CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218276Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	218276
Priority or standard	PRIORITY
Submit date(s)	4/5/2023
Received date(s)	4/5/2023
PDUFA goal date	12/5/2023
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	Electronic Stamp
Established/proper name	Iptacopan
(Proposed) proprietary name	FABHALTA
Pharmacologic class	Complement inhibitor
Other product name(s)	LNP023
Applicant	NOVARTIS PHARMACEUTICAL CORP
Dosage form(s)/formulation(s)	CAPSULE
Dosing regimen	200 mg orally twice daily
Applicant-proposed indication(s)/ population(s)	for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
SNOMED CT code for proposed indication disease term(s)[1]	1963002: Paroxysmal nocturnal hemoglobinuria (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	200 mg orally twice daily
Approved indication(s)/ population(s) (if applicable)	for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
SNOMED CT code for approved indication disease term(s)1	1963002: Paroxysmal nocturnal hemoglobinuria (disorder)

[1] For internal tracking purposes only.
Abbreviations: LNP023, iptacopan; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AP	alternative pathway
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
B/P	blood-to-plasma concentration
BID	twice daily
BLA	biologics license application
BTH	breakthrough hemolysis
C3G	C3 glomerulopathy
CL	clearance
CL/F	apparent clearance
CL_r	renal clearance
C_{max}	maximum plasma concentration
CMH	Cochran–Mantel–Haenszel
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
C_{trough}	trough concentration
CV%	percent coefficient of variation
CYP	cytochrome P450
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DCOA	Division of Clinical Outcome Assessment
DDI	drug-drug interaction
DILI	drug-induced liver injury
EC_{50}	half maximal effective concentration
EC_{90}	90% maximal effective concentration
eGFR	estimate glomerular filtration rate
E_{max}	maximum effect
ETASU	elements to assure safe use
EVH	extravascular hemolysis
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy- Fatigue
FAS	full analysis set
FB	factor B
FDA	Food and Drug Administration
$F_{u,inc}$	fraction unbound in an in vitro incubation
$F_{u,p}$	fraction unbound in plasma
GCP	good clinical practice
GLP	good laboratory practice
GMR	geometric mean ratio
Hb	hemoglobin
HD	high dose
HLM	human liver microsomes

IC_{50}	half maximal inhibitory concentration
IgAN	immunoglobulin A nephropathy
IND	investigational new drug
IVH	intravascular hemolysis
IVIVE	in vitro to in vivo extrapolation
IWRES	individual weighted residuals
J_{max}	in vitro maximal transport velocity
LDH	lactic acid or lactate dehydrogenase
LDL	low density lipoprotein
MAC	membrane attack complex
MAR	missing at random
MAVE	major adverse vascular events
MD	mid dose
MMRM	mixed model for repeated measures
MRHD	maximum recommended human dose
NDA	new drug application
NOAEL	no-observed-adverse-effect-level
NPDE	normalized prediction distribution errors
ODD	orphan drug designation
PBPK	physiologically-based pharmacokinetic
PE%	percent prediction error
PD	pharmacodynamic
PI	prescribing information
PIG-A	phosphatidylinositol glycan class A
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
PSA	parameter sensitivity analysis
QD	once daily
RBC	red blood cell
RCP	randomized controlled period
REMS	risk evaluation and mitigation strategy
REP	roll-over extension program
RSE	relative standard error
RTP	randomized treatment period
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
TA	transfusion avoidance
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
U.S	United States
TMDD	target-mediated drug disposition
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
VPC	visual predictive check

I. Executive Summary

1. Summary of Regulatory Action

The Applicant, Novartis Pharmaceutical Corporation, submitted this NDA for approval of iptacopan, proposed trade name (FABHALTA), a factor B complement inhibitor, for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). The proposed dosage is 200 mg orally twice daily with or without food.

The Applicant established substantial evidence of effectiveness for the proposed indication with two adequate and well-controlled trials, one (APPLY-PNH) that demonstrated improvement in hemoglobin (Hb) and transfusion avoidance in adults previously treated with a C5 complement inhibitor, and another (APPOINT PNH), that demonstrated an improvement in Hb in a treatment-naïve population.

Similar to other complement inhibitors, iptacopan has a serious risk of encapsulated organism infections, which requires a risk evaluation and mitigation strategy (REMS) with elements to assure safe use.

The application was reviewed by a multidisciplinary review team. Each discipline recommends approval, and the signatory authority concurs that the application should be approved. The overall benefit-risk profile is favorable as described in the Benefit-Risk Framework (Table 2). Postmarketing requirements include a registry and completion of the ongoing PNH trials to further characterize the long-term safety of iptacopan.

For detailed information supporting the basis for the approval, refer to the detailed section included in this Interdisciplinary Assessment document, the product quality review and other memoranda, such as the REMS review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• PNH is a rare, serious, and life-threatening chronic disease characerized by uncontrolled complement activation resulting in hemolytic anemia, which may require blood transfusions. Other manifestations include thromboembolism, bone marrow failure, dysphagia, abdominal pain, pulmonary hypertension, renal impairment, and erectile dysfunction. • The disease is caused by somatic mutations in the PIG-A gene in hematopoietic stem cells, leading to the loss of complement inhibitor proteins CD55 and CD59 on red blood cell surfaces. The loss of complement inhibition results in complement-mediated intravascular hemolysis. Extravascular hemolysis also occurs due to complement-mediated destruction of erythrocytes by the reticuloendothelial system (macrophages in the liver and spleen). • Prior to the availability of complement inhibitors, historical studies have shown the median survival to be between 10 and 15 years from the time of diagnosis.	• PNH is a rare and chronic disease resulting in serious clinical manifestations from dysregulated complement activation, including intravascular and extravascular hemolysis, leading to severe anemia, as well as thrombosis, bone marrow failure and other systemic manifestations. • PNH requires life-long therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Patients with PNH often require support with blood transfusions and/or anticoagulation. • Three drugs have been approved for PNH, all of which are complement inhibitors. Eculizumab, approved in 2007, and ravulizumab, approved in 2018, are C5 inhibitors (targeting intravascular hemolysis). Pegectacoplan, approved in 2021, is a C3 inhibitor (targeting both intravascular and extravascular hemolysis). – Eculizumab is administered as an intravenous infusion, and increases hemoglobin and reduces the need for RBC transfusions compared to placebo. – Ravulizumab is administered either subcutaneously or by intravenous infusion and is noninferior with regard to transfusion avoidance and hemolysis (measured by LDH) compared to eculizumab. – Pegcetacoplan is administered by subcutaneous injection and is superior in change from baseline hemoglobin and noninferior in transfusion avoidance compared to eculizumab. – All three drugs have warnings in the label for serious infections and are available only through a REMS with elements to assure safe use due to a risk of meningococcal infection (C5 inhibitors) or encapsulated organism infections (C3 inhibitor). • Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for PNH, but it is associated with high mortality (~30%) and morbidity rates.	• There are two C5 inhibitors and one C3 inhibitor approved for PNH, which have shown effect in terms of hemoglobin response, transfusion avoidance, and improvement in markers of hemolysis. Approved drugs for PNH are administered intravenously or by subcutaneous injection and carry serious infection risks. • HSCT is curative but has certain eligibility requirements and substantial morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• APPLY-PNH was a randomized, open-label study in adults with PNH and residual anemia (Hb <10 g/dL) despite treatment with a stable regimen of anti-C5 treatment for at least 6 months. Ninety-seven subjects were randomized to switch to iptacopan (n=62) or to continue anti-C5 treatment (eculizumab [n=23] or ravulizumab [n=12]) throughout the duration of the 24-week randomized controlled period. – At 24 weeks of therapy, having switched to iptacopan was superior to having continued on C5-inhibitors in achieving hematologic response (sustained increase of ≥ 2 g/dL in hemoglobin levels from baseline and/or sustained hemoglobin levels ≥ 12 g/dL), along with transfusion avoidance and reduced markers of hemolysis. About 82% of the iptacopan-treated subjects had a ≥ 2 g/dL increase in hemoglobin levels from baseline in the absence of RBC transfusions compared to 0% of anti-C5 treated subjects. Transfusion avoidance (absence of RBC transfusions between Day 14 and 168) occurred in 95% of iptacopan-treated subjects compared to 46% of anti-C5 treated subjects. • APPOINT-PNH was a single-arm study in adults with PNH with anemia (Hb <10 g/dL) and LDH >1.5 ULN who were not previously treated with a complement inhibitor. All 40 subjects received iptacopan for 24 weeks. – The majority of subjects (77.5%) achieved a sustained increase in hemoglobin levels from baseline of ≥2 g/dL in the absence of RBC transfusions. Such an effect would not be expected to occur spontaneously without treatment.	• Substantial evidence of effectiveness of iptacopan for the treatment of patients with PNH was established with two adequate and well-controlled trials, APPLY-PNH and APPOINT-PNH. • Based on APPLY-PNH, the benefits of iptacopan in adults with PNH previously on a C5 inhibitor include a large increase in hemoglobin that is expected to improve signs and symptoms of anemia as well as transfusion avoidance, a procedure that carries risks for infection and transfusion-related reactions. The superior benefits with the switch to iptacopan compared to continuing the FDA-approved C5 inhibitors, likely reflect iptacopan's effects on both intravascular and extravascular hemolysis. It is unclear how these benefits with iptacopan compare to the FDA-approved C3 inhibitor, pegcetacoplan, which also targets intra- and extravascular hemolysis, as there is no head-to-head comparison. • In C5-inhibitor naïve patients, iptacopan is expected to have similar benefits based on the large improvement in hemoglobin shown in APPOINT-PNH. • Iptacopan has the additional convenience of oral administration; all other FDA approved drugs for PNH are administered subcutaneously or by IV infusion.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• Iptacopan's safety was evaluated in the same population as efficacy. – In APPLY-PNH, serious adverse reactions were reported in 4.8% of subjects and included pyelonephritis, urinary tract infection, and COVID-19. In APPOINT-PNH, serious adverse reactions were reported in 5% of subjects and included COVID-19 and bacterial pneumonia. – The most common adverse reactions (≥10%) were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, and nausea. – Elevations in lipids, including LDL and triglycerides, occurred in clinical trials. Elevated lipids may require treatment with cholesterol lowering medications. • Similar to other complement inhibitors, serious infections due to encapsulated organsims were reported in clinical trials. Although no meningococal infections were reported, this remains an expected risk based on iptacopan's mechanism of action.	• The safety data submitted were sufficient to characterize the toxicity profile of iptacopan. • The risks of iptacopan are generally comparable to those of approved complement inhibitors for treatment of PNH. Similar to other complement inhibitors, a REMS with elements to assure safe use (ETASU) is required. The goal of the REMS is to mitigate the risk of serious infections caused by encapsulated organisms. The REMS will help ensure that 1) patients are up to date with vaccinations against encapsulated bacteria according to current Advisory Committee on Immunization Practices (ACIP) recommendations (or receive prophylactic antibiotics if iptacopan cannot be delayed until vaccinations are up to date); and 2) patients and prescribers are aware of early signs and symptoms of serious encapsulated bacterial infections and the need for immediate medical evaluation • The other risks of iptacopan are expected to be tolerability issues (e.g., headache, diarrhea) and/or are monitorable and actionable (e.g., lipid levels) • Postmarketing requirements will be issued at the time of approval to assess the long-term safety of iptacopan, as it may administered life-long for this chronic disease.

