without blood transfusion," and "without blood transfusion" was defined as a case where the subject did not receive blood transfusion on Days 14 to 168 and did not meet the blood transfusion criteria[48)] specified in the protocol. The marginal percentage of responders[49)] [95% CI] was 92.2% [82.5, 100.0], and the lower limit of the 95% CI exceeded the pre-specified threshold (15%).

Concerning safety, adverse events were observed in 92.5% (37 of 40) of subjects, and adverse drug reactions in 42.5% (17 of 40) of subjects. Table 41 shows adverse events observed in ≥5% of subjects. There were no deaths, and serious adverse events were observed in 20.0% (8 of 40) of subjects (COVID-19 in 2 subjects, and breakthrough haemolysis, pneumonia bacterial, type 2 diabetes mellitus, cataract, pneumonia, malignant melanoma, and infection in 1 each; 1 subject developed ≥1 event). Serious adverse drug reactions were observed in 5.0% (2 of 40) of subjects (pneumonia and infection in 1 subject each); the treatment with iptacopan

48) Red blood cells were transfused if either of the following was met:
- Hb level ≤9 g/dL (≤8 g/dL for Chinese subjects), with clinical signs or symptoms that justify blood transfusion.
- Hb level ≤7 g/dL (≤6 g/dL for Chinese subjects), with or without clinical signs or symptoms.

49) Since the logistic regression model did not converge, the mean response rate of the datasets prepared when imputing missing data not related to blood transfusion by multiple imputation was used as the marginal proportion. The 95% CI was calculated by the bootstrap method.

was continued for all of these events, and the events resolved after antibiotic administration, etc. There were no adverse events leading to treatment discontinuation.

Table 41. Adverse events observed in ≥5% of subjects (SAF)

	Iptacopan (N = 40)		Iptacopan (N = 40)
All adverse events	92.5 (37)	Conjunctivitis	5.0 (2)
Headache	30.0 (12)	Contusion	5.0 (2)
COVID-19	22.5 (9)	Dermatitis allergic	5.0 (2)
Upper respiratory tract infection	17.5 (7)	Epistaxis	5.0 (2)
Diarrhoea	15.0 (6)	Fatigue	5.0 (2)
Abdominal pain	7.5 (3)	Heavy menstrual bleeding	5.0 (2)
Constipation	7.5 (3)	Hyperlipidaemia	5.0 (2)
Iron deficiency	7.5 (3)	Hypertension	5.0 (2)
Pyrexia	7.5 (3)	Influenza	5.0 (2)
Vomiting	7.5 (3)	Lipids abnormal	5.0 (2)
Amylase increased	5.0 (2)	Nasal congestion	5.0 (2)
Asthenia	5.0 (2)	Nausea	5.0 (2)
Breakthrough haemolysis	5.0 (2)	Pain in extremity	5.0 (2)
C-reactive protein increased	5.0 (2)	Periarthritis	5.0 (2)
Cataract	5.0 (2)	Ureterolithiasis	5.0 (2)
Chest pain	5.0 (2)	Vision blurred	5.0 (2)

MedDRA/J ver 26.0, incidence % (n)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

On the basis of the investigations in Sections 7.R.1.1 to 7.R.1.4, PMDA considers that the clinically meaningful efficacy of iptacopan has been demonstrated in patients with PNH who have an inadequate response to complement C5 inhibitors, and it can also be expected to be effective in Japanese patients.

7.R.1.1 Design and main results of the global phase III study (Study C12302)

The applicant's explanation about the appropriateness of the design of the global phase III study (Study C12302) and the main study results:

The objective of Study C12302 was to demonstrate the efficacy and safety of iptacopan in patients with PNH who had an inadequate response to complement C5 inhibitors, the standard-of-care drug for PNH. The study population was therefore defined as patients presenting with anemia (Hb level <10.0 g/dL) even under treatment with the complement C5 inhibitor eculizumab or ravulizumab, which had been approved at the stage of study planning. Two primary endpoints, namely, "increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168 without blood transfusion" and "Hb level ≥12 g/dL between Day 126 and Day 168 without blood transfusion," were selected in view of the following: "Hb level improvement" and "transfusion independence" are considered as the main parameters required for a hematological response with complement inhibitors (*Front Immunol*. 2019;10:1157); an increase in Hb level by ≥2 g/dL corresponds to an increase achieved by transfusion of appropriately 2 units of red blood cells and was considered clinically meaningful; Hb level of ≥12 g/dL is close to the reference range; to maintain the effect, the criterion for Hb should be achieved at ≥3 of 4 measurement time points in the last 6 weeks (between Day 126 and Day 168) of the primary evaluation period. Iptacopan was considered effective if either of these endpoints demonstrated its superiority. The study was planned to demonstrate the superiority of iptacopan over a complement C5 inhibitor (eculizumab or ravulizumab) as the comparator. Since the use of a double dummy, double-blind design is difficult because

iptacopan and the complement C5 inhibitors are administered by different routes, and that the complement C5 inhibitor control group uses 2 drug products with different dosage regimens, the study was conducted in an open-label manner. However, since an objective measure (Hb) was used for the primary endpoints, bias in the evaluation was unlikely to occur.

Table 42 shows the achievement rates of the primary endpoints in the entire population and the Japanese population of Study C12302. In the entire population, both primary endpoints demonstrated the superiority of iptacopan over the complement C5 inhibitors (eculizumab or ravulizumab) [see Section 7.1]. Concerning efficacy in the Japanese population, although there are limitations to the interpretation of the results due to the limited number of subjects, no different trends were identified compared with those in the entire population.

Table 42. Achievement rates of the primary endpoints of Study C12302 (primary evaluation period; FAS)

		Entire population		Japanese population	
		Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)	Iptacopan (N = 6)	Complement C5 inhibitor (N = 3)
Increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168[a)] without blood transfusion	Proportion of responders % (No. of responders/No. of subjects evaluated)	85.0 (51/60)	0 (0/35)	66.7 (4/6)	0 (0/3)
	Adjusted intergroup difference [95% CI][b)]	80.2 [71.2, 87.6]		-	
Hb level ≥12 g/dL between Day 126 and Day 168[a)] without blood transfusion	Proportion of responders % (No. of responders/No. of subjects evaluated)	70.0 (42/60)	0 (0/35)	50.0 (3/6)	0 (0/3)
	Adjusted intergroup difference [95% CI][b)]	67.0 [56.4, 76.9]		-	

-, not calculated.

a) At ≥3 of 4 specified measurement time points

b) The predicted probability of response of each subject was calculated using a Logistic regression model with a common intercept using Firth's correction, with treatment group as the independent variable, and type of the complement C5 inhibitor used for prior treatment, prior blood transfusion for 6 months before randomization, sex, age (≥45 years, <45 years), and baseline Hb level (≥9 g/dL, <9 g/dL) as covariates, and the difference between the means of each group was used as the adjusted intergroup difference. The 95% CI was calculated by the bootstrap method.

Figure 1 shows changes in Hb level in Study C12302. In the iptacopan group, the Hb level improved to around 12 g/dL after Day 7 and was maintained until Day 168.

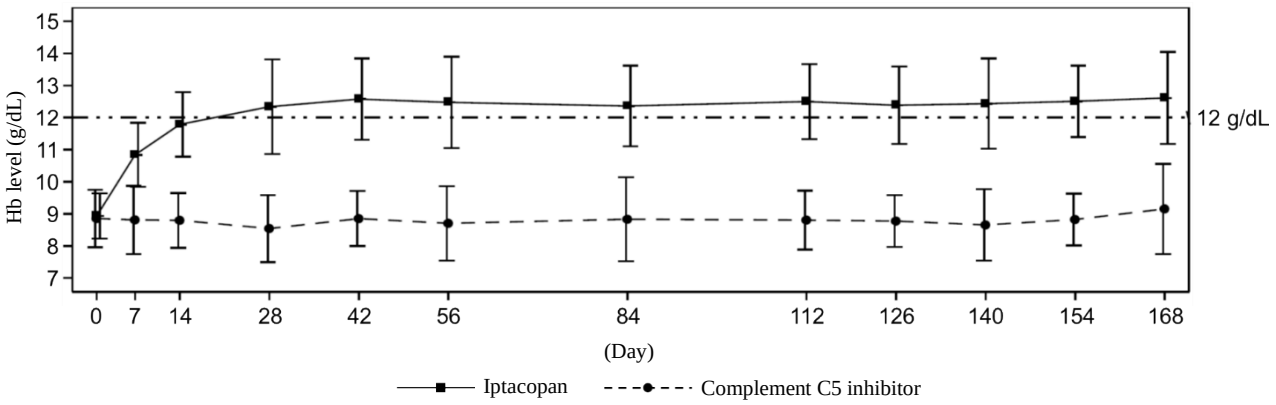

Figure 1. Changes in Hb level in Study C12302 (mean ± standard deviation; including Hb levels for 30 days after blood transfusion) (primary evaluation period; FAS)

Table 43 shows the results of the main secondary endpoints in Study C12302. In the entire population, the effect in terms of the "proportion of subjects with transfusion avoidance (without blood transfusion)," "change from baseline in Hb level," "change from baseline in reticulocyte count," "change from baseline in FACIT-Fatigue score,[50)]" and "onset of clinical breakthrough hemolysis[51)]" tended to be larger in the iptacopan group than in the complement C5 inhibitor group. For the "incidence of major adverse vascular events (MAVEs),"[52)] the intergroup ratio was not presented because an applicable event occurred in 1 subject in the iptacopan group during the primary evaluation period (24 weeks). The "ratio of LDH to baseline" was also similar in the iptacopan group and the complement C5 inhibitor group, and the mean LDH at baseline (267.5 U/L in the iptacopan group and 261.0 U/L in the complement C5 inhibitor group) was close to the reference range (ULN: 250 U/L). This suggests that intravascular hemolysis was controlled with the complement C5 inhibitor that had been administered before enrollment and the LDH level was maintained during the primary evaluation period. In the Japanese population, although stringent evaluation was difficult due to the limited number of subjects evaluated, no different trends were identified between the Japanese population and the entire population for most of the endpoints.

[50)] ACIT-Fatigue is a 13-item measure that assesses self-reported fatigue and its impact on daily activities and function. Each item is scored from 0 to 4 and the total score ranges from 0 to 52. Higher scores indicate more favorable health conditions (fatigue symptom is less severe or the quality of life is higher).

[51)] Defined as a case where either of the following 2 clinical criteria (Hb level, and signs and symptoms) is met and "LDH is >1.5 × ULN, with an increase compared to the most recent 2 assessments":

- Decrease in Hb level by ≥2 g/dL (compared to the most recent assessment or the assessment within 15 days).
- Macroscopic hemoglobinuria, pain attack, dysphagia, or other significant PNH-related clinical signs or symptoms.

[52)] MAVEs were defined as events classified as the following:
Acute peripheral vascular occlusion, amputation (non-traumatic/non-diabetic), cerebral artery occlusion/stroke, cerebral vein occlusion, skin thrombosis, gangrene (non-traumatic/non-diabetic), hepatic vein/portal vein thrombosis (Budd-chiari syndrome), mesenteric/visceral artery thrombosis or infarction, mesenteric/visceral vein thrombosis or infarction, myocardial infarction, pulmonary embolism, renal artery thrombosis, renal vein thrombosis, thrombophlebitis/deep vein thrombosis, transient ischemic attack, unstable angina, etc.