Abbreviations: COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; Hb, hemoglobin; HSCT, hematopoietic stem cell transplant; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; PIG-A, phosphatidylinositol glycan class A; PNH, paroxysmal nocturnal hemoglobinuria; RBC; red blood cell; REMS, risk evaluation and mitigation strategy

2.2. Conclusions Regarding Benefit-Risk

PNH is a rare, serious, life-threatening, and chronic hematologic disease caused by a somatic mutation in the phosphatidylinositol glycan class A gene leading to chronic hemolytic hemolysis, thrombosis. and other systemic effects. Spontaneous remissions do not occur without treatment. Complement inhibitors (ravulizumab, eculizumab, and pegcetacoplan) approved for PNH reduce the need for blood transfusions, stabilize/increase hemoglobin, and stabilize/reduce hemolysis.

The benefits of iptacopan (factor B complement inhibitor) for the treatment of adults with PNH were established in subjects with anemia despite prior anti-C5 treatment and in those with anemia who were complement inhibitor naïve. Switching to iptacopan in those with anemia despite prior C5 inhibitor therapy (ravulizumab or eculizumab) was markedly more efficacious than continuing on the C5 inhibitor therapy with regard to hemoglobin improvement (which is expected to improve the signs and symptoms of anemia) and transfusion avoidance (a procedure that carries risks). These benefits were associated with a reduction in hemolysis. Similar benefits are expected in the complement inhibitor naïve population based on the demonstrated improvement in hemoglobin in this population that would not have been expected to occur spontaneously. The trials were not designed to assess other benefits (e.g., thrombosis or mortality). Iptacopan is administered orally, which is likely to be preferred by some patients over the subcutaneous injection or intravenous infusion routes of the other approved products.

These benefits outweigh the risks of iptacopan, which are comparable to other approved complement inhibitors and include a risk for serious infections from encapsulated organisms for which a REMS will be required. Other risks are tolerability issues (e.g., headache, diarrhea) or can be monitored (e.g., lipid abnormalities). The long-term safety of iptacopan will be further assessed with postmarketing requirements.

II. Interdisciplinary Assessment

3. Introduction

The Applicant, Novartis Pharmaceutical Corp., seeks approval of iptacopan under the 505(b)(1) regulatory pathway for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). Iptacopan is an oral complement inhibitor that targets factor B (FB) to selectively inhibit the alternative pathway, resulting in hematologic response and transfusion avoidance (TA). The recommended dosage for iptacopan is 200 mg orally twice daily (BID). Data supporting the indication for iptacopan were derived primarily from the results of the APPLY-PNH and APPOINT-PNH trials. Iptacopan was granted orphan drug designation (ODD) on July 31, 2020, and breakthrough therapy designation on December 1, 2020.

PNH is a rare acquired hematopoietic stem cell disorder defined by complement mediated hemolysis, thrombosis, and bone marrow failure. The worldwide incidence is approximately 0.1 to 0.2/100,000 persons/year (Devalet et al. 2015). In patients with PNH, stem cells acquire a mutation in the X-linked gene phosphatidylinositol glycan class A (PIG-A). This gene is necessary in the synthesis of the glycosyl phosphatidylinositol anchor, which is needed for some proteins to attach to the cell membrane (Brodsky 2014). Two of these proteins, CD55 and CD59, are normally present on the cell surface of red blood cells (RBCs). Without these two proteins, red cells are susceptible to the action of complement, which leads to hemolysis. The various clinical manifestations of PNH include anemia, thrombosis, and smooth muscle dystonia. Anemia can be due to the combination of hemolysis (intravascular and extravascular) and bone marrow failure. Subsequently, patients with anemia can present with symptoms such as fatigue, dyspnea, and hemoglobinuria (Brodsky 2014). Thrombosis is the most common cause of mortality in patients with PNH. Patients also have deregulation of smooth muscle tone; therefore, patients with PNH can have abdominal pain, esophageal spasm, and erectile dysfunction. Another symptom is acute or chronic kidney disease due to microvascular thrombosis in the kidney (Brodsky 2014).

Currently approved therapies in the United States (U.S) for PNH are eculizumab (C5 inhibitor administered intravenously), ravulizumab (longer acting C5 inhibitor administered intravenously or subcutaneously), and pegcetacoplan (C3 inhibitor administered subcutaneously). Approvals are based on clinically meaningful improvement in hemolysis (i.e., transfusion avoidance, hemoglobin (Hb) stabilization, change in hemoglobin and other markers of hemolysis). All approved products have a risk of serious infections due to encapsulated organisms and/or meningococcal infections (Alexion Pharmaceuticals 2020; Alexion Pharmaceuticals 2018). The only cure for PNH is hematopoietic stem cell transplantation. However, this therapy carries significant risks, including graft-versus-host disease and transplant-related mortality, and some patients lack a suitable donor (Brodsky 2014).

Substantial evidence of effectiveness was established based on two adequate and well-controlled trials, APPLY-PNH in subjects who had prior experience with a complement inhibitor and APPOINT-PNH a study in subjects naïve to complement inhibitor treatment. Each study also serves as confirmatory evidence for the other to establish benefit in patients with PNH who have

received previous complement inhibitor therapy and in patients with PNH naïve to complement inhibitor therapy. A brief description of the study results is provided below.

APPLY-PNH (NCT04558918) was a multicenter, randomized, open-label, active-controlled, 24-week study in 97 adult subjects with PNH with residual anemia (hemoglobin <10 g/dL) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months. APPLY-PNH met its prespecified two primary endpoints to demonstrate superiority of iptacopan to anti-C5 in achieving hematological response after 24 weeks of treatment. Superiority was also demonstrated in key secondary endpoints of transfusion avoidance, change from baseline in hemoglobin levels, and change from baseline in absolute reticulocyte counts.

APPOINT-PNH (NCT04820530), is a single arm study in 40 adult subjects with PNH who were not previously treated with a complement inhibitor. The majority of subjects achieved sustained an increase in hemoglobin levels from baseline of ≥2 g/dL in the absence of RBC transfusions. Results from this trial are persuasive as hemoglobin levels would not improve spontaneously without treatment.

The safety database for iptacopan was adequate for the proposed indication, dosing regimen, and intended patient population. Overall, iptacopan has an acceptable safety profile in both complement inhibitor-naïve patients and in patients previously treated with a complement inhibitor. The most significant risk is serious infections from encapsulated organisms for which a risk evaluation and mitigation strategy (REMS) will be required. The most common adverse reactions in subjects who received iptacopan were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, and nausea.

A detailed discussion of these findings is included in the pertinent sections of this review.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Analyses of the Key Secondary Endpoint of Transfusion Avoidance in APPLY-PNH

3.1.2. Key Safety Review Issues

3.1.2.1. Serious Infections

3.1.2.2. Lipid Abnormalities

3.1.2.3. Thrombocytopenia

3.2. Approach to the Clinical Review

Table 3 provides an overview of the clinical trials submitted to establish the efficacy and safety of iptacopan.

The assessment of benefit was based on Study APPLY-PNH, a multicenter, randomized, open-label, actively-controlled study designed to compare iptacopan to anti-C5 therapy (eculizumab or ravulizumab) and Study APPOINT-PNH, a single-arm trial in subjects with treatment naïve PNH. The assessment of risk was based primarily on data derived from the randomized controlled period (RCP) of APPLY-PNH and the core-treatment period of APPOINT-PNH, but also included an analysis of the pooled PNH safety set (SAF) in subjects receiving iptacopan in APPLY-PNH, APPOINT-PNH, CLNP023X2204, CLNP023X2201, CLFG316X2201, and CLNP023C12001B.

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Iptacopan

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
CLNP023C12302 APPLY-PNH	Adults with PNH with residual anemia despite prior anti-C5 treatment	Control type: Active-comparator Randomization: 8:5 Blinding: None Biomarkers: None Innovative design features: None	Drug: iptacopan Dosage: 200 mg Number treated: 62 Duration (quantity and units): 24 wk Drug: eculizumab Dosage: 300 mg/30mL Number treated: 23 Duration (quantity and units): 24 wk Drug: ravulizumab Dosage: 300 mg/30 mL, 300 mg/3 mL, 1100 mg/11 mL Number treated: 12 Duration (quantity and units): 24 wk	Primary: Sustained increase in Hb levels from baseline of ≥2 g/dL in the absence of RBC transfusions. Sustained Hb levels ≥12 g/dL in the absence of RBC transfusions. Secondary: RBC transfusion avoidance, change from baseline in Hb levels, FACIT-Fatigue scores reticulocyte count, and % change in LDH levels, annualized rate of clinical BTH, MAVEs.	91;97	Centers: 39 Countries: Brazil Czech Republic, France, Germany, taly, Japan, Netherlands, Republic of orea, Spain, Taiwan, United ingdom, United States

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
CLNP023C12301 APPOINT-PNH (NCT04820530)	Adults with PNH naïve to complement inhibitor therapy (including anti-C5)	Control type: None Randomization: Open-label Blinding: None Biomarkers: None Innovative design features: None	Drug: iptacopan Dosage: 200 mg Number treated: 40 Duration (quantity and units): 24 wk	Primary: Sustained increase from baseline in Hb levels of ≥2 g/dL in the absence of RBC transfusions. Secondary: Sustained Hb levels ≥12 g/dL in the absence of RBC transfusions, RBC transfusion avoidance, change from baseline in Hb levels, % change in LDH levels, reticulocyte count, and FACIT-Fatigue score, annualized rate of clinical BTH, MAVEs.	40;40	Centers: 16 Countries: China, France, Germany, taly, Malaysia, Republic of orea, Singapore, United ingdom