Table 43. Results of the main secondary endpoints in Study C12302 (primary evaluation period; FAS)

		Entire population		Japanese population	
		Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)	Iptacopan (N = 6)	Complement C5 inhibitor (N = 3)
Transfusion avoidance (no blood transfusion)	Proportion of subjects who achieved the endpoint, % (No. of responders/No. of subjects evaluated)	95.2 (59/62)	40.0 (14/35)	100.0 (6/6)	100.0 (3/3)
	Adjusted intergroup difference [95% CI][a)]	68.9 [51.4, 83.9]		-	
Hb level	Mean change from baseline on Day 168[b) c)] (g/dL)	3.68	0.31	2.98	−0.22
	Adjusted intergroup difference [95% CI][e)] for the change from baseline between Day 126 and Day 168[d)]	3.66 [3.20, 4.12]		-	
Reticulocyte count	Mean change from baseline on Day 168[b)] ($\times 10^9$/L)	−120.07	−10.21	−86.48	−3.87
	Adjusted intergroup difference [95% CI][e)] for the change from baseline between Day 126 and Day [d)]	−116.15 [−132.04, −100.26]		-	
FACIT-Fatigue score	Mean change from baseline on Day 168[b)]	8.5	1.1	0.8	2.3
	Adjusted intergroup difference [95% CI][e)] for the change from baseline between Day 126 and Day 168[d)]	8.29 [5.28, 11.29]		-	
Clinical breakthrough hemolysis	Incidence, % (n)	3.2 (2)	17.1 (6)	0	0
	Intergroup ratio [95% CI][f)] for the adjusted annual incidence rate	0.10 [0.02, 0.61]		-	
MAVEs	Incidence, % (n)	1.6 (1)	0	0	0
	Intergroup ratio [95% CI][f)] for the adjusted annual incidence rate	-		-	
LDH	Mean change from baseline on Day 168[b)] (U/L)	7.6	7.9	7.2	7.0
	Adjusted intergroup difference [95% CI][e)] for the ratio to baseline between Day 126 and Day 168[d)]	0.99 [0.89, 1.10]		-	

-, not calculated.

a) The predicted probability of response of each subject was calculated using a Logistic regression model with a common intercept, with treatment group as the independent variable, and type of the complement C5 inhibitor used for prior treatment, prior blood transfusion for 6 months before randomization, sex, age (≥45 years, <45 years), and baseline Hb level (≥9 g/dL, <9 g/dL) as covariates, and the difference between the means of each group was used as the adjusted intergroup difference. The 95% CI was calculated by the bootstrap method.

b) Calculated based only on subjects with data both at baseline and on Day 168.

c) Including Hb levels for 30 days after blood transfusion.

d) Mean of the visits between Day 126 and Day168

e) Estimated using a mixed-effects model for repeated measures, with type of the complement C5 inhibitor used for prior treatment, prior blood transfusion for 6 months before randomization, age (≥45 years, <45 years), sex, treatment group, baseline value of each endpoint, and time point as fixed effects, and treatment group and time point, and time point and baseline values as interaction terms. An unstructured covariance matrix was used to model the within-subject correlation between the time points. For LDH, log-transformed baseline value was used as a fixed effect.

f) The adjusted annual incidence rate of clinical breakthrough hemolysis was estimated using a negative binomial model with treatment group as a factor. The adjusted annual incidence rate of MAVEs was estimated using a Poisson model with treatment group as a factor. For both endpoints, the period from Day 1 to the end of the study or the end of the primary evaluation period, whichever is earlier, was set as an offset variable.

PMDA's view:

Since the objective of Study C12302 was to demonstrate the efficacy of iptacopan in patients with PNH who had an inadequate response to complement C5 inhibitors, the study population, comparators, primary endpoints, etc. set for the study are reasonable. Use of an open-label design is unavoidable in view of the comparators, and selection of an objective measure for the primary endpoints is also reasonable from the viewpoint of reducing bias. In Study C12302, the proportion of subjects who achieved the endpoint was higher in the iptacopan group than in the complement C5 inhibitor group for both of the 2 primary endpoints "increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168 without blood transfusion" and "Hb level ≥12 g/dL between Day 126 and Day168 without blood transfusion. These results demonstrated the superiority of iptacopan over complement C5 inhibitors, and the results of the main secondary endpoints were also appropriate and supported the results of the primary endpoints. It can therefore be concluded that the efficacy of iptacopan was demonstrated in patients with PNH who have an inadequate response to complement C5 inhibitors. Although the number of Japanese subjects is limited, none of the primary endpoints showed different trends between the Japanese population and the entire population, and the results of the main secondary endpoints were also generally similar. These findings suggest that the results in the Japanese population are

generally consistent with those in the entire population. The efficacy of iptacopan can therefore also be expected in the Japanese population.

7.R.1.2 Design and main results of the global phase III study (Study C12301)

The applicant's explanation about the appropriateness of the design of Study C12301 and the main study results:

Study C12301 is a global study involving countries where complement C5 inhibitors have been approved and countries where these drugs have not been approved. For this reason, it was conducted as a single-group study without using either placebo or a complement C5 inhibitor as the comparator. The study population consisted of complement inhibitor treatment-naïve patients with PNH presenting with hemolysis (LDH is >1.5 × ULN) and anemia (Hb <10 g/dL; excluding patients with bone-marrow failure), and the objective of the study was to confirm the efficacy and safety of iptacopan in treatment-naïve patients with intravascular hemolysis. The primary endpoint was the response defined as "increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168 without blood transfusion," and the threshold was set as 15% in reference to the results of simulating the proportion of subjects achieving an increase in Hb level by ≥2 g/dL from baseline with eculizumab.[53)] Although Japan also participated in Study C12301, Japanese patients were not enrolled in the study.

Table 44 shows the results of the efficacy endpoint in Study C12301. The lower limit of the 95% CI for the proportion of subjects with an increase in Hb level by ≥2 g/dL without blood transfusion (marginal proportion), assessed as the primary endpoint, exceeded the pre-specified threshold value of 15%. The results of secondary endpoints also supported the results of the primary endpoint. These results indicate that iptacopan showed a similar efficacy to that in Study C12302 in terms of similar primary and secondary endpoints to those in Study C12302.

[53)] The proportion of subjects achieving an increase in Hb level by ≥2 g/dL from baseline with eculizumab was simulated based on the mean Hb levels and the standard deviation at baseline and Week 26 in the eculizumab group in the global phase III study that investigated the non-inferiority of ravulizumab to eculizumab in complement inhibitor treatment-naïve patients (ALXN1210-PNH-301 study) (*Blood*. 2019;133:530-539. *Haematologica*. 2021;106: 230-237., etc.) and the foreign phase III study that investigated the superiority of eculizumab over placebo (TRIUMPH study) (*N Engl J Med*. 2006;355:1233-1243. *Oncologist*. 2008;13:993-1000). The proportion of such subjects was estimated to be 14.7% in the ALXN1210-PNH-301 study and 4.49% in the TRIUMPH study.

Table 44. Results of the primary and secondary endpoints in Study C12301 (primary evaluation period; FAS)

Endpoints	Iptacopan (N = 40)
Primary endpoint	
Marginal proportion of responders % [95% CI][b] based on increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168[a] without blood transfusion (No. of responders/No. of subjects evaluated)	92.2 [82.5, 100.0] (31/33)
Secondary endpoints	
Marginal proportion of responders % [95% CI][b] based on Hb level ≥12 g/dL between Day 126 and Day 168[a] without blood transfusion (No. of responders/No. of subjects evaluated)	62.8 [47.5, 77.5] (19/33)
Marginal proportion of subjects with transfusion avoidance (without blood transfusion) % [95% CI][b] (No. of responders/No. of subjects evaluated)	97.6 [92.5, 100.0] (40/40)
Adjusted mean [95% CI][d] of the change from baseline in Hb level[c] (g/dL)	4.28 [3.87, 4.70]
Adjusted mean [95% CI][d] of the change from baseline in FACIT-Fatigue score[c]	10.75 [8.66, 12.84]
Adjusted mean [95% CI][d] of the change from baseline in reticulocyte count[c] ($\times 10^9$/L)	−82.48 [−89.33, −75.62]
Adjusted annual incidence rate of clinical breakthrough hemolysis [95% CI][e]	0.00 [0.00, 0.17]
Adjusted annual incidence rate of MAVEs [95% CI][e]	0.00 [0.00, 0.17]
Adjusted mean [95% CI][d] of the percent change from baseline in LDH level[c]	−83.55 [−84.90, −82.08]

a) At ≥3 of 4 specified measurement time points
b) Since the logistic regression model did not converge, the mean response rate of the datasets prepared when imputing missing data not related to blood transfusion by multiple imputation was used as the marginal proportion. The 95% CI was calculated by the bootstrap method.
c) Mean of the visits between Day 126 and Day 168
d) Estimated using a mixed-effects model for repeated measures, with age (≥45 years, <45 years), sex, prior blood transfusion before the start of the study treatment, time point, and baseline value of each endpoint as fixed effects, and time point and baseline value as an interaction term. For LDH, log-transformed baseline value was used as a fixed effect.
e) The 95% CI was calculated by the Wilson method.

PMDA's view:

Study C12301 is a global study conducted in countries where complement C5 inhibitors have been approved as well as countries where these drugs have not been approved, and it is difficult to adjust the design from the viewpoint of extrinsic ethnic factors. In case the use of such a study design cannot be helped, a method of not selecting placebo or a complement C5 inhibitor as the comparator throughout the study, but modifying the method of efficacy evaluation is one option for adjusting the design. It is therefore unavoidable to conduct Study C12301 as an uncontrolled study. However, while the results of the primary and secondary endpoints in Study C12301 suggest the efficacy of iptacopan in complement inhibitor treatment-naïve patients with PNH, it cannot be concluded that iptacopan showed adequate efficacy in these patients. In addition, since Japanese subjects were not enrolled in the study, it is not feasible to investigate the consistency of results in the entire study and the Japanese subpopulation for the purpose of extrapolating the results of the entire study to Japanese complement inhibitor treatment-naïve patients with PNH. Accordingly, the efficacy of iptacopan in this patient population cannot be predicted based only on the clinical study results obtained to date, and it is therefore not recommendable to use iptacopan in this patient population. A decision will be made based on the discussions at the Expert Discussion. The clinical positioning and indication of iptacopan are discussed in Section 7.R.3, also taking the above interpretation of the results of Study C12301 into account.

7.R.1.3 Efficacy by patient characteristics

The applicant's explanation about the efficacy of iptacopan by patient characteristics:

Table 45 shows the efficacy results by main patient characteristics, for the 2 primary endpoints of Study C12302. The efficacy tended to be higher in the iptacopan group than the complement C5 inhibitor group for both populations.

Table 45. Results of the efficacy results of Study C12302 by main patient characteristics (primary evaluation period; FAS)

		Proportion of responders based on increase in Hb level by ≥2 g/dL from baseline between Day 126 and Day 168 without blood transfusion			Proportion of responders based on Hb level ≥12 g/dL between Day 126 and Day 168 without blood transfusion		
		Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)	Adjusted intergroup difference [95% CI][a)]	Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)	Adjusted intergroup difference [95% CI][a)]
Overall		85.0 (51/60)	0 (0/35)	80.2 [71.2, 87.6]	70.0 (42/60)	0 (0/35)	67.0 [56.4, 76.9]
Age	<45 years	87.0 (20/23)	0 (0/16)	77.7 [63.6, 86.7]	69.6 (16/23)	0 (0/16)	67.8 [49.1, 79.7]
	≥45 years	83.8 (31/37)	0 (0/19)	77.8 [65.4, 87.6]	70.3 (26/37)	0 (0/19)	64.3 [48.6, 78.0]
Sex	Male	78.9 (15/19)	0 (0/11)	73.2 [54.8, 88.3]	63.2 (12/19)	0 (0/11)	51.6 [29.5, 69.3]
	Female	87.8 (36/41)	0 (0/24)	85.5 [75.4, 94.5]	73.2 (30/41)	0 (0/24)	69.0 [56.0, 80.2]
Time from diagnosis	<5 years	83.3 (15/18)	0 (0/11)	72.4 [50.6, 81.7]	66.7 (12/18)	0 (0/11)	59.8 [31.3, 74.5]
	≥5 years	85.7 (36/42)	0 (0/24)	80.4 [69.7, 88.1]	71.4 (30/42)	0 (0/24)	68.7 [55.9, 79.6]
Baseline Hb level	<9 g/dL	77.4 (24/31)	0 (0/18)	72.2 [57.7, 84.4]	48.4 (15/31)	0 (0/18)	44.6 [27.5, 61.0]
	≥9 g/dL	93.1 (27/29)	0 (0/17)	85.5 [75.5, 89.7]	93.1 (27/29)	0 (0/17)	85.4 [75.1, 89.7]
Past history of MAVEs	Yes	100 (12/12)	0 (0/10)	91.6 [88.9, 91.7]	83.3 (10/12)	0 (0/10)	60.9 [26.7, 78.7]
	No	81.3 (39/48)	0 (0/25)	79.4 [68.1, 89.3]	66.7 (32/48)	0 (0/25)	64.6 [52.4, 75.6]
Prior treatment	Eculizumab	86.8 (33/38)	0 (0/23)	80.6 [69.5, 88.9]	71.1 (27/38)	0 (0/23)	65.3 [50.8, 77.2]
	Ravulizumab	81.8 (18/22)	0 (0/12)	76.7 [57.3, 84.8]	68.2 (15/22)	0 (0/12)	66.3 [42.4, 78.9]
Prior blood transfusion within 6 months	Yes	81.8 (27/33)	0 (0/21)	75.6 [62.4, 86.1]	57.6 (19/33)	0 (0/21)	53.6 [37.5, 68.4]
	No	88.9 (24/27)	0 (0/14)	83.4 [67.6, 88.2]	85.2 (23/27)	0 (0/14)	81.3 [64.5, 87.1]
No. of times of blood transfusion within 6 months	<2	83.8 (31/37)	0 (0/21)	77.7 [65.4, 87.5]	75.7 (28/37)	0 (0/21)	71.4 [57.7, 82.9]
	≥2	87.0 (20/23)	0 (0/14)	75.5 [60.1, 85.7]	60.9 (14/23)	0 (0/14)	54.4 [33.5, 70.9]
Baseline LDH level	≤1.5 × ULN	83.9 (47/56)	0 (0/32)	82.3 [72.3, 90.9]	69.6 (39/56)	0 (0/32)	68.6 [56.6, 79.9]
	>1.5 × ULN	100 (4/4)	0 (0/3)	77.5 [66.6, 77.5]	75.0 (3/4)	0 (0/3)	57.5 [25.0, 77.5]
Duration of treatment with complement C5 inhibitors	<12 months	81.8 (9/11)	0 (0/6)	57.1 [−7.8, 76.2]	54.5 (6/11)	0 (0/6)	41.4 [−19, 66.5]
	≥12 months	85.7 (42/49)	0 (0/29)	80.0 [70.1, 88.2]	73.5 (36/49)	0 (0/29)	69.2 [57.6, 79.7]

Proportion of responders % (No. of responders/No. of subjects evaluated)

a) The predicted probability of response of each subject was calculated using a Logistic regression model with a common intercept using Firth's correction, with treatment group as the independent variable, and type of the complement C5 inhibitor used for prior treatment, prior blood transfusion for 6 months before randomization, sex, age (≥45 years, <45 years), and baseline Hb level (≥9 g/dL, <9 g/dL) as covariates, and the difference between the means of each group was used as the adjusted intergroup difference. The 95% CI was calculated by the bootstrap method.

PMDA's view:

Since the proportion of responders tended to be higher in the iptacopan group than the complement C5 inhibitor group regardless of patient characteristics, although the number of subjects is limited in some subgroups, the values or changes are unlikely to significantly affect the efficacy of iptacopan for any of the patient characteristics examined.

7.R.1.4 Long-term efficacy

The applicant's explanation about the long-term efficacy of iptacopan:

Figure 2 shows changes in Hb level (mean) up to Day 336 (Week 48) in Study C12302. In the iptacopan group, the increase in Hb level observed in the primary evaluation period was maintained until Day 336. In the population of subjects switched from the complement C5 inhibitor to iptacopan, the Hb level showed an increasing trend on Day 175 that was maintained after Day 196 throughout the treatment extension period. The results in the Japanese population were generally consistent with those in the entire population. In view of the above, iptacopan demonstrated sustained efficacy and is also expected to have such sustained efficacy in the Japanese population.

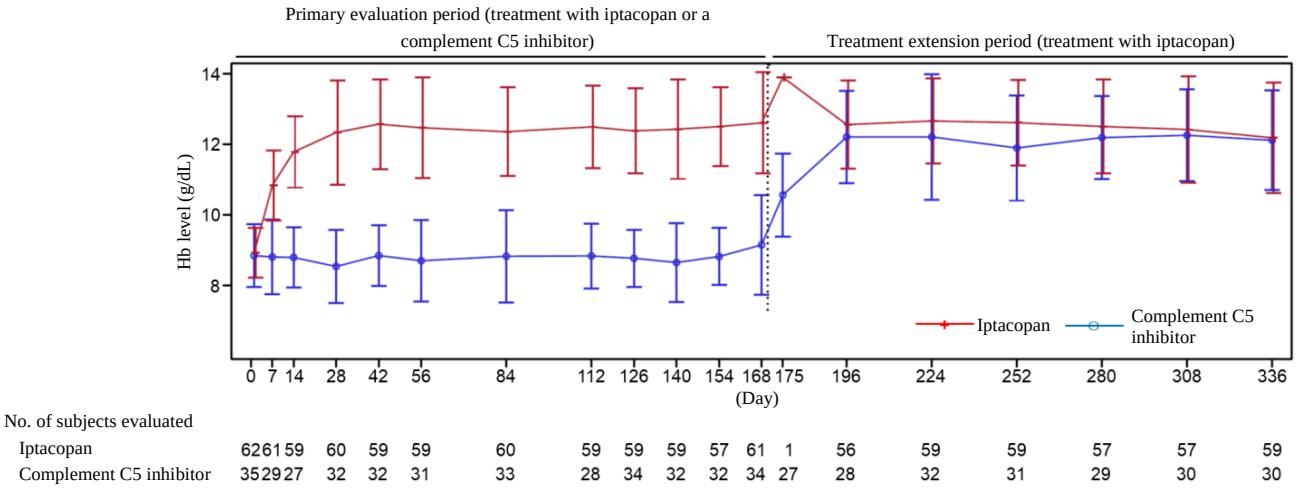

Figure 2. Changes in Hb level in Study C12302 (mean ± standard deviation) (entire treatment period; FAS)

PMDA's view:

On the basis of the results up to Week 48 in Study C12302, the long-term efficacy of iptacopan can be expected to be maintained during extended treatment in patients with PNH who have an inadequate response to complement C5 inhibitors. Since the results in the Japanese population were consistent with those in the entire population, the sustained efficacy of iptacopan demonstrated in Study C12302 can also be expected in Japanese patients with PNH who have an inadequate response to complement C5 inhibitors.

7.R.2 Safety

PMDA's view:

On the basis of the reviews in Sections 7.R.2.1 to 7.R.2.3, although the safety profile of iptacopan showed no major concerns compared with that of complement C5 inhibitors (eculizumab and ravulizumab) in the clinical studies of iptacopan, attention should be paid to infections with encapsulated bacteria such as *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae* during the use of iptacopan. Therefore, appropriate measures such as vaccination should be taken. Attention should also be paid to the risk of dyslipidemia. In the Japanese population, although there are limitations to the interpretation of the results due to the limited number of subjects, study results suggested no Japanese-specific safety concerns.

In view of the above, the safety of iptacopan is manageable if it is used only at a suitable medical institution and only under the supervision of a physician who is familiar with the diagnosis and treatment of PNH and is also fully capable of managing the risks, etc. associated with iptacopan, in cooperation with a physician who is familiar with the diagnosis and treatment of infections with encapsulated bacteria such as *Meningococcus*, as with complement C5 inhibitors. However, as described above, since the number of Japanese subjects investigated in clinical studies is extremely limited, there are limitations to the assessment on whether the safety of iptacopan in the entire population is similar to that in the Japanese population, and the risk-benefit balance of iptacopan in Japanese patients with PNH derived mainly based on safety information in the entire population includes many estimations. Therefore, information on the safety of iptacopan should be collected by post-

marketing surveillance [see Section 7.R.5] and the effect of the information on the risk-benefit balance should be investigated.

7.R.2.1 Safety of iptacopan in comparison with complement C5 inhibitors

The applicant's explanation about the safety of iptacopan in comparison with complement C5 inhibitors (eculizumab and ravulizumab):

Table 46 shows the incidence of adverse events in the primary evaluation period of Study C12302. The incidence of adverse events was similar in the iptacopan group and the complement C5 inhibitor group. Adverse events that were more common in the iptacopan group than the complement C5 inhibitor group were headache and dizziness, and all of the events observed were mild or moderate. While the incidence of adverse drug reactions was higher in the iptacopan group than the complement C5 inhibitor group, a serious adverse drug reaction was observed only in 1 subject (blood creatine phosphokinase increased) in the iptacopan group. This subject also received ciclosporin and eltrombopag, suggesting the possible involvement of these drugs. In the Japanese population, adverse events observed in the iptacopan group were headache, nasopharyngitis, basal cell carcinoma, C-reactive protein increased, conjunctival haemorrhage, depressive symptoms, dyslipidaemia, eczema, haematuria, pollakiuria, procedural vomiting, pyrexia, and rhinitis allergic in 1 subject each (some subjects developed ≥1 event), and those observed in the complement C5 inhibitor group were cholecystitis, nasal herpes, and oral herpes in 1 subject each (some subjects developed ≥1 event); there were no adverse drug reactions. These results indicate that there were no trends that may cause safety concerns with iptacopan, compared with complement C5 inhibitors.