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
CLNP023X2204	Adults with PNH who have active signs of hemolysis, without concomitant complement inhibition	Control type: None Randomization: 1:1 Blinding: None Biomarkers: None Innovative design features: None	Drug: iptacopan Dosage: 1: 25 mg - >100 mg, 2: 50 mg - >200 mg Number treated: 7 in sequence 1, 6 in sequence 2. Duration (quantity and units): 12 wk	Primary: Percentage of subjects with 60% reduction in LDH or LDH below upper limit of normal (ULN) up to 12 weeks of treatment. Secondary: LDH, and other relevant parameters such as but not restricted to hemoglobin and RBC up to Week 4 for each dose.	10; 13	Centers: 5 Countries: Republic of orea, Singapore, Malaysia, and Taiwan

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
CLNP023X2201	Adults with PNH who have signs of active hemolysis on anti-C5 treatment	Control type: None Randomization: Open-label Blinding: None Biomarkers: None Innovative design features: None	Drug: iptacopan Dosage: 200 mg Number treated: 16 Duration (quantity and units): 12 wk	Primary: LDH level at study week 13 Secondary: All safety parameters including blood chemistry, hematology, urinalysis, ECG evaluation, vital signs, adverse events, transfusions, patient-reported outcomes (PROs), patient diary	15;16	Centers: 4 Countries: France, Germany, taly

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
CLFG316X2201	Subjects with PNH who have hemolysis	Control type: None Randomization: None Blinding: None Biomarkers: None Innovative design features: None	Drug: iptacopan Dosage: 200 mg Number treated: 9 Duration (quantity and units): 4 wk Drug: LFG316* Dosage: 20 mg/kg Number treated: 10 Duration (quantity and units): 4 wk	Primary: Reduction in serum LDH levels within the first 4 weeks of treatment. Secondary: Standard safety monitoring with increased vigilance for infections. Measurement of serum concentrations of LFG316.	10;10	Centers: 7 Countries: Japan, Czech Republic, and Lithuania.

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
CLNP023C12001B PNH REP	Adults with PNH who have completed phase 2 or phase 3 studies with iptacopan	Control type: None Randomization: Open-label Blinding: None Biomarkers: None Innovative design features: None	Drug: iptacopan Dosage: 200 mg Number treated: 104 Duration (quantity and units): 36 mo	Primary objective: To characterize the long-term safety and tolerability of iptacopan in subjects with PNH who have completed PNH Phase 2 and Phase 3 studies with iptacopan.	167; 104	Centers: Countries: Brazil China, Czech Republic, France, Germany, taly, Japan, Lithuania, Malaysia, Netherlands, Republic of orea, Singapore, Spain, Taiwan, United ingdom, United States

Source: Reviewer.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled."
* LFG316 is an investigational anti-C5 ant body
Abbreviations: anti-C5, anti-complement 5 monoclonal antibody; BID, twice daily; BTH, breakthrough hemolysis; d, day; DB, double-blind; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; h, hour; Hb, hemoglobin; LDH, lactate dehydrogenase; LTE, long-term extension; MAVEs, major adverse vascular events; MC, multicenter; mo, month(s) N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; PNH, paroxysmal nocturnal hemoglobinuria; R, randomized; RBC, red blood cell, wk, week(s); y, year(s)

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Section 6 (efficacy) includes a discussion of the FACIT-Fatigue endpoint
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	Refer to DCOA Review (DARRTS Reference ID: 5264308)
X	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Primary Pharmacology

The complement system is a key component of the innate immune system and comprises three pathways: classical, lectin, and alternative, which converge at the proteolytic cleavage of C3. Different pathways are activated depending on the trigger, but each ultimately leads to the terminal pathway and phagocytic elimination through C3-dependent opsonization,

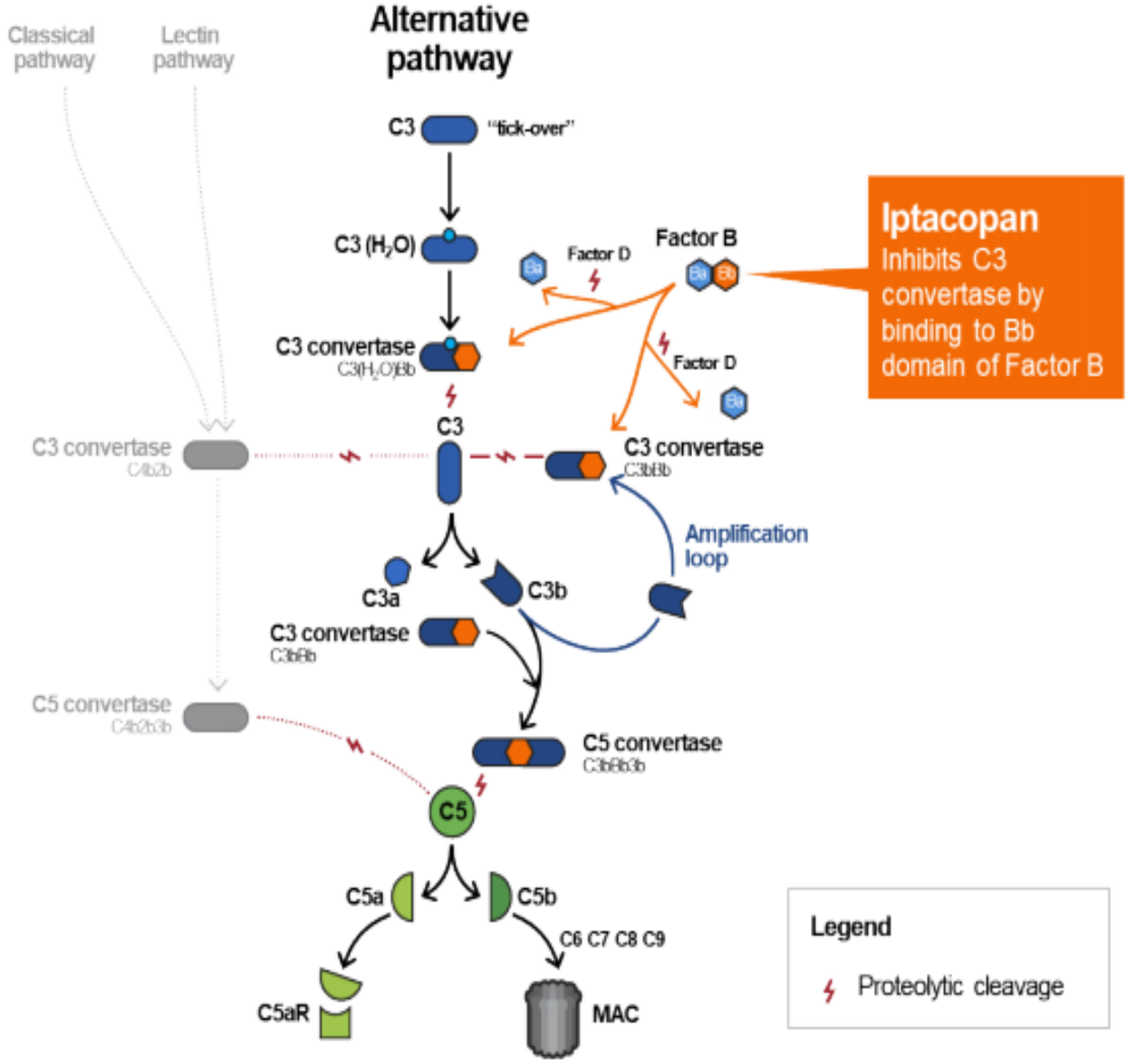
anaphylatoxin-mediated inflammatory cell recruitment, and cell lysis through generation of the membrane attack complex (MAC). The alternative pathway (AP) also acts as an amplification loop for the other two pathways. Alternative pathway activation is known to contribute to the inappropriate targeting and lysis of red blood cells in PNH.

Hemolytic anemia in PNH is linked to mutation of the PIG-A gene and to deficiencies in complement regulator proteins CD55 and CD59, which renders erythrocytes susceptible to complement attack. Intravascular hemolysis (IVH) is mediated by the downstream MAC and extravascular hemolysis (EVH) is facilitated by C3b opsonization in PNH.

Alternative pathway activation depends on the proteolytic cleavage of FB, a serine protease that binds to C3(H2O), which is cleaved into Ba and Bb subunits by complement factor D (see Figure 2). The Bb subunit of FB binds to C3(H2O) to generate the C3(H2O)Bb complex, known as AP C3 convertase (C3BbBb), which cleaves C3 into C3a and C3b. In PNH, inhibition of FB is expected to block AP activation, and thus reduce MAC-mediated IVH and C3b-mediated EVH.

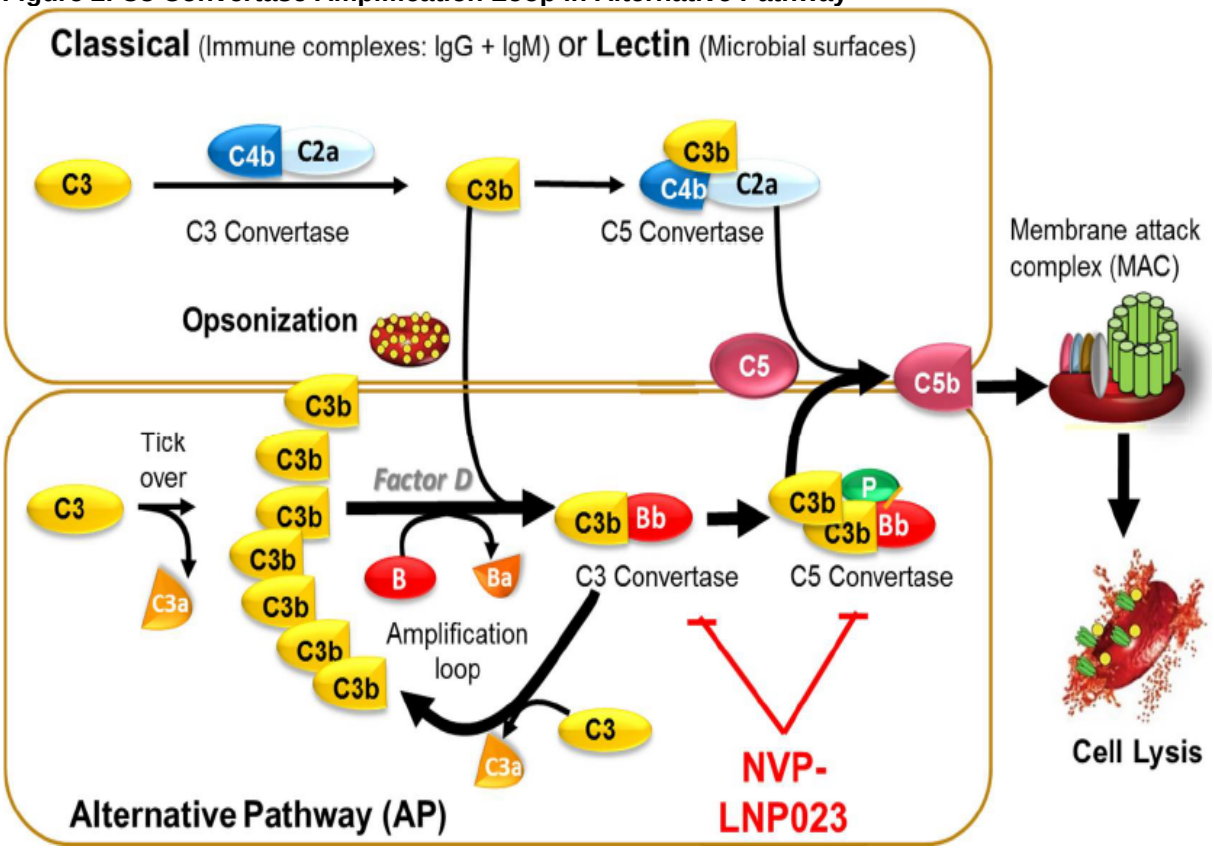
Iptacopan is a small molecule complement FB inhibitor (see Figure 1). It inhibited FB activity in vitro (half maximal inhibitory concentration = 9.6 nM) in a time-resolved fluorescence resonance energy transfer-based competitive binding assay. Selective blockade of AP activation by iptacopan was observed in serum samples from mouse, rat, dog, rabbit, monkey, and human, demonstrating half maximal inhibitory concentration values in the nM range without impacting classical or lectin pathway activation at concentrations up to 100 µM, as assessed in zymosan-induced MAC deposition assay and Wieslab assay. Iptacopan's potency and specificity in inhibiting FB and AP while sparing other complement activation pathways supports the therapeutic rationale underpinning its development for PNH.