Table 46. Summary of adverse events in Study C12302 (primary evaluation period; SAF)

	Entire population		Japanese population	
	Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)	Iptacopan (N = 6)	Complement C5 inhibitor (N = 3)
Adverse events	82.3 (51)	80.0 (28)	100.0 (6)	66.7 (2)
Adverse drug reactions	25.8 (16)	8.6 (3)	0	0
Deaths	0	0	0	0
Serious adverse events	9.7 (6)	14.3 (5)	16.7 (1)	0
Serious adverse drug reactions	1.6 (1)	0	0	0
Adverse events leading to treatment discontinuation	0	0	0	0
Adverse events observed in ≥5% of subjects in ether group in the entire population				
Headache	16.1 (10)	2.9 (1)	16.7 (1)	0
Diarrhoea	14.5 (9)	5.7 (2)	0	0
Nasopharyngitis	11.3 (7)	5.7 (2)	16.7 (1)	0
Nausea	9.7 (6)	2.9 (1)	0	0
COVID-19	8.1 (5)	25.7 (9)	0	0
Arthralgia	8.1 (5)	2.9 (1)	0	0
Urinary tract infection	8.1 (5)	2.9 (1)	0	0
Blood lactate dehydrogenase increased	6.5 (4)	8.6 (3)	0	0
Abdominal pain	6.5 (4)	2.9 (1)	0	0
Dizziness	6.5 (4)	0	0	0
Back pain	4.8 (3)	5.7 (2)	0	0
Breakthrough haemolysis	3.2 (2)	17.1 (6)	0	0
Pyrexia	3.2 (2)	8.6 (3)	16.7 (1)	0
Upper respiratory tract infection	3.2 (2)	8.6 (3)	0	0
Sinusitis	3.2 (2)	8.6 (3)	0	0
Extravascular haemolysis	0	5.7 (2)	0	0
Adverse events observed in ≥2 subjects in either group in the entire population				
Headache	6.5 (4)	2.9 (1)	0	0
Arthralgia	4.8 (3)	0	0	0
Nausea	4.8 (3)	2.9 (1)	0	0
Diarrhoea	3.2 (2)	0	0	0
Hot flush	3.2 (2)	0	0	0
Thrombocytopenia	3.2 (2)	0	0	0

MedDRA/J ver 25.1, incidence % (n)

PMDA's view:

On the basis of the incidence of adverse events and adverse drug reactions in the primary evaluation period of Study C12302 and the applicant's explanation, there are no trends that may cause safety concerns with iptacopan, compared with complement C5 inhibitors. The Japanese population shows no trends towards increased risk compared with the entire population, although there are limitations to the interpretation of the results due to the very limited number of subjects.

7.R.2.2 Long-term safety

The applicant's explanation about the long-term safety of iptacopan:

In the assessment of the long-term safety of iptacopan, the number of evaluable subjects from Studies C12302 and C12301 is limited; therefore, the data up to the final analysis in these studies, as well as the data of iptacopan200 mg BID administration in other clinical studies in patients with PNH (data up to the final analysis of Studies X2201, X2204, and LFG316X2201[13)] and data from Study C12001B[14)] as of the data cut-off on [redacted], 20[redacted]) were pooled (PNH pooled analysis). The PNH pooled analysis included 171 subjects who received iptacopan 200 mg BID, and these subjects were handled as the long-term pooled SAF. Table 47 shows the

incidence of adverse events by time to onset in the PNH pooled analysis. The incidence of adverse events by period did not tend to increase with increasing duration of iptacopan treatment.

Table 47. Summary of adverse events by time to onset in the PNH pooled analysis (long-term pooled SAF)

	Months 0 to 3 (N = 171)	Months 3 to 6 (N = 171)	Months 6 to 9 (N = 168)	Months 9 to 12 (N = 160)	Months 12 to 15 (N = 125)	Months 15 to 18 (N = 74)	Months 18 to 21 (N = 45)	Months 21 to 24 (N = 29)	After Month 24 (N = 18)	Entire period (N = 171)
Adverse events	69.0 (118)	53.2 (91)	44.6 (75)	50.6 (81)	36.8 (46)	20.3 (15)	26.7 (12)	17.2 (5)	61.1 (11)	94.2 (161)
Adverse drug reactions	19.3 (33)	8.2 (14)	5.4 (9)	4.4 (7)	3.2 (4)	2.7 (2)	4.4 (2)	3.4 (1)	11.1 (2)	28.7 (49)
Serious adverse events	4.7 (8)	4.7 (8)	3.0 (5)	6.3 (10)	3.2 (4)	2.7 (2)	4.4 (2)	3.4 (1)	16.7 (3)	22.2 (38)
Adverse events leading to treatment discontinuation	0.6 (1)	0	0	0.6 (1)	0	0	0	0	0	1.2 (2)

Incidence % (n)

PMDA's view:

On the basis of the incidence of adverse events with iptacopan by time of onset in the PNH pooled analysis, adverse events are unlikely to occur more frequently with increasing duration of iptacopan treatment, and the safety of iptacopan will not greatly change over the course of time.

7.R.2.3 Adverse events of special interest

The sections below present the applicant's explanations about encapsulated bacterial infections, hemolysis, thrombosis, platelet count decreased, dyslipidemia, hypersensitivity, and effects on the thyroid gland and testes. These are defined as adverse events of special interest, of which the concern is the mechanism of action of iptacopan, the known safety profile of complement inhibitors, and available clinical and non-clinical data of iptacopan.

7.R.2.3.1 Encapsulated bacterial infections

The applicant's explanation about encapsulated bacterial infections:

The complement system is important for the elimination of encapsulated bacteria such as *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae* from the body. *Meningococcus* is recognized by antibodies or complement, and the complement system is then activated and kills the bacteria by forming a MAC on its membrane (*Front Immunol*. 2021;12:747594). *Pneumococcus* is killed by antibody-dependent cellular phagocytosis, and this bactericidal activity is enhanced by C3b opsonization that is induced by activation of the complement system (*Front Immunol*. 2021;12:732146). It has not been clarified whether MAC formation or C3b opsonization contributes greatly to killing *Haemophilus influenzae*. However, since iptacopan inhibits upstream of the AP and prevents both MAC formation and C3b opsonization, iptacopan administration may pose the risk of infection with such encapsulated bacteria. Taking this into account, in Studies C12302 and C12301, subjects who had not received vaccination or required additional vaccination had to receive a meningococcal vaccine at least 2 weeks before their first dose of study treatment. For *Pneumococcus* and *Haemophilus influenzae*, subjects who had not previously received vaccination had to receive vaccines, if

available in the study country or region,[54] at least 2 weeks before their first dose of study treatment. If iptacopan treatment had to be started within 2 weeks after each vaccination, prophylactic antibiotics were administered.

In the primary evaluation period of Study C12302, encapsulated bacterial infections[55] were observed only in 1.6% (1 of 62) of subjects (bronchitis haemophilus) in the iptacopan group. The event was not assessed as an adverse drug reaction, was non-serious, and resolved during the treatment extension period of iptacopan.

In the PNH pooled analysis, encapsulated bacterial infections were observed in 8.2% (14 of 171) of subjects, and the events were pneumonia bacterial in 3 subjects, otitis media, cellulitis, and cystitis escherichia in 2 subjects each, and bronchitis haemophilus, urinary tract infection pseudomonal, staphylococcal skin infection, carbuncle, erysipelas, and furuncle in 1 subject each (1 subject developed ≥1 event). Serious adverse events were observed in 2.9% (5 of 171) of subjects (pneumonia bacterial and cellulitis in 2 subjects each, and urinary tract infection pseudomonal in 1 subject). None of these were assessed as adverse drug reactions and all of the events resolved. There were no adverse events leading to treatment discontinuation.

In the Japanese population, encapsulated bacterial infections were observed in 6.7% (1 of 15) of subjects (cellulitis) in the PNH pooled analysis. The event was not assessed as an adverse drug reaction and resolved.

In view of the above, the risk of encapsulated bacterial infections associated with iptacopan showed no clinically significant trends in clinical studies, and is therefore considered controllable by taking appropriate measures. To reduce the risk of encapsulated bacterial infections, the package insert will include a precautionary statement to the effect that vaccines against *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae* should be administered at least 2 weeks before the start of iptacopan treatment in principle, and appropriate measures should immediately be taken if such infections are suspected.

PMDA's view:
The incidence of encapsulated bacterial infections showed no clinically significant trends in clinical studies. However, in view of the mechanism of action of iptacopan, due attention should be paid to encapsulated bacterial infections and appropriate measures should be taken during iptacopan treatment. Iptacopan should therefore be used only at a suitable medical institution and only under the supervision of a physician who is familiar with the diagnosis and treatment of PNH and is also fully capable of managing the risks, etc. associated with iptacopan. Particularly for meningococcal infection, which may rapidly become severe and occasionally result in death, it is appropriate to use iptacopan in cooperation with a physician who is familiar with the diagnosis and treatment of such infection. As part of the efforts, precautionary statements should be included in the package insert and materials for healthcare professionals and patients to thoroughly ensure that

[54] In Japan, pneumococcal vaccination was specified as a must, whereas influenza vaccination was not essential, based on the package insert of each vaccine at the time of study conduct.
[55] Events classified as the MedDRA/J HLT "Bacillary infections," "Haemophilus infections," "Klebsiella infections," "Neisseria infections," "Pseudomonal infections," "Salmonella infections," "Staphylococcal infections," "Streptococcal infections," or "Escherichia infections," or as the MedDRA/J PT "anal gonococcal infection," "Bacillus test positive," "epiglottic abscess," "Haemophilus test positive," "Klebsiella test positive," "Neisseria test positive," "otitis media," "pneumonia bacterial," "Pseudomonas test positive," "Salmonella test positive," "Staphylococcus test positive," "Streptobacillus test positive," "Streptococcus test positive," "tonsillitis bacterial," "cellulitis," "carbuncle," "otitis media acute," "disseminated gonococcal infection," or "wound cellulitis."

vaccination history against *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae* is confirmed before the start of iptacopan treatment, and that patients who have not received vaccination or requires additional vaccination receive the necessary vaccine.

7.R.2.3.2 Hemolysis

The applicant's explanation about hemolysis:

Table 48 shows the incidence of hemolysis in the broad sense[56)] in the primary evaluation period of Study C12302 and the primary evaluation period of Study C12301. Serious adverse events classified as hemolysis in the narrow sense[57)] were not observed in the iptacopan group, but were observed in 5.7% (2 of 35) of subjects (breakthrough haemolysis and extravascular haemolysis) in the complement C5 inhibitor group in the primary evaluation period of Study C12302. There were no adverse events leading to treatment discontinuation classified as hemolysis in the narrow sense. In the primary evaluation period of Study C12301, there were no serious adverse events classified as hemolysis in the narrow sense.