Figure 1. Mechanism of Action of Iptacopan Targeting the Alternative Complement Pathway by Binding to Factor B Inhibiting C3 Convertase and C3b Amplification Loop



Source: Applicant's submission
Abbreviations: Ba, factor Ba component; Bb, factor Bb component; C3a, complement component 3a; C3b, complement component 3b; C5a, complement component 5a; C5b, complement component 5b; C5ar, complement component 5a receptor; MAC, membrane attack complex

Figure 2. C3 Convertase Amplification Loop in Alternative Pathway



Source: Applicant's submission
Abbreviations: AP, alternative pathway; Ba, factor B subunit Ba; Bb, factor B subunit Bb; C2a, complement component 2a; C3a, complement component 3a; C3b, complement component 3b; C4b; complement component 4b; C5b, complement component 5b; IgG, Immunoglobulin G; IgM, Immunoglobulin M; NVP-LNP023, Novartis Pharmaceuticals iptacopan; MAC, membrane attack complex; P, properdin

Proof of Concept Studies

The pharmacology of iptacopan as a potential treatment for PNH was characterized in clinically relevant in vitro and in vivo studies.

In vitro assays using erythrocytes from patients with PNH showed that iptacopan inhibited both hemolysis and C3 deposition, suggesting that iptacopan may prevent both IVH and EVH features of PNH. Furthermore, iptacopan inhibited hemolysis in sera from patients with other diseases associated with dysregulation of the AP, such as atypical hemolytic uremic syndrome, C3 glomerulopathy (C3G), and membranoproliferative glomerulonephritis (see Table 5).

Chronic exposure to iptacopan in vivo led to inhibition of the AP-based ex vivo MAC formation (Table 5). Iptacopan also inhibited disease development and progression in other disease models, including the serum transfer arthritis mouse model and the passive Heymann nephritis rat model (Table 5). The inhibitory effect of iptacopan on hemolysis, C3 cleavage, MAC formation, and AP activation suggests iptacopan might beneficially impact complement mediated IVH and EVH in patients with PNH.

Table 5. Pharmacological Effects of Iptacopan on Alternative Pathway In Vitro, Ex Vivo, and In Vivo Alternative Pathway-Related Disease Models

			AP Inhibition Parameters		
In Vitro Assays	**AP-Related Diseases/ Disease Characteristics**	**Iptacopan Concentration**	**Hemolysis inhibition**	**C3 Cleavage/ Deposition Inhibit.**	**FB Binding**
PNH surrogate assay	PNH (erythrocytes)/ Somatic mutations in the PIG-A gene in hematopoietic stem cells resulting in a deficiency of GPI anchored proteins including complement regulators CD55 and CD59 which make RBCs vulnerable to complement-mediated lysis		Yes[1] IC_{50}=114 nM, IC_{90}=742 nM	Yes C3 deposition IC_{50}=400 nM	NA
			Comparison: Eculizumab, current PNH therapy, anti-C5 antibody: Hemolysis inhibition IC_{50}=132nM, IC_{90}=264nM, C3 deposition was minimal		
Sheep red blood cells hemolysis assay	C3G (serum)/ Mutations in complement regulatory proteins or by autoantibodies that stabilize the C3 convertases or neutralize factor H (FH)	150 or 600nM	Yes	NA	NA
	MPGN (serum)/ Closely related to C3G but both C3 and Ig deposition occurs		Yes	NA	NA
	aHUS (serum)/ Genetic mutations or autoantibodies against FH on the cell surface		Yes	NA	NA
Binding/Affinity assay	aHUS (serum)/ Genetic mutations or autoantibodies against FH on the cell surface		NA	Yes IC_{50}=54nM	Yes IC_{50}=37nM
Ex Vivo Assays	**AP Activity Analysis**	**Iptacopan Dose (mg/kg)**	**AP Inhibition Parameters**		
MAC deposition assay[2]	Iptacopan treated monkey and dog (serum)	Monkey 10, 50, or 100 Dog 5, 30, or 150, p.o., q.d.	Full inhibition of AP activity (up to 98.6%) based on MAC formation		

In Vivo AP-Related Diseases	Disease Characteristics	Iptacopan Dose (mg/kg)	AP Inhibition Parameters C3 Cleavage/Deposition Inhibition
LPS-induced: mechanistic model (mice)	LPS-induced AP activation	30 p.o.	Yes (Full inhibition of C3d+iC3b deposition)[3]
Serum transfer (K/BxN) arthritis model (mice)	Essential involvement of AP for disease development	20, 60, or 180 p.o. BID	Yes (Reduction of Ba, C3d, and C5a level) Disease inhibited at ≥60 mg/kg
Passive Heymann nephritis (PHN): Membranous nephropathy, glomerulonephritis model (rats)	Essential involvement of complement for disease development	20 or 60 p.o. BID 14 days	Yes (Inhibition of C3 and C5-b9 deposition), Disease progression inhibited

Source: Reviewer's analysis
[1] In 100% acidified serum from healthy donor
[2] Zymosan A MAC deposition assay using serum samples from toxicology studies RD-2019-00023, RD-2018-00505, RD-2020-00544, RD-2015-00106
[3] C3 convertase splits C3 into C3a and C3b, C3b is cleaved into iCb and then further into C3d by complement factor I
Abbreviations: aHUS, atypical hemolytic uremic syndrome; AP, alternative pathway; Ba, factor Ba component, BID, twice daily; C3a, complement component 3a; C3b, complement component 3b; C3d, complement component 3d; C3G, C3 glomerulopathy; C5a, complement component 5a; FB, factor B; FH, Factor H; GPI, glycosylphosphatidylinositol; IC_{50}, half-maximal inhibitory concentration; iC3b, inactivated C3b; LPS, lipopolysaccharides; MAC, membrane attack complex; MPGN, membranoproliferative glomerulonephritis; NA, not applicable; PHN, passive heymann nephritis; PIG-A, phosphatidylinositol glycan class A; PNH, paroxysmal nocturnal hemoglobinuria; p.o., oral administration; q.d., once daily; RBC, red blood cell

5.2. Clinical Pharmacology / Pharmacokinetics

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Complement factor B inhibitor
Mechanism of action	Iptacopan binds to Factor B of the alternative complement pathway and regulates the cleavage of C3, generation of downstream effectors, and the amplification of the terminal pathway. In PNH, intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC), while extravascular hemolysis (EVH) is facilitated by C3b opsonization. Iptacopan acts proximally in the alternative pathway of the complement cascade to control both C3b-mediated EVH and terminal complement-mediated IVH.
Active moieties	Iptacopan
QT prolongation	At a dose of up to 1,200 mg, iptacopan does not prolong the QT interval to any clinically relevant extent. See IRT-team review in DARRTS dated April 24, 2023, and July 6, 2023 (Reference ID: 5162658 and 5203107)
	General Information
Bioanalysis	Plasma iptacopan concentrations were measured using a validated liquid chromatography-mass spectrometry (LC-MS/MS) method
Healthy subjects versus patients	Plasma pharmacokinetics of iptacopan are generally similar in healthy subjects and subjects with PNH
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	**Table 7. Iptacopan Pharmacokinetics Parameters in Subjects With PNH** **Iptacopan Dosage** | **C_{max} (ng/mL)** | **AUC (day·h/mL)** 200 mg twice daily | 4163 (1330) | 2991 (1009) Source: Population Pharmacokinetic analysis Pharmacokinetics parameters are presented as mean (SD) Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PNH, paroxysmal nocturnal hemoglobinuria; SD, standard deviation
Range of effective dosage(s) or exposure	Pivotal trials evaluated an iptacopan dose of 200 mg twice daily. In Study C12302 (APPLY-PNH), after 24 weeks of treatment with iptacopan, the response rate compared to continued anti-C5 treatment was 81.5% (82.3% vs. 0%) for hemoglobin improvement defined as sustained increase of hemoglobin levels ≥2 g/dL from baseline and 67% (67.7% vs. 0%) for absolute sustained hemoglobin level ≥12 g/dL without a need for RBC transfusion. In APPOINT-PNH (Study C12301), after 24 weeks of treatment with iptacopan, the response rate was 77.5% for hemoglobin improvement, without a need for RBC transfusion. Refer to Section 6 for the efficacy review of the pivotal trials.
Maximally tolerated dosage or exposure	The highest tested single dose administration was 1,200 mg under fasted condition in healthy subjects (Study CLNP023A2107). The highest multiple dose administration was 200 mg twice daily for 24 weeks (Study C12302 and C12301). Refer to Section 7.6 for the safety review.

Characteristic	Drug Information
Dosage proportionality	At doses between 25 mg and 200 mg, iptacopan exposure was overall less than dose proportional. However, doses of 100 mg and 200 mg were approximately dose proportional. The dose proportionality of iptacopan appears to be mediated by saturable binding to the target plasma protein Factor B (see Section 14.2).
Accumulation	At the recommended dosing regimen of 200 mg twice daily, accumulation was approximately 1.4-fold
Time to achieve steady state	At the recommended dosing regimen of 200 mg twice daily, steady state is achieved in approximately 5 days.
Bridge between to-be-marketed and clinical trial formulations	The tablet formulation used in the Phase 3 studies is the intended final commercial formulation. The difference between the late phase formulation used in Phase 3 and the commercial formulation is (b) (4) A bioequivalence study is not required to bridge the Phase 3 drug product with the proposed commercial drug product. Similarity between the two formulations was shown in comparative dissolution testing in three dissolution media across the physiologically relevant pH range.
	Absorption
Bioavailability	There are scarce data on the absolute bioavailability (F) of iptacopan in humans since there was no comparative IV dosing submitted. The Applicant suggests an estimate of approximately 70.6% based on human ADME Study A2101, where the mean oral absorption of iptacopan could be estimated as at least 70.6% based on urinary excreted radioactivity of 24.8% plus 45.8% of dose in feces attributed to metabolites.
T_{max}	Median T_{max} values at steady state were 1.5 to 2 h post dose across the dose range of 100 to 200 mg twice daily.
Food effect (fed/fasted) Geometric least square mean and 90% CI	Following 100 mg tablet taken with a high-fat, high-calorie breakfast: $AUC_{0-\infty}$ fed/fasted ratio (90% CI): 0.89 (0.82-0.96) C_{max} fed/fasted ratio (90% CI): 0.97 (0.82-1.14) t_{max} (median): 1.76 h (fasted); 1.26 h (fed) High-fat meal does not change the exposure of iptacopan to a clinically meaningful degree. Iptacopan can be taken with or without food. This is also consistent with the phase 3 studies C12301 and C12302 where participants received iptacopan regardless of food intake. The proposed dose for clinical use is the 200 mg dose. The food effect at the proposed 200 mg dose is not expected to change in a clinically meaningful manner compared to that of the 100 mg based on the approximately dose proportional PK at the dose range of 100 to 200 mg.

Characteristic	Drug Information
	Distribution
Volume of distribution	In healthy volunteers, the apparent volume of distribution during the terminal elimination phase (V_z/F) following oral administration of 200 mg BID is 288 L.
Plasma protein binding	Protein binding to the target plasma protein Factor B is concentration dependent at tested concentrations in vitro and in vivo. In vitro, over the concentration range of 1000 ng/mL to 10000 ng/mL iptacopan was 93% to 75% protein bound. In vivo, over the concentration range of 100 ng/mL to 5000 ng/mL, iptacopan was approximately 99% to 75% protein bound. Binding of iptacopan to plasma proteins is concentration dependent possibly due to saturable binding to drug target Factor B.
Drug as substrate of transporters	Iptacopan is a substrate of P-gp, BCRP, MRP2, OATP1B1 and OATP1B3. Iptacopan is not a substrate of OAT1, OAT2, OAT3, and OCT2.
	Elimination
Mass balance results	Following single-dose administration of a 100 mg iptacopan capsule containing approximately 100 µCi of [^{14}C] iptacopan, 24.8% of the radioactivity was recovered in urine and 71.5% was recovered in feces. Unchanged iptacopan represented 17.9% of the administered dose in urine and 16.8% in feces (human ADME Study CLNP023A2101). In feces, 7 drug-related components were detected with the most abundant metabolite being M2 (27%), followed by iptacopan (16.8%), and M7 (8.3%). Other metabolites detected in feces represent <5% of the dose. In urine, a total of 7 drug-related components were detected with the most abundant metabolite being M1 (3.8%), followed by acyl glucuronide M9 (1.6%). Other metabolites represent <0.5%.
Clearance	CL/F is 7.96 L/h. Source: Summary of Clinical Pharmacology.
Half-life	Elimination half-life is approximately 25 h following 200 mg twice daily.
Metabolic pathway(s)	Metabolism of iptacopan includes N- and O-dealkylation, oxidation, and dehydrogenation, mostly driven by CYP2C8 (98%) with a small contribution from CYP2D6 (2%). Iptacopan undergoes phase 2 metabolism through glucuronidation by UGT1A1, UGT1A3, and UGT1A8.
Primary excretion pathways (% dosage)	Hepatic metabolism followed by excretion of metabolites in feces and urine.
	Intrinsic Factors and Specific Populations
Body weight	Although body weight is a significant covariate on iptacopan clearance based on population pharmacokinetic analyses, the impact on iptacopan exposures is modest. Subjects with low body weight (5th percentile of 47.4 kg) and high body weight (95th percentile of 100 kg) had 11% higher and 10% lower AUC_{0-24}, respectively compared to reference patients (69.5 kg), hence adjustment of dose based on body weight is not necessary.
Age	Based on population pharmacokinetic analyses, age does not have a clinically meaningful effect on iptacopan PK.

Characteristic	Drug Information
Renal impairment	A dedicated renal impairment study was not conducted. Based on population pharmacokinetic analyses, baseline estimated Glomerular Filtration Rate (eGFR) is a significant covariate on iptacopan clearance. eGFR was calculated by the Applicant using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al. 2009). Mean eGFR (range) was 84.8 (27.5 - 142.8) mL/min/1.73m^2. The population PK dataset consisted of subjects with mild (27%), moderate (24%) or severe renal impairment (3%). Apparent clearance increases with increasing baseline eGFR. AUC_{0-24} in subjects with eGFR of 34.3 mL/min/1.73 m^2 (5th percentile of the pooled data) was 38% higher than the reference population (eGFR of 87.5 mL/min/1.73 m^2) (Source Table 7-8 population PK report). Because there are no exposure dependent changes in safety parameters in the clinical trials, the impact of mild and moderate renal impairment is considered to be not clinically relevant. However, there are limited data in subjects with severe renal impairment (eGFR 15 to 30 mL/min/1.73 m^2) and there is uncertainty that the potential increase in iptacopan exposures in these patients may well go beyond the current clinical experience. Therefore, the clinical pharmacology team recommends avoiding use in patients with severe renal impairment (<30 mL mL/min/1.73 m^2). Iptacopan is being evaluated for renal indications in patients with IgA nephropathy (IgAN) and C3 glomerulopathy (C3G). PK data from these ongoing clinical trials may inform the dosing recommendations in patients with severe renal impairment.
Hepatic impairment	Iptacopan undergoes extensive hepatic metabolism based on the results of the human ADME Study CLNP023A2101. The target plasma protein Factor B is produced by the liver. Iptacopan binds directly to and inhibits Factor B. A dedicated hepatic impairment study CLNP023A2105 was conducted in subjects with normal hepatic function and mild (Child-Pugh A), moderate (Child-Pugh B), and severe hepatic impairment (Child-Pugh C). Following administration of a single 200 mg dose of iptacopan, mean total iptacopan C_{max} and AUC_{inf} did not change to a clinically relevant degree in any hepatic impairment group compared to the normal reference group. However, the geometric mean ratio (GMR) of unbound C_{max} and AUC_{inf} in subjects with mild, moderate, and severe hepatic impairment relative to the normal reference group was 1.38, 1.67, and 2.11 (for C_{max}), and 1.48, 1.58, and 3.71 (for AUC_{inf}), respectively. The increase in unbound exposures with mild and moderate hepatic impairment is within the observed clinical exposures and the exposure-safety relationships (for both total and unbound exposures). Therefore, this extent of exposure is not expected to impact safety parameters, and dose adjustments in patients with mild and moderate hepatic impairment is not necessary. However, the increase in unbound exposure in severe hepatic impairment is beyond the current clinical experience and there is uncertainty of the impact on safety at such high exposures at steady state. The clinical pharmacology team also found dose adjustment for severe hepatic impairment not permissible due to (1) the poor predictability of the PK behavior at steady state attributable to the nonlinear PK and lower hepatic Factor B production in subjects with hepatic impairment, and (2) the availability of only one strength of 200 mg. Therefore, the review team does not recommend the use of iptacopan in PNH patients with severe hepatic impairment.

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Perpetrator and Victim)
Inhibition/induction of metabolism	Effect as perpetrator In vitro studies showed that treatment with iptacopan caused no time-dependent inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Time-dependent inhibition was only determined for CYP2C8. The induction potential of iptacopan by measuring CYP1A2, CYP2B6, CYP2C9, CYP3A4 mRNA appears to be low. The inhibition effects of iptacopan were assessed by physiologically-based pharmacokinetic (PBPK) modeling and simulation using repaglinide as a CYP2C8 substrate, where AUC_{inf} and C_{max} did not change to a clinically relevant degree when coadministered with iptacopan. In addition, iptacopan is not expected to inhibit CYP2C8 based on its Ki value and expected clinical concentration. Hence, no dose adjustment is necessary when co-administered with CYP2C8 substrates. Effect as victim: Iptacopan is a CYP2C8 substrate. The Applicant conducted a clinical drug-drug interaction (DDI) study CLNP023A2104, which assessed the interaction of clopidogrel (moderate CYP2C8 inhibitor (FDA 2023)) on iptacopan PK. In the presence of clopidogrel, iptacopan GMR for $C_{max,}$ AUC_{last}, $AUC_{0-\infty}$ was 1.05, 1.33, and 1.36, respectively. Because there is no iptacopan exposure dependent changes in safety parameters with this extent of exposure seen in the clinical trials, no dose adjustment is needed when iptacopan is concomitantly administered with moderate CYP2C8 inhibitors. However, the worst-case scenario for CYP2C8 inhibition may not have been captured by the interaction with clopidogrel, as clopidogrel is only a moderate inhibitor of CYP2C8. The interaction with a strong CYP2C8 inhibitor e.g., gemfibrozil, was evaluated using Physiologically Based Pharmacokinetic (PBPK) modeling. However, the current model cannot be adequately validated to assess this interaction in-silico. Therefore, in the absence of data and the uncertainly that the potential increase in iptacopan exposures may well go beyond the available clinical exposure, the clinical pharmacology team does not recommend the use of iptacopan in the presence of a strong CYP2C8 inhibitor (e.g., gemfibrozil). The induction effect of rifampin (CYP2C8 inducer, OATP1B1 inhibitor (FDA 2023) was assessed by PBPK modeling and simulation. As stated earlier, because the current PBPK model cannot be adequately validated, this interaction cannot be assessed in-silico. However, to address a potential decrease in iptacopan exposures with a CYP2C8 inducer, the label will recommend monitoring for efficacy and discontinue use of CYP2C8 inducers if loss of efficacy is evident.