Table 48. Incidence of hemolysis in Studies C12302 and C12301 (primary evaluation period; SAF)

	Study C12302 (primary evaluation period)		Study C12301 (primary evaluation period)
	Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)	Iptacopan (N = 40)
Hemolysis (broad)	16.1 (10)	28.6 (10)	2.5 (1)
Blood lactate dehydrogenase increased	6.5 (4)	8.6 (3)	0
Breakthrough haemolysis	3.2 (2)	17.1 (6)	0
Blood creatinine increased	1.6 (1)	0	2.5 (1)
Haemoglobinuria	1.6 (1)	0	0
Ocular icterus	1.6 (1)	0	0
Extravascular haemolysis	0	5.7 (2)	0
Jaundice	0	2.9 (1)	0

MedDRA/J ver. 25.1, incidence % (n)

In the entire treatment period of Study C12302, hemolysis in the broad sense was observed in 21.0% (13 of 62) of subjects in the iptacopan-continued population and 15.6% (15 of 96) of subjects in the iptacopan-treated population. Hemolysis-related adverse events that occurred in ≥2 subjects in either population were breakthrough haemolysis (6 subjects in the iptacopan-continued population and 7 subjects in the iptacopan-treated population; the same order, hereinafter), blood lactate dehydrogenase increased (6 subjects and 6 subjects), and jaundice (1 subject and 2 subjects). There were no serious adverse events or adverse events leading to treatment discontinuation classified as hemolysis in the narrow sense. In the Japanese population, there were no adverse events of hemolysis. In the entire treatment period of Study C12301, hemolysis in the broad sense was observed in 7.5% (3 of 40) of subjects (breakthrough haemolysis in 2 subjects and blood creatinine increased in 1 subject). Of these, the event (breakthrough haemolysis) in 1 subject was the only serious adverse event, and it was not assessed as an adverse drug reaction and resolved. There were no adverse events of hemolysis leading to treatment discontinuation.

[56)] Events classified as the MedDRA/J HLT "haemolyses NEC," or as the MedDRA/J PT "blood creatinine increased," "blood lactate dehydrogenase increased," "haemoglobin decreased," or "haemolytic anaemia."

[57)] Events classified as the MedDRA/J PT "breakthrough haemolysis," "haemolysis," "extravascular haemolysis," "intravascular haemolysis," "haemoglobinaemia," "haemolysis neonatal," or "jaundice acholuric."

Concerning adverse events of hemolysis associated with discontinuation of iptacopan treatment, there was only 1 discontinued subject (study discontinuation due to pregnancy) in the iptacopan group in the primary evaluation period of Study C12302. This subject was switched from iptacopan to a complement C5 inhibitor, and did not develop hemolysis in the broad sense after discontinuation of iptacopan treatment. In the treatment extension period of Study C12302, 2 subjects discontinued the treatment with iptacopan during the study period or at the end of the study. Both subjects were switched from iptacopan to a complement C5 inhibitor, and 1 of them developed an adverse event of hemolysis after discontinuation of iptacopan treatment. This subject did not enter the roll-over extension program (Study C12001B) after completing Study C12302. After switching to a complement C5 inhibitor, the subject had a decrease in Hb level and required red blood cell transfusion. In Study C12301, none of the subjects discontinued the treatment with iptacopan.

The above results indicate that there are no safety concerns about hemolysis during iptacopan treatment because the incidence of hemolysis was lower in the iptacopan group than the complement C5 inhibitor group. Concerning hemolysis after discontinuation of iptacopan treatment, there are limitations to the evaluation because the number of discontinued subjects is limited. However, since 1 subject developed hemolysis after discontinuation of iptacopan treatment, and that hemolysis is also considered a potential risk in the use of other complement inhibitors, hemolysis may occur after treatment discontinuation in the use of iptacopan. Precautionary statements will therefore be included in the package insert to the effect that attention should be paid to signs and symptoms of hemolysis after treatment discontinuation. The $t_{1/2}$ (mean ± standard deviation) following multiple oral doses of iptacopan 200 mg BID is 25 ± 11 hours [see Section 6.2.2], suggesting that iptacopan is eliminated in approximately 2 weeks after the last dose of iptacopan in most patients. Therefore, attention should be paid to signs and symptoms of hemolysis for 2 weeks after discontinuation of iptacopan treatment.

PMDA's view:
Since the incidence of hemolysis was lower in the iptacopan group than in the complement C5 inhibitor group in the primary evaluation period of Study C12302, the risk of hemolysis during iptacopan treatment is not greater than that with compliment C5 inhibitors. Concerning the risk of hemolysis after discontinuation of iptacopan treatment, since iptacopan may cause more serious hemolysis as with complement C5 inhibitors, the applicant's response (precautionary statements will be included in the package insert to the effect that attention should be paid to signs and symptoms of hemolysis for 2 weeks after discontinuation of iptacopan treatment, taking the timing of elimination into consideration) is reasonable.

7.R.2.3.3 Thrombosis

The applicant's explanation about thrombosis:
Thrombosis-related adverse events[58)] were observed in 1.6% (1 of 62) of subjects (transient ischaemic attack and hemiparesis) in the iptacopan group but not in the complement C5 inhibitor group in the primary evaluation period of Study C12302. In the entire treatment period, thrombosis-related adverse events were observed in

[58)] Events classified as the MedDRA/J SMQ "embolic and thrombotic events (broad)" or as the PT "angina pectoris."

3.2% (2 of 62) of subjects (transient ischaemic attack in 2 subjects and hemiparesis in 1 subject; 1 subject developed ≥1 event) in the iptacopan-continued population, and 3.1% (3 of 96) of subjects (transient ischaemic attack in 2 subjects, and hemiparesis and portal vein thrombosis in 1 subject each; 1 subject developed ≥1 event) in the iptacopan-treated population. Serious adverse events were observed in 1.6% (1 of 62) of subjects (transient ischaemic attack) in the iptacopan group in the primary evaluation period, and in 1.6% (1 of 62) of subjects (transient ischaemic attack) in the iptacopan-continued population and 2.1% (2 of 96) of subjects (transient ischaemic attack and portal vein thrombosis in 1 subject each) in the iptacopan-treated population in the entire treatment period. None of these were assessed as adverse drug reactions and all of the events resolved. There were no adverse events leading to treatment discontinuation throughout the administration period. In the Japanese population, there were no thrombosis-related adverse events. In Study C12301, no thrombosis-related adverse events were observed throughout the administration period.

In view of the above, the applicant considers it unnecessary to provide particular precautions regarding thrombosis during iptacopan treatment.

PMDA's view:
On the basis of the incidence of thrombosis-related adverse events in Studies C12302 and C12301, and the applicant's explanation, treatment with iptacopan is unlikely to increase the risk of thrombosis, and the applicant's policy not to provide precautions regarding thrombosis is therefore reasonable.

7.R.2.3.4 Platelet count decreased

The applicant's explanation about platelet count decreased:
Adverse events of platelet count decreased[59)] were observed in 6.5% (4 of 62) of subjects (thrombocytopenia in 3 subjects and platelet count decreased in 1 subject) in the iptacopan group, but not in the complement C5 inhibitor group in the primary evaluation period of Study C12302; there were no serious adverse events or adverse events leading to treatment discontinuation. In the entire treatment period, adverse events of platelet count decreased were observed in 6.5% (4 of 62) of subjects (thrombocytopenia in 3 subjects and platelet count decreased in 1 subject) in the iptacopan-continued population, and 9.4% (9 of 96) of subjects (thrombocytopenia in 5 subjects and platelet count decreased in 4 subjects) in the iptacopan-treated population. A serious adverse event was observed in 1 subject (platelet count decreased) in the iptacopan-treated population. The event was assessed as an adverse drug reaction and did not resolve. Since this subject had Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 platelet count decreased at baseline, the underlying disease, etc. may have affected the onset of the event. There were no adverse events leading to treatment discontinuation throughout the administration period. In the Japanese population, there were no adverse events of platelet count decreased. In Study C12301, no adverse events of platelet count decreased were observed throughout the administration period.

[59)] Events classified as the MedDRA/J PT "platelet count decreased" or "thrombocytopenia."

The above results indicate that there were no significant concerns about platelet count decreased during iptacopan treatment. The occurrence of platelet count decreased during iptacopan treatment in clinical studies will be described under “Other Adverse Reactions” in the package insert to provide precautions.

PMDA’s view:

Although the incidence of adverse events of platelet count decreased was higher in the iptacopan group than the complement C5 inhibitor group in the primary evaluation period of Study C12302, platelet count decreased observed at baseline in 1 subject was the only serious adverse drug reaction, suggesting that the risk of platelet count decreased does not compromise the usefulness of iptacopan. The applicant’s explanation that the incidence of platelet count decreased will be described under “Other Adverse Reactions” in the package insert to provide precautions, is therefore reasonable.

7.R.2.3.5 Dyslipidemia

The applicant’s explanation about dyslipidemia:

Concerning dyslipidemia, Table 49 shows changes in lipid parameters (total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides) in Studies C12302 and C12301. In Study C12302, these parameters showed almost no changes from baseline in the complement C5 inhibitor group, but tended to increase at Week 24 or 48 compared to those at baseline in iptacopan-treated subjects. Table 50 shows the proportion of subjects with lipid parameters exceeding the ULN[60)] after the start of the study treatment. In the primary evaluation period of Study C12302, lipid parameters tended to be higher in the iptacopan group than the complement C5 inhibitor group. These parameters also tended to be high following administration of iptacopan in the entire treatment period in Studies C12302 and C12301. There were no subjects with total cholesterol or triglyceride levels of CTCAE Grade 2 at baseline in either study. Such levels were not observed in the complement C5 inhibitor group of Study 12302 even after the start of the study treatment, but were observed in iptacopan-treated subjects after the start of the study treatment (1 subject for cholesterol [Study C12302] and 5 subjects for triglycerides [4 in Study C12302 and 1 in Study C12301]). There were no subjects with total cholesterol or triglyceride levels of CTCAE Grade ≥3 in either study. The LDL cholesterol level was >160 mg/dL at baseline only in 1 subject in the iptacopan group in Study C12302. Such levels were observed in 16 iptacopan-treated subjects after the start of the study treatment (14 subjects in Study C12302 and 2 subjects in Study C12301) and 6 of them (all in Study C12302) had LDL cholesterol levels >190 mg/dL. In the complement C5 inhibitor group, there were no subjects with LDL cholesterol levels >160 mg/dL either at baseline or after the start of the study treatment.

60) Total cholesterol, 200 mg/dL; LDL cholesterol, 130 mg/dL; triglycerides, 149 mg/dL.