Characteristic	Drug Information
Inhibition/induction of transporter systems	Effect as perpetrator In vitro studies showed that treatment with iptacopan did not inhibit BCRP, MRP2, BSEP, OAT1 and MATE2-K. Iptacopan inhibits P-gp, OATP1B1, OATP1B3, MATE1, OCT1, OCT2, and OAT3 in vitro. The Applicant conducted a clinical DDI study CLNP023A2104, which investigated the interaction of iptacopan on digoxin (P-gp substrate) and rosuvastatin (BCRP, OATP1B1, OATP1B3 substrate). Digoxin and rosuvastatin exposures did not change significantly in the presence of iptacopan. In addition, iptacopan is not expected to inhibit OCT1/2, OAT3, MATE1 based on its Ki value and expected clinical concentration. Overall, the potential for iptacopan to inhibit drug transporters appears to be low. Effect as victim: Iptacopan is a substrate of P-gp, BCRP, MRP2, OATP1B1 and OATP1B3. Iptacopan is not a substrate of OAT1, OAT2, OAT3, and OCT2. The Applicant conducted a clinical DDI study CLNP023A2104, which investigated the interaction of cyclosporine (OATP1B1, OATP1B3, BCRP and P-gp inhibitor (FDA 2023)) on iptacopan PK. In the presence of cyclosporine, iptacopan GMR for $C_{max,}$ AUC_{last}, $AUC_{0-\infty}$ was 1.41, 1.46, and 1.50, respectively. Because there is no iptacopan exposure dependent changes in safety parameters seen with this extent of exposure in the clinical trials, no dose adjustment is needed for iptacopan-treated subjects co-administered P-gp, BCRP, OATP1B1, OATP1B3 inhibitors.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{last}, area under the concentration-time curve to the last measurable concentration; AUC_{0-24}, area under the concentration time curve 0 to 24 h; $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CI, confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CYP2C8, cytochrome P450 family 2 subfamily C member 8; CYP, cytochrome P450; C3b, complement component 3b; C3G, C3 glomerulopathy; DARRTS, Document Archiving, Reporting and Regulatory Tracking System; DDI, drug-drug interaction; eGFR, glomerular filtration rate; EPC, Established pharmacologic class; EVH, extravascular hemolysis; F, bioavailability; GMR, geometric mean ratio; H, hour; IgAN, IgA nephropathy; IRT, Integrated Review Template; IV, intravenous; IVH, intravascular hemolysis; Ki value, inhibitory constant; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MAC, membrane attack complex; MATE1, multidrug and toxin extrusion transporter 1; MATE2-K, multidrug and toxin extrusion transporter 2-K; Min, minute; mRNA, messenger RNA; MRP2, multidrug resistance protein 2; M, metabolite; M, metabolite; M, metabolite; M, metabolite; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic PNH, paroxysmal nocturnal hemoglobinuria; P-gp, P-glycoprotein; QT, QT interval; RBC, red blood cell; T_{max}, time to maximum concentration; UGT, uridine diphosphate glucuronosyltransferase; vs, versus; V_z/F, apparent volume of distribution during terminal phase

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The recommended dose of iptacopan is 200 mg orally BID. Iptacopan can be taken with or without food. If one or more doses are missed, patients are advised to take one dose of iptacopan as soon as possible and then to resume the regular dosing schedule. PNH is a disease that requires chronic treatment.

Dosage Selection for Phase 3 Trials

The iptacopan 200 mg twice daily dose was selected for the phase 3 trials based on the pharmacokinetic/pharmacodynamic (PK/PD) data from phase 2 studies in subjects with PNH. In the phase 2 study CLNP023X2204, two dosage regimens were assessed: 100 mg BID and 200 mg BID. Iptacopan 100 mg and 200 mg BID reduced lactate dehydrogenase (LDH) and extravascular hemolytic markers, including bilirubin, and increased hemoglobin in treatment-naïve subjects with PNH. In the phase 2 study CLNP023X2201, two dosage regimens were assessed: 50 mg BID and 200 mg BID. Iptacopan 50 mg and 200 mg BID reduced LDH and extravascular hemolytic markers, including bilirubin, and normalized hemoglobin in subjects with PNH treated with anti-C5 therapies. However, the 200 mg iptacopan dose showed better improvements on LDH reductions from baseline. Overall, the Applicant stated that the response reached with 200 mg BID approached the plateau of the dose-response relationship for PD markers and, hence, the 200 mg BID was selected for the phase 3 studies.

Assessment of the Proposed Dose

PK/PD analyses were conducted for three complement pathway biomarkers, including Wieslab assay, Bb, and sC5b-9. The modeling dataset contained a total of 247 subjects, with 88 (35.6%) healthy volunteers, 103 (41.7%) subjects with immunoglobulin A nephropathy (IgAN), 27 (10.9%) subjects with C3G, and 29 (11.7%) subjects with PNH. The PK/PD model-estimated 90% maximal effective concentrations (EC_{90}; for both previously treated subjects and treatment-naïve subjects) were 1281, 521, and 682 ng/mL for Wieslab assay, Bb, and sC5b-9, respectively. Based on the population PK analysis, the steady-state trough concentration for 200 mg BID was approximately 1900 ng/mL, which was higher than the estimated EC_{90s} for all three biomarkers and was at the plateau of the exposure-response relationship for the three biomarkers. See Appendix 14.5 for additional details.

Exposure-response analyses were performed with 161 subjects with PNH (53 [33%] anti-C5 treatment-naïve subjects and 108 [67%] anti-C5 treatment-experienced subjects) for two efficacy endpoints, LDH and hemoglobin. The EC_{90} values were estimated as 270 ng/mL for LDH and 1970 ng/mL for hemoglobin. Based on the population PK analysis, the steady-state average concentration for 200 mg BID was approximately 2949 ng/mL in this subject population, which was higher than the estimated EC_{90} for both efficacy endpoints and was at the plateau of the exposure-response relationship for the two efficacy endpoints. The model estimated steady-state trough concentration of 1900 ng/mL was above the EC_{90} of LDH and close to the EC_{90} of

hemoglobin. One hundred percent and 89% of the subjects were expected to reach the steady-state average concentration greater than or equal to the EC_{90} for LDH and hemoglobin, respectively, after receiving the 200 mg BID dosing. See Appendix 14.5 for additional details.

With regard to safety, there were no iptacopan-dependent increases in safety parameters. Taken together, based on the exposure-PD, -efficacy, and -safety relationships, the proposed iptacopan dose of 200 mg BID is acceptable.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. Study CLNP023C12302 (APPLY-PNH)

Study Title

A randomized, multicenter, active-comparator controlled, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult patients with PNH and residual anemia, despite treatment with an intravenous anti-C5 antibody

Primary Objective

The primary objective was to demonstrate superiority of iptacopan compared to anti-C5 antibody treatment in the proportion of subjects achieving hematological response. Two hematological responder endpoints were defined as primary endpoints:

- Increase from baseline hemoglobin (Hb) levels ≥2 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.
- Hemoglobin levels ≥12 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.

Secondary Objectives

- To demonstrate superiority of iptacopan to anti-C5 antibody treatment in transfusion avoidance as the proportion of subjects who remain free from transfusions
- To demonstrate superiority of iptacopan to anti-C5 antibody treatment in average change in hemoglobin
- To demonstrate superiority of iptacopan to anti-C5 antibody treatment in improving fatigue using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) questionnaire
- To demonstrate superiority of iptacopan to anti-C5 antibody treatment in average change in reticulocyte counts
- To demonstrate superiority of iptacopan to anti-C5 antibody treatment in average percent change in LDH
- To demonstrate superiority of iptacopan to anti-C5 antibody treatment, in the rate of breakthrough hemolysis (BTH)

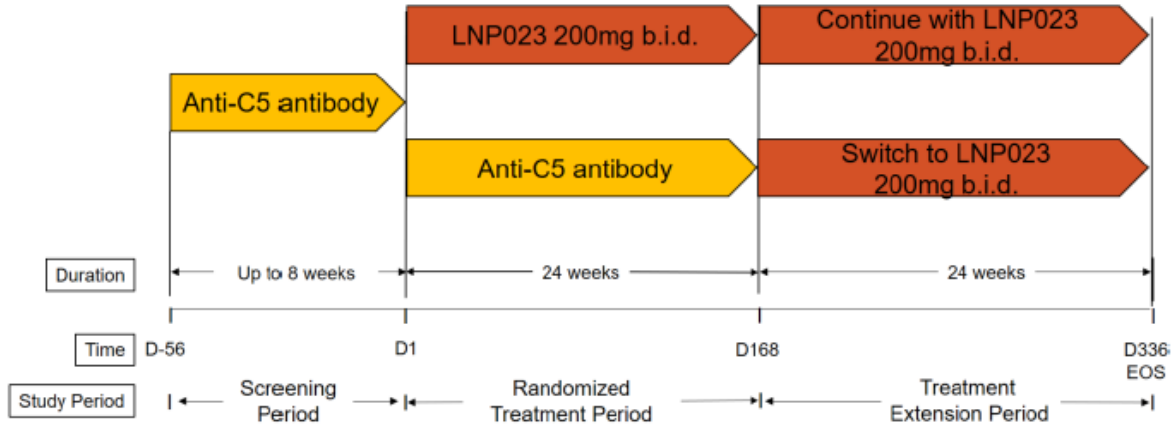
- To assess the rates of major adverse vascular events (MAVEs including thrombosis) of iptacopan compared to anti-C5 antibody treatment

6.2.1.1. Design, Study CLNP023C12302 (APPLY-PNH)

Results from APPLY-PNH serve as the primary basis of the benefit evaluation. For more complete details of the study design, see the protocol synopsis included in Section 15.1.

APPLY-PNH is a multicenter, international, randomized, open-label, active comparator-controlled study in subjects with PNH and residual anemia (hemoglobin <10 g/dL) despite prior anti-C5 treatment (eculizumab or ravulizumab). The trial schema is shown in Figure 3. Subjects were randomized in an 8:5 ratio to receive either iptacopan 200 mg orally twice daily or to continue anti-C5 treatment throughout the duration of the 24-week RCP. The dose of eculizumab or ravulizumab was continued at the subject's current dosing regimen prior to study entry, which was consistent with the US approved prescribing for each product. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose is body weight-independent, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose is based on body weight. Randomization was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months. Following completion of the 24-week RCP, all subjects were eligible to enroll in a 24-week treatment extension period and receive iptacopan monotherapy. Subsequently, subjects were eligible to enter a separate long-term extension study.