Table 49. Changes in lipid parameters (SAF and long-term SAF)

	Study C12302			Study C12301
	Primary evaluation period		Entire treatment period	Entire treatment period
	Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)	Iptacopan-treated population (N = 96)	Iptacopan (N = 40)
Total cholesterol (mg/dL)				
Baseline	157.8 ± 31.18 (62)	137.2 ± 35.06 (35)	151.5 ± 32.61 (96)	163.1 ± 33.84 (40)
Week 24	195.4 ± 39.54 (60)	139.1 ± 32.81 (34)	188.5 ± 43.57 (92)	179.9 ± 28.15 (40)
Week 48			192.5 ± 38.77 (59)	173.5 ± 33.25 (39)
LDL cholesterol (mg/dL)				
Baseline	80.8 ± 23.96 (61)	66.9 ± 29.20 (35)	76.1 ± 26.13 (95)	85.9 ± 30.73 (40)
Week 24	113.4 ± 36.76 (59)	67.6 ± 29.13 (33)	108.9 ± 39.83 (90)	105.0 ± 26.86 (39)
Week 48			110.0 ± 33.64 (58)	98.9 ± 27.07 (38)
Triglycerides				
Baseline	104.6 ± 43.44 (61)	99.1 ± 38.40 (35)	102.8 ± 42.43 (95)	96.2 ± 40.34 (40)
Week 24	122.5 ± 64.71 (59)	100.3 ± 37.74 (33)	120.0 ± 58.67 (90)	112.5 ± 48.36 (39)
Week 48			121.3 ± 65.60 (58)	118.0 ± 72.77 (38)

Mean ± standard deviation (No. of subjects evaluated)

Table 50. Proportion of subjects with lipid parameters exceeding the ULN (SAF and long-term SAF)

	Study C12302			Study C12301
	Primary evaluation period		Entire treatment period	Entire treatment period
	Iptacopan (N = 62)	Complement C5 inhibitor (N = 35)	Iptacopan-treated population (N = 96)	Iptacopan (N = 40)
Total cholesterol				
Baseline	12.9 (8/62)	5.7 (2/35)	10.4 (10/96)	15.0 (6/40)
After the start of study treatment[a)]	48.4 (30/62)	11.4 (4/35)	49.0 (47/96)	40.0 (16/40)
LDL cholesterol				
Baseline	1.6 (1/61)	5.7 (2/35)	3.2 (3/95)	10.0 (4/40)
After the start of study treatment[a)]	32.8 (20/61)	8.6 (3/35)	33.7 (32/95)	35.0 (14/40)
Triglycerides				
Baseline	14.8 (9/61)	14.3 (5/35)	12.6 (12/95)	7.5 (3/40)
After the start of study treatment[a)]	32.8 (20/61)	20.0 (7/35)	34.7 (33/95)	42.5 (17/40)

Proportion of subjects, % (No. of applicable subjects/No. of subjects evaluated)
a) Based on the worst value after the start of the study treatment.

Dyslipidemia-related adverse events[61)] were observed in 3.2% (2 of 62) of subjects (blood cholesterol increased, low density lipoprotein increased, and hypercholesterolaemia in 1 subject each; 1 subject developed ≥1 event) only in the iptacopan group in the primary evaluation period of Study C12302, and 3.1% (3 of 96) of subjects (blood cholesterol increased, low density lipoprotein increased, hypercholesterolaemia, and hypertriglyceridaemia in 1 subject each; 1 subject developed ≥1 event) in the iptacopan-treated population in the entire treatment period of Study C12302. Of these, 2 events (blood cholesterol increased and low-density lipoprotein increased) in 1 subject were adverse drug reactions, but the treatment with iptacopan was continued. This subject had been complicated by hyperlipidemia since approximately 1 year before the start of the study treatment. Blood cholesterol increased did not resolve, and low-density lipoprotein increased resolved. In Study C12302, there were no dyslipidemia-related serious adverse events or adverse events leading to treatment discontinuation. In the entire treatment period of Study C12301, dyslipidemia-related adverse events were

61) Events classified as the MedDRA/J PT "blood cholesterol increased," "blood triglycerides increased," "hypercholesterolaemia," "hyperlipidaemia," "hypertriglyceridaemia," "intermediate density lipoprotein increased," "lipids increased," "lipoprotein (a) increased," "low-density lipoprotein increased," "non-high-density lipoprotein cholesterol increased," total cholesterol/HDL ratio increased," or "very low-density lipoprotein increased."

observed in 7.5% (3 of 40) of subjects (hyperlipidaemia in 2 subjects and blood triglycerides increased in 1 subject). Of these, the event (blood triglycerides increased) in 1 subject was assessed as an adverse drug reaction, but the treatment with iptacopan was continued. The event was resolving. In Study C12301, there were no dyslipidemia-related serious adverse events or adverse events leading to treatment discontinuation.

In the primary evaluation period of Study C12302, lipid parameters increased in the iptacopan group. However, all mean values at Weeks 24 and 48 were within the respective reference ranges, and there were few dyslipidemia-related adverse events. In patients with anemia, a positive correlation between total cholesterol and Hb levels was reported (*Am J Med Sci*. 2007;334:331-333), and increases in total cholesterol and LDL cholesterol levels were also positively correlated with the increase in Hb level in iptacopan-treated subjects in Study C12302.[62)] Therefore, the increase in Hb level and anemia correction due to iptacopan treatment may have led to increased total cholesterol and LDL cholesterol levels. Since attention should be paid to increases in total cholesterol and LDL cholesterol levels, information will be provided in the package insert to the effect that treatment with iptacopan may increase total cholesterol and LDL cholesterol levels. Adverse events related to triglyceride levels[63)] were observed in 1 subject in Study C12302 and 3 subjects in Study C12301, but all of the events were mild. The applicant therefore considers it unnecessary to include precautionary statements regarding triglyceride levels in the package insert.

PMDA's view:
Concerning the increases in lipid parameters observed in Studies C12302 and C12301, although the mean values were within the respective reference ranges, the proportion of subjects with levels exceeding the ULN tended to be higher in the iptacopan group. Particularly for LDL cholesterol, there were subjects with levels >190 mg/dL. Therefore, treatment with iptacopan may increase the risk of dyslipidemia such as hyper-LDL-cholesterolemia. The package insert should therefore include a precautionary statement to the effect that blood tests should be performed on a regular basis during iptacopan treatment.

7.R.2.3.6 Hypersensitivity

The applicant's explanation about hypersensitivity:
For hypersensitivity, adverse events classified under the MedDRA/J SMQ "hypersensitivity (narrow)" were observed in 8.1% (5 of 62) of subjects (rash erythematous in 2 subjects, and dermatitis acneiform, rash macular, rhinitis allergic, eczema, and swelling face in 1 subject each; 1 subject developed ≥1 event) in the iptacopan group, and 2.9% (1 of 35) of subjects (drug hypersensitivity) in the complement C5 inhibitor group in the primary evaluation period of Study C12302. In the entire treatment period of Study C12302, such events were observed in 11.3% (7 of 62) of subjects (rash erythematous in 2 subjects, and dermatitis acneiform, rash macular, dermatitis allergic, rhinitis allergic, rash, eczema, and swelling face in 1 subject; 1 subject developed ≥1 event) in the iptacopan-continued population, and 8.3% (8 of 96) of subjects (rash erythematous in 2 subjects, and dermatitis acneiform, rash macular, dermatitis allergic, rhinitis allergic, rash, eczema, swelling face, and

62) For all scheduled visits in the primary evaluation period of Study C12302, correlations between the change from baseline in Hb level and changes from baseline in total cholesterol and LDL cholesterol levels were investigated. As a result, the overall correlation coefficient for the combined iptacopan and complement C5 inhibitor group was 0.61 for total cholesterol and Hb, and 0.59 for LDL cholesterol and Hb.
63) Events classified as the MedDRA/J PT "blood triglycerides increased," "hyperlipidaemia," "hypertriglyceridaemia," or "lipids increased."

infusion-related reaction in 1 subject each; some subjects developed ≥1 event) in the iptacopan-treated population. Of these, 3 events (rash erythematous, dermatitis acneiform, and rash macular) in 1 subject in the primary evaluation period of Study C12302 were adverse drug reactions. Dermatitis acneiform did not resolve, but both other events resolved. In the treatment extension period of Study C12302, no new adverse drug reactions were observed. In the primary evaluation period and the treatment extension period of Study C12302, there were no serious adverse events or adverse events leading to treatment discontinuation. In the Japanese population of Study C12302, events classified under "hypersensitivity (narrow)" were observed in 2 subjects (eczema and rhinitis allergic in 1 subject each) in the iptacopan group in the primary evaluation period. All of these events were non-serious, and none were assessed as adverse drug reactions. In the treatment extension period of Study C12302. no new adverse events were observed in the Japanese population. In the entire treatment period of Study C12301, events classified under "hypersensitivity (narrow)" were observed in 10.0% (4 of 40) of subjects (dermatitis allergic in 2 subjects, and rash, erythema multiforme, rash maculo-papular, and urticaria in 1 subject; some subjects developed ≥1 event). There were no adverse drug reactions, serious adverse events, or adverse events leading to treatment discontinuation.

In view of the above, the applicant considers it unnecessary to provide particular precautions regarding hypersensitivity during iptacopan treatment.

PMDA's view:
Although hypersensitivity was observed during iptacopan treatment in clinical studies, the event was not assessed as an adverse drug reaction in all subjects, except for 1, and there were no serious adverse events or adverse events leading to treatment discontinuation. Therefore, the applicant's explanation (it is unnecessary to include particular precautionary statements regarding hypersensitivity in the package insert at present) is reasonable.

7.R.2.3.7 Effects on the thyroid gland

The applicant's explanation about effects on the thyroid gland:
Effects on the thyroid gland were investigated because hypertrophy of thyroid follicular epithelial cells, increased thyroid weight, and minimal, transient changes in hormone concentration were observed in repeated-dose toxicity studies in rats and dogs [see Section 5.2]. Of the adverse events observed in the primary evaluation period of Study C12302, only the event (hypothyroidism) in 1 subject in the iptacopan group was classified as the MedDRA/J SMQ "hypothyroidism (broad)." The event was not assessed as an adverse drug reaction, and the study treatment was continued (the event did not resolve). In the Japanese population, there were no events classified as the MedDRA/J SMQ "hypothyroidism (broad)." Of the adverse events observed in the primary evaluation period of Study C12301, only the event (reverse tri-iodothyronine increased) in 1 subject was classified as "hypothyroidism (broad)." The event was assessed as an adverse drug reaction, but the study treatment was continued (the event resolved). In the treatment extension periods of Studies C12302 and C12301, no new events classified as "hypothyroidism (broad)" were observed. There were no serious adverse events in either study.

In view of the above, the applicant considers it unnecessary to include precautionary statements regarding the effects of iptacopan treatment on the thyroid gland in the package insert at present.

PMDA's view:
Of the adverse events that occurred in clinical studies, events in 2 subjects were classified as "hypothyroidism (broad)." The event in 1 subject was assessed as an adverse drug reaction, but there were no serious adverse events or adverse events leading to treatment discontinuation. Therefore, the applicant's explanation (it is unnecessary to include precautionary statements regarding effects on the thyroid gland in the package insert at present) is reasonable.

7.R.2.3.8 Effects on the testes

The applicant's explanation about effects on the testes:
Effects on the testes were investigated because testicular toxicities (degeneration of the seminiferous tubule and cell debris in the epididymal duct lumen) were observed in repeated-dose toxicity studies in rats and dogs [see Section 5.2]. Adverse events related to degeneration of the seminiferous tubule[64)] were not observed in Study C12302. In the primary evaluation period of Study C12301, blood follicle-stimulating hormone increased and dihydrotestosterone decreased were observed in 1 subject. Both of these adverse events were assessed as adverse drug reactions, but were non-serious and mild, and the study treatment was continued. One event was resolving and the other resolved. In the treatment extension period of Study C12301, there were no adverse events related to degeneration of the seminiferous tubule.