Figure 3. Study Design – APPLY-PNH



Source: Applicant's Clinical Trial Protocol for APPLY-PNH
Abbreviations: b.i.d, twice daily; D, day; EOS, end of study; LNP023, iptacopan; PNH, paroxysmal nocturnal hemoglobinuria

Clinical Reviewer Comment:

An open-label study is reasonable as subjects continued their current anti-C5 therapy and the dosing regimen is different for eculizumab and ravulizumab, therefore, a double-blind trial was not feasible. The randomized treatment period (RTP) of 24 weeks is sufficient to determine benefit and is consistent with other approved drugs for PNH.

The comparators (eculizumab and ravulizumab) are approved drugs for PNH.

6.2.1.2. Eligibility Criteria, Study CLNP023C12302 (APPLY-PNH)

Key eligibility criteria are summarized in this section, and the full criteria are available in Section 15.1.

Inclusion Criteria

1. Male and female participants ≥18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with RBCs and with white blood cells granulocyte/monocyte clone size ≥10%
2. Stable regimen (dose and intervals) of anti-C5 antibody treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization
3. Mean hemoglobin level <10 g/dL
4. Vaccination against Neisseria meningitidis infection is required prior to the start of treatment. If the subject has not been previously vaccinated or if a booster is required, vaccine should be given according to local regulations at least 2 weeks prior to first dosing. If treatment has to start earlier than 2 weeks postvaccination, prophylactic antibiotic treatment must be initiated
5. If not received previously, vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* infections should be given if available and according to local regulations. The vaccines should be given at least 2 weeks prior to first dosing. If iptacopan treatment has to start earlier than 2 weeks postvaccination, prophylactic antibiotic treatment must be initiated

Exclusion Criteria

1. Individuals on a stable eculizumab dose but with a dosing interval of 11 days or less, or individuals on stable ravulizumab dose but with a dosing interval of less than 8 weeks
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
3. Known or suspected hereditary complement deficiency at screening
4. History of hematopoietic stem cell transplantation
5. Subjects with laboratory evidence of bone marrow failure (reticulocytes $<100\times10^9$/L (or $<100\times10^6$/mL); platelets $<30\times10^9$/L (or $<30\times10^6$/mL); neutrophils $<500\times10^6$/L (or $<500\times10^3$/mL)
6. Active systemic bacterial, viral (including coronavirus disease 2019 [COVID-19]) or fungal infection within 14 days prior to study drug administration
7. A history of recurrent invasive infections caused by encapsulated organisms, e.g., meningococcus or pneumococcus
8. Major concurrent comorbidities, including but not limited to severe kidney disease (e.g., estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2, dialysis), advanced cardiac disease (e.g., New York Heart Association class IV), severe pulmonary disease (e.g., severe pulmonary hypertension [World Health Organization class IV]), or hepatic disease (e.g., active hepatitis) that, in the opinion of the investigator, precludes participation in the study

9. Liver disease, such as active hepatitis B virus or hepatitis C virus infection defined as hepatitis B surface antigen positive or hepatitis C virus RNA positive, or liver injury as indicated by abnormal liver function tests at screening:
    a. Any single parameter of alanine aminotransferase (ALT), gamma-glutamyl transferase, alkaline phosphatase must not exceed 3×upper limit of normal (ULN)

Clinical Reviewer Comment:

The subject population is acceptable to assess the benefit of iptacopan for the treatment of PNH. The population includes subjects with hemolytic anemia despite receiving approved therapy.

6.2.1.3. Statistical Analysis Plan, Study CLNP023C12302 (APPLY-PNH)

Study Endpoints

Family of Two Primary Endpoints

1. Proportions of participants achieving a sustained increase in hemoglobin levels from baseline ≥2 g/dL between Day 126 (Week 18) and Day 168 (Week 24) in the absence of transfusions between Day 14 and Day 168
2. Proportions of participants achieving sustained hemoglobin levels ≥12 g/dL between Day 126 and Day 168 in the absence of transfusions between Day 14 and Day 168

The need for administration of red blood cell transfusion was defined as follows:

- Hemoglobin level ≤9 g/dL with signs and/or symptoms of sufficient severity to warrant a transfusion. Signs and symptoms that warrant a transfusion included severe or worsening of fatigue, severe or worsening dyspnea, palpitation/angina (or worsening symptoms), change in mental status (syncope, light-headedness, confusion, stroke, transient ischemic attack).
- Hemoglobin of ≤7 g/dL, regardless of presence of clinical signs and/or symptoms

Key Secondary Endpoints

1. Proportions of participants who are transfusion free by protocol-specified criteria between Day 14 and Day 168. The protocol-specified criteria for transfusions are described above.
2. Differences in average change from baseline in hemoglobin levels between Day 126 and Day 168.
3. Differences in average score changes from baseline evaluated between Day 126 and Day 168 of FACIT-Fatigue. A further description of the FACIT-Fatigue scale is discussed below.
4. Differences in average changes from baseline in reticulocyte counts evaluated between Day 126 and Day 168
5. Differences in average percent change from baseline in LDH evaluated between Day 126 and Day 168
6. Rates of BTH between Day 1 and Day 168. Clinical breakthrough hemolysis was defined in the protocol as a decrease in Hb >2 g/dL within 15 days or at the latest assessment, gross

hemoglobinuria, pain, dysphagia, or other PNH symptoms, and LDH >1.5x ULN compared to the last two assessments. Subclinical BTH was defined as a decrease in Hb <2 g/dL, moderate hemoglobinuria with no other clinical symptoms, and LDH >1.5x ULN. The protocol states that the assessment of BTH could be based on the local laboratory results.

7. Rates of MAVEs between Day 1 and Day 168. Major adverse vascular events were defined in the protocol as acute peripheral vascular occlusion, amputation (non-traumatic; nondiabetic), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, dermal thrombosis, gangrene (non-traumatic; nondiabetic), hepatic/portal vein thrombosis (Budd-Chiari syndrome), mesenteric/visceral arterial thrombosis or infarction, mesenteric/visceral vein thrombosis or infarction, myocardial infarction, pulmonary embolus, renal arterial thrombosis, renal vein thrombosis, thrombophlebitis / deep vein thrombosis, transient ischemic attack, unstable angina, or other, which would need to be specified. This endpoint was not adjudicated.

FACIT-Fatigue

As described in the review by the Division of Clinical Outcomes Assessment (DCOA) (final review in the Document Archiving, Reporting and Regulatory Tracking System [DARRTS] dated October 20, 2023), *"The FACIT-Fatigue is a 13-item patient-reported outcome (PRO) questionnaire designed to assess fatigue-related symptoms and impacts. Each item is rated on a five-point verbal rating scale (VRS) ranging from "Not at all," to "Very much." The recall period is the previous 7 days ("past 7 days"). The FACIT-Fatigue was administered electronically at Screening and at baseline, Day 1, Day 7, Day 14, Day 42, Day 84, Day 126, Day 140, Day 154, and Day 168 in both trials. The FACIT-Fatigue generates a total score ranging from 0 to 52, where a higher score equates to less fatigue."* The DCOA team did not review the instrument for validity and other measurement properties as it has previously been accepted and labeled for the context of PNH.

Clinical Reviewer Comment:

The primary endpoints of increase in hemoglobin, along with the key secondary endpoint of transfusion avoidance, is clinically meaningful in a population that is anemic despite receiving standard of care therapy with an approved drug for PNH. These endpoints have been used to support benefit for other approved drugs to treat PNH (see Section 3).

The Applicant selected to measure hematologic response based on the last six weeks of the 24 weeks (day 126 to 168) at the end of the randomized treatment period with four assessments, and 3 out of 4 meeting the criterion, in order to demonstrate a durable hematological response. This approach is reasonable, by measuring multiple timepoints in a 6-week period the hematologic response is likely due to effect of the study drug rather than fluctuations due to other factors (e.g., hydration status, illness or laboratory error).

The study was open-label and therefore there is a concern that bias may have been introduced given the nature of the trial design. The majority of endpoints were objective as they were based on laboratory measures (i.e., hemoglobin response, LDH, reticulocyte count). However, bias may have been introduced when determining the need for red blood cell transfusions. The Applicant decreased the risk of bias by including guidelines for when a subject should receive a transfusion, which included a hemoglobin <7g/dL or a hemoglobin level of ≤ 9 g/dL with signs

and/or symptoms to warrant a transfusion. In the protocol, the Applicant describes the signs and symptoms that would warrant a transfusion, including severe or worsening of fatigue, severe or worsening dyspnea, palpitation/angina and change in mental status (syncope, light-headedness, confusion, stroke, transient ischemic attack). In clinical practice, patients are often transfused when symptomatic from anemia. The guidelines for transfusions were reasonable and the risk of bias for the transfusion endpoint is likely minimized. However, PRO endpoints such as FACIT-Fatigue can potentially be impacted by the subjects' knowledge of treatment assignment and therefore this endpoint is difficult to interpret in an open-label trial. See Study results below for further discussion.

The definition of BTH, as described above is acceptable. While there is no standardized definition for BTH, elevated LDH level is the most commonly used biomarker (Brodsky et al. 2021).

Analysis Populations

- The randomized analysis set consisted of all randomized subjects.
- The full analysis set (FAS) consisted of all randomized subjects but excluded subjects to whom a randomization number had been assigned in error.
- The safety set included all subjects who received at least one dose of study treatment.

Randomization

Participants were randomized in an 8:5 ratio to either iptacopan monotherapy at a dose of 200 mg BID or anti-C5 antibody treatment, respectively. The randomization was stratified based on the type of prior anti-C5 antibody treatment (eculizumab/ravulizumab) and based on the transfusion history as reported during the last 6 months prior to randomization (i.e., transfusion received/not received).

Sample Size Determination

Under an assumption that participants on iptacopan treatment would achieve a proportion of 50% of responders having an increase of ≥2 g/dL from baseline compared to a proportion of 16% of responders on anti-C5 antibody treatment, the planned sample size of 56 participants on iptacopan and 35 participants on anti-C5 antibody treatment would provide 83.2% power for this endpoint at a one-sided significance level of 0.0125. Power for the endpoint corresponding to the achievement of sustained levels of hemoglobin ≥12 g/dL was 89.1%, calculated under the assumption that the proportions were 35% on iptacopan treatment and 5% on anti-C5 antibody treatment at a one-sided significance level of 0.0125. Power for the simultaneous test could not be exactly derived, but a minimum power corresponding to assuming a Bonferroni adjustment was approximately 95% for the marginal power assumptions.