In view of the above, the applicant considers it unnecessary to include precautionary statements regarding the effects of iptacopan treatment on the testes in the package insert at present.

PMDA's view:
Although an adverse event related to degeneration of the seminiferous tubule was observed in 1 subject and assessed as an adverse drug reaction in clinical studies, the event was non-serious and mild, and did not lead to discontinuation of the study treatment. Therefore, the applicant's explanation (it is unnecessary to include precautionary statements regarding effects on the testes in the package insert at present) is reasonable.

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64) Events observed in male subjects and classified as any of the following MedDRA/J PTs:
Aspermia, asthenospermia, azoospermia, blood follicle stimulating hormone abnormal, blood follicle stimulating hormone decreased, blood follicle stimulating hormone increased, blood luteinising hormone abnormal, blood luteinising hormone decreased, blood luteinising hormone increased, blood testosterone abnormal, blood testosterone decreased, blood testosterone free abnormal, blood testosterone free decreased, blood testosterone free increased, blood testosterone increased, dihydrotestosterone decreased, dihydrotestosterone increased, follicle stimulating hormone deficiency, gonadotrophin deficiency, hypogonadism, hypogonadism male, hypospermia, infertility male, luteinising hormone deficiency, microorchidism, necrospermia, oligoasthenoteratozoospermia, oligoasthenozoospermia, primary hypogonadism, pyospermia, secondary hypogonadism, semen analysis abnormal, semen liquefaction abnormal, semen liquefaction prolonged, semen liquefaction shortened, semen viscosity abnormal, semen viscosity decreased, semen viscosity increased, semen volume abnormal, semen volume decreased, semen volume increased, sperm analysis abnormal, sperm concentration abnormal, sperm concentration decreased, sperm concentration zero, spermatic cord pain, spermatozoa abnormal, spermatozoa morphology abnormal, spermatozoa progressive motility abnormal, spermatozoa progressive motility decreased, teratospermia, testicular atrophy, testicular disorder, testicular failure, testicular failure primary, testicular hyperfunction, testicular hypertrophy, testicular mass, testicular necrosis, testicular oedema, testicular pain, testicular scan abnormal, testicular swelling, testis discomfort, testotoxicosis, total sperm count decreased, ultrasound prostate abnormal, and ultrasound testes abnormal.

7.R.3 Clinical positioning and indication

The applicant's explanation about the clinical positioning and indication of iptacopan:

In Japan, drug therapy for PNH consisted mainly of complement C5 inhibitors, and these drugs are effective in reducing symptoms and complications in patients with PNH. However, since complement C5 inhibitors inhibit only the terminal complement pathway, C3, which is upstream of the complement pathway, accumulates (and causes opsonization) on the membrane of PNH red blood cells, which induces extravascular hemolysis. Thus, anemia is not satisfactorily corrected in some patients. Iptacopan is a complement inhibitor that regulates both intravascular and extravascular hemolysis by binding to the active site of FB upstream of the complement pathway, to inhibit the degradation of C3 convertase and thereby preventing AP activation. Iptacopan is administered by the oral route, which may reduce the treatment burden on patients, including frequent hospital visits and local site reactions associated with injections.

Concerning the efficacy of iptacopan, its superiority over complement C5 inhibitors was demonstrated in Study C12302 in patients with PNH who have an inadequate response to complement C5 inhibitors (eculizumab or ravulizumab) [see Section 7.R.1.1]. The efficacy of iptacopan was demonstrated in Study C12301 in complement inhibitor treatment-naïve patients with PNH, although no Japanese subjects were enrolled in the study [see Section 7.R.1.2]. Concerning the safety of iptacopan, its safety profile was similar to that of complement C5 inhibitors in Study C12302, and the safety of iptacopan is considered manageable if it is used under the supervision of a physician who has adequate knowledge of PNH, as with existing complement inhibitors [see Section 7.R.2]. In Study C12302, the efficacy and safety of iptacopan in the Japanese population showed no major differences that may cause clinical concerns, compared with those in the entire population [see Sections 7.R.1.1 and 7.R.2].

In view of the above, considering that iptacopan can be positioned as a treatment option for patients with PNH with or without prior treatment with complement C5 inhibitors, the indication for iptacopan was set as "paroxysmal nocturnal hemoglobinuria."

PMDA's view:

The superiority of iptacopan over complement C5 inhibitors was demonstrated in Study C12302 in patients with PNH who had an inadequate response to complement C5 inhibitors, and the efficacy of iptacopan in the Japanese population can be considered generally consistent with that in the entire population [see Section 7.R.1.1]. In addition, there were no trends towards significantly inferior safety in the iptacopan group, compared with the complement C5 inhibitor group, and the safety of iptacopan is manageable if it is used under the supervision of a physician who has adequate knowledge of PNH, as with the case of eculizumab and ravulizumab [see Section 7.R.2]. Iptacopan can therefore be clinically used as a drug for the treatment of PNH in patients with an inadequate response to complement C5 inhibitors. On the other hand, although the efficacy of iptacopan was suggested in Study C12301 in complement inhibitor treatment-naïve patients with PNH, Japanese subjects were not enrolled in the study, and the efficacy in Japanese complement inhibitor treatment-naïve patients with PNH is unknown [see Section 7.R.1.2]. Therefore, it is reasonable to position iptacopan as a treatment option for patients with PNH who have an inadequate response to complement C5 inhibitors.

In view of the above, it is appropriate to set the indication of iptacopan as "paroxysmal nocturnal hemoglobinuria," and then include a precautionary statement in "Precautions Concerning Indication" to the effect that iptacopan should be used in patients with an inadequate response even on appropriate treatment with a complement C5 inhibitor." Regarding the clinical positioning and indication of iptacopan, and the descriptions in "Precautions Concerning the Indication," a final decision will be made based on the discussions at the Expert Discussion.

7.R.4 Dosage and administration

The applicant's explanation about the dosage and administration of iptacopan:

In the foreign phase II study in patients with PNH who had an inadequate response to eculizumab (Study X2201) [see Section 6.2.4], coadministration of eculizumab and iptacopan 200 mg BID (Cohort 1) decreased LDH levels to below the ULN in 60.0% (6 of 10) of subjects at Week 13. In the foreign phase II study in complement inhibitor treatment-naïve patients with PNH (Study X2204) [see Section 6.2.5], all subjects treated with iptacopan 25 mg or 50 mg BID for 4 weeks, followed by iptacopan100 mg or 200 mg experienced a response defined as "decrease in LDH by ≥60% from baseline or to below the ULN by Week 12," assessed as the primary endpoint (12 subjects [7 in the iptacopan 25/100 mg group and 5 in the 50/200 mg group]). In both studies, administration of iptacopan 200 mg BID posed no particular safety concerns. In the Japanese phase I study in Japanese healthy adults (Study X1102), there were no particular safety concerns when iptacopan was administered as a single dose of 25 to 400 mg.

In view of the above, the 200 mg BID dose of iptacopan was employed in Study C12302, and Japanese patients were also enrolled in the study.

The results of Study C12302 demonstrated the efficacy of iptacopan [see Section 7.R.1.1], and there were no clinically significant concerns about the safety of iptacopan compared with that of eculizumab and ravulizumab [see Section 7.R.2]. The efficacy and safety of iptacopan in the Japanese population also showed no differences that may cause clinical concerns compared with those in the entire population. The applicant therefore considers that the recommended dosage and administration is iptacopan 200 mg BID, as in Study C12302.

PMDA's view:

It is appropriate to select iptacopan 200 mg BID as the usual dosage and administration in Japan, since (a) Study C12302 demonstrated the efficacy of iptacopan 200 mg BID and also showed consistent results between the entire population and the Japanese population [see Section 7.R.1.1], and (b) the safety of iptacopan was considered manageable if appropriate measures are taken to respond to the risks associated with iptacopan under the supervision of a physician who has adequate knowledge of PNH [see Section 7.R.2].

7.R.5 Post-marketing investigations

The applicant plans to conduct a specified use-results survey covering all patients treated with iptacopan, as shown in Table 51, after the market launch.

Table 51. Outline of specified use-results survey (draft)

Objective	To confirm the safety and efficacy of iptacopan in patients with PNH in the clinical setting.
Survey method	All-case surveillance
Population	All patients with PNH treated with iptacopan
Target sample size	100 patients for safety analysis
Observation period	48 weeks
Main survey items	• Patient characteristics: Age, sex, date of PNH diagnosis, past history (including meningococcal infection), status of vaccination (against *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae*), prior treatment for PNH, status of blood transfusion, concurrent illness, etc. • Status of iptacopan treatment: Administration period, daily dose, status of continuation/discontinuation (including the reason for discontinuation) • Concomitant drugs/therapies • Course: Hb, LDH, indirect bilirubin, blood transfusion (yes/no), etc. • Adverse events: Date of onset, seriousness, outcome, relationship to iptacopan, action taken for iptacopan, etc.

PMDA's view:

Japanese patients with PNH treated with iptacopan in Study C12302 are extremely limited, and the incidence of encapsulated bacterial infections and hemolysis after discontinuation of iptacopan treatment is therefore not clear. The applicant should continuously investigate the incidence of these events and their risk factors, etc., even in the post-marketing setting, because they affect the risk-benefit balance of iptacopan treatment. In addition, since such information should desirably be provided to healthcare professionals as quickly as possible so that it can be used to determine the appropriateness of the use of iptacopan, a post-marketing survey covering all treated patients should be conducted, as proposed by the applicant.

8. Results of Compliance Assessment Concerning the New Drug Application Data and the Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to document-based inspection and data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there are no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there are no obstacles to conducting the review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that iptacopan has efficacy in the treatment of paroxysmal nocturnal hemoglobinuria, and that iptacopan has acceptable safety in view of its benefits. Iptacopan is clinically meaningful because it offers a new treatment option for patients with paroxysmal nocturnal hemoglobinuria. PMDA considers that the appropriateness of the target patient population for iptacopan and precautionary statements should be further disscussed.

PMDA has concluded that iptacopan may be approved if it is not considered to pose any particular problems based on the comments of the Expert Discussion.

Review Report (2)

May 17, 2024

Product Submitted for Approval

Brand Name	Fabhalta Capsules 200 mg
Non-proprietary Name	Iptacopan Hydrochloride Hydrate
Applicant	Novartis Pharma K.K.
Date of Application	August 7, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

At the Expert Discussion, the expert advisors supported the PMDA's conclusion described in Section "7.R.1 Efficacy" of the Review Report (1).

1.2 Safety

At the Expert Discussion, the expert advisors supported the PMDA's conclusion described in Section "7.R.2 Safety" of the Review Report (1).

In view of the discussions at the Expert Discussion, PMDA concluded that to the applicant should include the following precautionary statements in the Warnings section of the package insert. The applicant responded accordingly.

Warnings

1. Inhibition of the complement pathway by iptacopan may cause serious infections with encapsulated bacteria such as *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae*. Meningococcal infection, in particular, can rapidly become severe and may result in death. Due attention should be paid to the following points:
   1.1 During iptacopan treatment, the patient should be carefully monitored for early signs (e.g., pyrexia, headache, nuchal rigidity) of infection with *Meningococcus*, etc. If serious infection with

Meningococcus, etc. is suspected, the patient should be examined immediately and appropriate measures such as antibiotic treatment should be taken.

1.2 The patient's vaccination history against *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae* type b should be confirmed. If the patient's vaccination history is not confirmed or additional vaccination is required, the necessary vaccine should be administered before the start of iptacopan treatment in principle. Additional vaccination during iptacopan treatment should be considered as needed.

1.3 Meningococcal infection may lead to fatal outcome. Iptacopan should be administered under the supervision of a physician who is fully capable of managing emergencies at a suitable medical facility, or in cooperation with a medical facility where meningococcal infection can be diagnosed and treated.

1.4 The patient should be informed of the risk of infections with encapsulated bacteria such as *Meningococcus* to ensure that he/she can learn the early signs of such infections. The patient should be cautioned to contact his/her primary physician if any infection-related symptoms occur.

2. Iptacopan should be administered under the supervision of a physician with adequate knowledge of paroxysmal nocturnal hemoglobinuria only when its expected therapeutic benefits are considered to outweigh its possible risks. Prior to the start of iptacopan treatment, the patient or his/her family should be clearly informed of the efficacy of iptacopan and associated risks, including the fact that iptacopan does not completely cure the disease, to give consent.

1.3 Indication

At the Expert Discussion, the expert advisors supported the PMDA's conclusion described in Section "7.R.3 Clinical positioning and indication" of the Review Report (1).

In view of the discussions at the Expert Discussion, PMDA concluded that it is appropriate to set the indication of the product, as proposed by the applicant for the new drug application, and provide descriptions in "Precautions Concerning Indication," as shown below. The applicant responded accordingly.

Indication

Paroxysmal nocturnal hemoglobinuria

Precautions Concerning Indication

1. Iptacopan should be used in patients with an inadequate response to even appropriate treatment with a complement (C5) inhibitor.
2. Iptacopan binds to complement factor B to inhibit the alternative complement pathway. Patients treated with iptacopan may therefore be susceptible to infections with encapsulated bacteria such as *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae*. Iptacopan should be used in eligible patients by a physician with a full understanding of its efficacy and safety after carefully assessing the appropriateness of the use of iptacopan. To initiate treatment with iptacopan, The patient's vaccination history against *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae* type b should be confirmed. If it is not confirmed or additional vaccination is required, the necessary vaccine should be administered

at least 2 weeks before the start of iptacopan treatment in principle. Additional vaccination during iptacopan treatment should be considered as needed.

1.4 Dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusion described in Section "7.R.4 Dosage and administration" of the Review Report (1).

In view of the discussions at the Expert Discussion, PMDA concluded that the dosage and administration of the product should be set as proposed by the applicant for the new drug application, and that precautionary statements in "Precautions Concerning Dosage and Administration" should be provided as shown below, taking the dosing interval relative to prior treatment specified in the protocol of the global phase III study (Study C12302) into account. The applicant responded accordingly.

Dosage and Administration

The usual adult dosage is 200 mg of iptacopan administered orally twice daily.

Precautions Concerning Dosage and Administration

When switching from a complement (C5) inhibitor to iptacopan, the later therapy should be started, considering the dosing interval relative to prior treatment, to reduce the risk of hemolysis associated with discontinuation of the complement (C5) inhibitor.

- Patients on prior eculizumab (genetical recombination) regimen should start treatment with iptacopan 1 week after the last dose of eculizumab (genetical recombination).
- Patients on prior ravulizumab (genetical recombination) regimen should start treatment with iptacopan around 6 weeks after the last dose of ravulizumab (genetical recombination).

1.5 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion described in Section "7.R.5 Post-marketing investigations" of the Review Report (1).

Regarding the current risk management plan (draft) of the product, PMDA concluded that infections, including meningococcal infection and other encapsulated bacterial infections, and hemolysis after discontinuation of iptacopan treatment are important risks in the use of iptacopan in view of the reviews in Section "7.R.2 Safety" of the Review Report (1) and Section 1.2 of the Review Report (2). Regarding the infection-related risk, the applicant explained that "pneumococcal infection" will be specified as an important identified risk, because the mechanism of action of iptacopan and the serious bacterial pneumonia reported as an infection probably due to *Pneumococcus* in 2 subjects in the PNH pooled analysis suggest a definite relationship between pneumococcal infection and iptacopan, and that "meningococcal infection," "infections (other than pneumococcal infection and meningococcal infection)," and "serious hemolysis after discontinuation of iptacopan treatment" will be specified as important potential risks, because the relationship between these events and iptacopan has not been fully confirmed based on their incidence in clinical studies or other evidence.

PMDA concluded that these decisions by the applicant are reasonable, and that the safety and efficacy specifications should be set as shown in Table 52 and the additional pharmacovigilance activities and additional risk minimization activities as shown in Table 53 should be conducted. PMDA also concluded that the planning of the specified use-results surveys shown in Table 54 is reasonable.

Table 52. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Pneumococcal infection	• Meningococcal infection • Infections (other than pneumococcal infection and meningococcal infection) • Serious hemolysis due to discontinuation of iptacopan treatment	• None
Efficacy specifications		
• None		

Table 53. Summary of additional pharmacovigilance activities and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance)	• Provision of information collected through early post-marketing phase vigilance • Preparation and provision of materials for healthcare professionals • Preparation and provision of materials for patients

Table 54. Outline of specified use-results survey (draft)

Objective	To confirm the safety and efficacy of iptacopan in patients with PNH in the clinical setting.
Survey method	All-case surveillance
Population	All patients with PNH treated with iptacopan
Target sample size	100 patients for safety analysis
Observation period	48 weeks
Main survey items	• Patient characteristics: Age, sex, date of diagnosis of PNH, past history (including meningococcal infection), status of vaccination (against *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae*), prior treatment for PNH, status of blood transfusion, concurrent illness, laboratory tests (white blood cell count, red blood cell count, etc.), etc. • Status of iptacopan treatment: Duration of administration, daily dose, status of continuation/discontinuation (including the reason for discontinuation) • Concomitant drugs/therapies • Course: Hb, LDH, indirect bilirubin, blood transfusion (yes/no), etc. • Adverse events: Date of onset, seriousness, outcome, relationship to iptacopan, action taken for iptacopan, clinical course, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

Paroxysmal nocturnal hemoglobinuria

Dosage and Administration

The usual adult dosage is 200 mg of iptacopan administered orally twice daily.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since the number of Japanese patients treated with the product in clinical studies is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a specified number of patients have been accrued. The purposes of the survey are to identify the characteristics of these patients and to collect safety and efficacy data on the product without delay, thereby taking the necessary measures to facilitate the proper use of the product.
3. Prior to market launch, the applicant is required to take necessary measures to ensure that the product is used only at a suitable medical institution and only under the supervision of a physician who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks, etc. associated with the product, in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

Appendix

List of Abbreviations

aHUS	Atypical hemolytic uremic syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Alternative complement pathway
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
$AUC_{0\text{-}inf}$	AUC up to infinity
AUC_{tau}	AUC from time of administration to the end of the dosing interval
Bb	Fragment Bb of Factor B
BCRP	Breast cancer resistance protein
BID	bis in die
BSEP	bile salt export pump
C3	Complement component 3
C3a, C3b	An active metabolite of C3
C3d	C3 breakdown product
C3G	C3 glomerulopathy
C5	Complement component 5
C5a, C5b	An active metabolite of C5
Ca	Calcium
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent clearance after administration of the drug
CL_{int}	Intrinsic clearance
$CL_{int,app}$	Apparent intrinsic clearance
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CPP	Critical process parameter
CQA	Critical quality attribute
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
DMSO	Dimethylsulfoxide
DNP	Dinitrophenyl
Drug interaction guideline	“Guideline on drug interaction for drug development and appropriate provision of information” (PSEHB/PED Notification No. 0723-4 dated July 23, 2018, issued by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
EC_{50}	50% effective concentration
Eculizumab	Eculizumab (genetical recombination)
eGFR	Estimated glomerular filtration rate
EGTA	Ethylene glycol-bis(β-aminoethyl ether)-*N*,*N*,*N*’,*N*’-tetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
E_{max}	Maximum effect
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FB	Complement factor B
FMO	Flavin-containing monooxygenase

$f_{u,p}$	Fraction unbound in plasma
Fx1A	Fraction 1A
GC	Gas chromatography
Hb	Hemoglobin
hERG	Human ether-à-go-go-related gene
HLT	High level terms
HPLC	High performance liquid chromatography
iC3b	Inactivated C3b
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare)
$IndC_{50}$	Concentration of Inducer that Supports the Half Maximal Induction/Suppression
IgA	Immunoglobulin A
IgM	Immunoglobulin M
IR	Infrared absorption spectrum
ka	Absorption rate constant
K_I	Inhibitor concentration causing half-maximal inactivation
$K_{I,u}$	Unbound inhibitor concentration causing half-maximal inactivation
k_{inact}	Maximum inactivation rate constant
$K_{m,app}$	Apparent Michaelis-Menten constant
KLH	Keyhole limpet hemocyanin
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LPS	Lipopolysaccharide
MAC	Membrane attack complex
MAO	Monoamine oxidase
MATE	Multidrug and toxin extrusion
MAVE	Major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
MDCK	Madin-Darby canine kidney
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MPGN	Membranoproliferative glomerulonephritis
mRNA	Messenger ribonucleic acid
MRP2	Multidrug resistance protein 2
MS	Mass spectrum
mTOR	Mammalian target of rapamycin
NMR	Nuclear magnetic resonance spectrum
NOEL	No observed effect level
NR	Neutral red
NT-proBNP	N-terminal pro-brain natriuretic peptide
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically based pharmacokinetic

P-gp	P-glycoprotein
PIGA	Phosphatidylinositol glycan class A
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	Paroxysmal Nocturnal Hemoglobinuria
PTP	Press through packaging
QD	quaque die
QT	QT interval
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
Ravulizumab	Ravulizumab (genetical recombination)
RH	Relative humidity
SAF	Safety set
SOC	System organ class
SRBC	Sheep red blood cell
$t_{1/2}$	Elimination half-life
T3	Triiodo thyronine
T4	Thyroxine
Tg	Transgenic
t_{max}	Time to reach maximum concentration
TR-FRET	Time-resolved fluorescence resonance energy transfer
TSH	Thyroid stimulating hormone
UGT	Uridine diphosphate-glucuronosyltransferase
ULN	Upper limit of normal
UTP/UCREA	Urinary total protein/urinary creatinine
UV/VIS	Ultraviolet-visible spectrum
UVA	Ultraviolet A
Vc/F	Apparent central volume of distribution
V_{max}	Maximum reaction velocity