Nominal power for prioritized secondary endpoints of transfusion avoidance, change in hemoglobin, FACIT-Fatigue, reticulocyte counts was estimated to be between 85% and 90% at full study alpha (one-sided 0.025), without considering the adjustment for multiple testing derived from the procedure used. The power of LDH, BTH, and MAVE were estimated to be lower.

Reviewer Comment: The assumption of 50% was derived from experience from eculizumab in patients with PNH. PNH Study 1, NCT00122330 was a randomized, double-blind, placebo-controlled 26-week study in 87 subjects with PNH with at least four transfusions in the prior 12 months. Subjects were randomized 1:1 to placebo or eculizumab. Approximately 50% of subjects achieved the primary endpoint of hemoglobin stabilization compared to none in the placebo arm. The Applicant's assumption was acceptable (Alexion Pharmaceuticals 2020).

Analysis of the Primary Efficacy Endpoints

Primary Analyses

For each primary endpoint in the primary endpoint family, the permutation test based on conditional logistic regression was prespecified as the primary analysis method, with randomization strata, sex, indicator variable of age ≥45 years, and indicator variable of baseline hemoglobin ≥9 g/dL as factors. In case of nonconvergence in any of the multiple imputed datasets arising from sparsity or no response in one of the treatment arms in at least one imputed dataset, the logistic regression model based on Firth's penalized maximum likelihood method would be used as an alternative method.

Handling of Missing Values

Multiple imputation was performed 100 times based on the randomized treatment labels with the following imputation rules:

- For subjects withdrawing from study follow up after discontinuation of iptacopan, their pretreatment levels of Hb were used in the analysis throughout the study via the copy-reference method.
- For anti-C5 randomized subjects withdrawing from the study, missing data were imputed under a missing at random (MAR) assumption.
- For subjects with intermittent missing data during study follow-up where reasons for missingness were assumed to be unrelated to response or compliance status, their missing data were imputed under a MAR assumption.

For subjects with missing hemoglobin data, the need for transfusion was derived from the multiple imputation method with imputed values ≤9 g/dL considered sufficient to warrant a transfusion.

The permutation test was used to test each primary endpoint. For each permutation, the 100 results from 100 multiply imputed datasets were combined using Rubin's rule to obtain a single p-value for each permutation. The reference distribution of the p-values was derived using 50,000 permuted realizations of the treatment labels within each randomization stratum and obtaining the p-values of each of the two endpoints for each realization of permuted treatment labels. The observed p-value with the actual treatment labels was compared with the 1.25^{th} percentiles (or 1.375^{th} percentile as appropriate) of the 50,000 resulting p-values from fits with permuted treatment labels for each of the two endpoints.

Statistical Reviewer Comment:

In the "safe to proceed" letter dated September 28, 2020, the Agency recommended that the primary analysis for all binary endpoints be based on the stratified Cochran-Mantel-Haenszel (CMH) test. The Agency re-emphasized this recommendation and informed the Applicant that the determination of drug efficacy would be based on the primary analysis of CMH during the pre-NDA meeting dated December 14, 2022. The Applicant acknowledged the Agency's recommendation.

For results of primary endpoints included in the label, the Agency recommended that the Applicant report the analysis results based on the CMH test with randomization stratification factors and imputation of missing data as nonresponders.

Sensitivity Analyses

The sensitivities of the primary analysis results with respect to the handling of missing data were evaluated using tipping point analyses. In these methods, missing values in each treatment group were imputed separately, and an adjustment of the assumed treatment effect 'delta' for the iptacopan group was applied to the imputed values. The primary analysis was repeated by applying the delta value in the iptacopan group, resulting in a lower hemoglobin value than the imputed value.

Additional sensitivity analyses on the two primary endpoints were performed where missing central lab hemoglobin data were replaced by available local lab data collected at the same visit, using the same regression model that was used for the primary efficacy analysis.

Supplementary Analyses

For the purpose of the efficacy assessment, a supplementary estimand was performed considering the use of rescue therapy (as defined in the study protocol) under intercurrent events as treatment failure according to the rules listed below. The supplementary estimand had the same population, treatment of interest, and summary measure as the primary estimand. In addition, the marginal proportions difference and ratio were computed using a logistic regression model.

- The regression model, which was used for the primary efficacy analysis, was performed for the supplementary analyses on the two primary endpoints. Participants who met the criteria for administration of RBC transfusions or received a transfusion between Day 14 and Day 168 were considered treatment failures.
- Participants who used rescue medication and rescue therapy during the randomized treatment period between Day 1 and Day 168 were considered treatment failures.
- Discontinuations of study medication for any reason were handled with the treatment policy strategy.

Subgroup Analyses

Subgroup analyses of the primary endpoints were performed for the following variables:

- Length of time since diagnosis
- Age categories

- Sex
- Baseline hemoglobin
- History of MAVE prior to screening
- Transfusions in the last 6 months prior to starting study treatment
- Number of transfusions in the last 6 months prior to starting study treatment

Statistical Reviewer Comment:

The Applicant originally performed the subgroup analyses using the logistic regression model. Per the Agency's recommendation, the Applicant reanalyzed these subgroups using the CMH test with nonresponder imputation for missing data.

Analysis of the Secondary Efficacy Endpoints

Transfusion Avoidance

Transfusion avoidance was evaluated by using logistic regression comparing the proportion of participants not receiving and not meeting the criteria of administration of RBC transfusion between Day 14 and Day 168, similar to the comparison applied to the primary estimand by means of the odds ratio with standardized marginal proportions derived similarly (including in both cases the prespecified randomization strata and covariates). The logistic regression model included the following covariates: prior anti-C5 treatment, transfusion history, sex, age (indicator of age ≥45 years), and an indicator variable of baseline hemoglobin ≥9 g/dL. In case of nonconvergence arising from sparsity or no response in one of the treatment arms, the logistic regression model based on Firth's penalized maximum likelihood method would be implemented.

Statistical Reviewer Comment:

Refer to Section 6.3.1 for detailed review issues for the transfusion avoidance endpoint.

Change From Baseline in Hemoglobin Levels

Changes in hemoglobin levels from baseline were compared between groups under the hypothetical situation in which participants would not have received RBC transfusions on any of the treatments. For this analysis, if a participant had received a transfusion during the randomized treatment period, then the hemoglobin values 30 days following the transfusion were considered missing and hemoglobin data were imputed. The model for the comparison between treatments was a mixed model for repeated measures (MMRM) considering an unstructured covariance structure. The model included main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥45 years), sex, treatment, visit, baseline hemoglobin, and the interactions between visits and treatment and visits and baseline levels. The treatment contrasts were computed as the comparison of treatments corresponding to the average measured in the last 6 weeks of randomized treatment (i.e., the visits occurring between Day 126 and Day 168).

Change From Baseline in FACIT-Fatigue Scores

The model for the comparison between treatments was an MMRM considering an unstructured covariance structure. The model included main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥45 years), sex, treatment, visit and baseline scores of fatigue, and the interactions between visits and treatment and visits and baseline levels. The comparison between treatments was based on the average of treatment estimates derived for visits occurring between Day 126 and Day 168.

Change From Baseline in Reticulocyte Counts

The comparison of the change from baseline in absolute reticulocyte counts was derived from an MMRM, including data collected throughout the study and where baseline was defined as the value on Day 1. The model for the comparison between treatments was an MMRM considering an unstructured covariance structure. The model included main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥45 years), sex, treatment, visit, baseline reticulocyte count, and the interactions between visits and treatment and visits and baseline levels. The comparison between treatments was based on the average of model-derived estimates for each treatment obtained at visits occurring between Day 126 and Day 168.

Percent Change From Baseline in LDH

The treatment effect on percent change from baseline in LDH was assessed using an MMRM of log transformed ratio to baseline based on all observations collected during the randomized treatment period. The model for the comparison between treatments was an MMRM considering an unstructured covariance structure. The model included main effect of prior anti-C5 treatment, transfusion history, age (indicator of age ≥45 years), sex, treatment, visit, log-transformed baseline LDH, and the interactions between visits and treatment and visits and log-transformed baseline levels. Treatment comparisons were derived based on the average of the log transformed ratio from baseline in each treatment estimated between Day 126 and Day 168.

Rates of Clinical Breakthrough Hemolysis

The comparison of rates of clinical BTH was conducted using a negative binomial model. The model included the following covariates: treatment, randomization strata (prior anti-C5 antibody treatment, transfusion history), sex, age (indicator of age ≥45 years), and indicator variable of baseline hemoglobin ≥9 g/dL. Following the treatment policy strategy for handling treatment discontinuations, the offset variable was defined as the time from Day 1 until the end of study or the end of the randomized treatment period, whichever came first.

If the above model failed to converge or give valid estimates (if all events were in one level of at least one of the covariates) due to low frequency of occurrences, then the model was run considering only treatment as a factor in the negative binomial model. If the model failed to converge or give valid estimates, then a Poisson model with treatment as a factor was fitted. If there is one treatment with no observed events and rate ratio cannot be computed, then rate difference and corresponding p-value were presented.

Rates of Major Adverse Vascular Events

The comparison of rates of MAVEs was conducted using a negative binomial model. Due to the expected low frequency of occurrences, no covariates were planned to be included. Only treatment was added as a factor in the negative binomial model. Following the treatment policy strategy for handling treatment discontinuations, the offset variable was defined as the time from Day 1 until the end of study or the end of the randomized treatment period, whichever came first.

If the model failed to converge or to give valid estimates, then a Poisson model with treatment as a factor was fitted. If there was one treatment having no events and rate ratio could not be computed, then rate difference and corresponding p-value were presented.

Handling of Missing Values for Secondary Endpoints

For primary analyses of key secondary endpoints, missing data during the study follow-up were imputed by using the following principles: intermittent missing data were imputed according to the MAR assumption; missing data due to withdrawal from the study were imputed using a "copy-reference" in the iptacopan arm and according to the MAR in the control arm.

Statistical Reviewer Comment:

Refer to Section 6.3.1 for detailed review issues of the transfusion avoidance endpoint.

For continuous endpoints included in the label, the Agency recommended that the Applicant report the analysis results based on the MMRM model using the observed data because the MMRM has already handled missing data with the MAR assumption.

Supportive Analyses

To complement the secondary estimand analysis of average changes in hemoglobin under a hypothetical strategy, the analysis comparing average changes in hemoglobin was repeated using a treatment policy approach to obtain the comparison of the combination of iptacopan + transfusions as needed to anti-C5 antibody treatment + transfusions as needed.

Changes from baseline in LDH, FACIT-Fatigue, and reticulocytes were performed under a hypothetical strategy. For these analyses, the values on these three endpoints in the 30 days following transfusion were considered missing and the values were imputed.

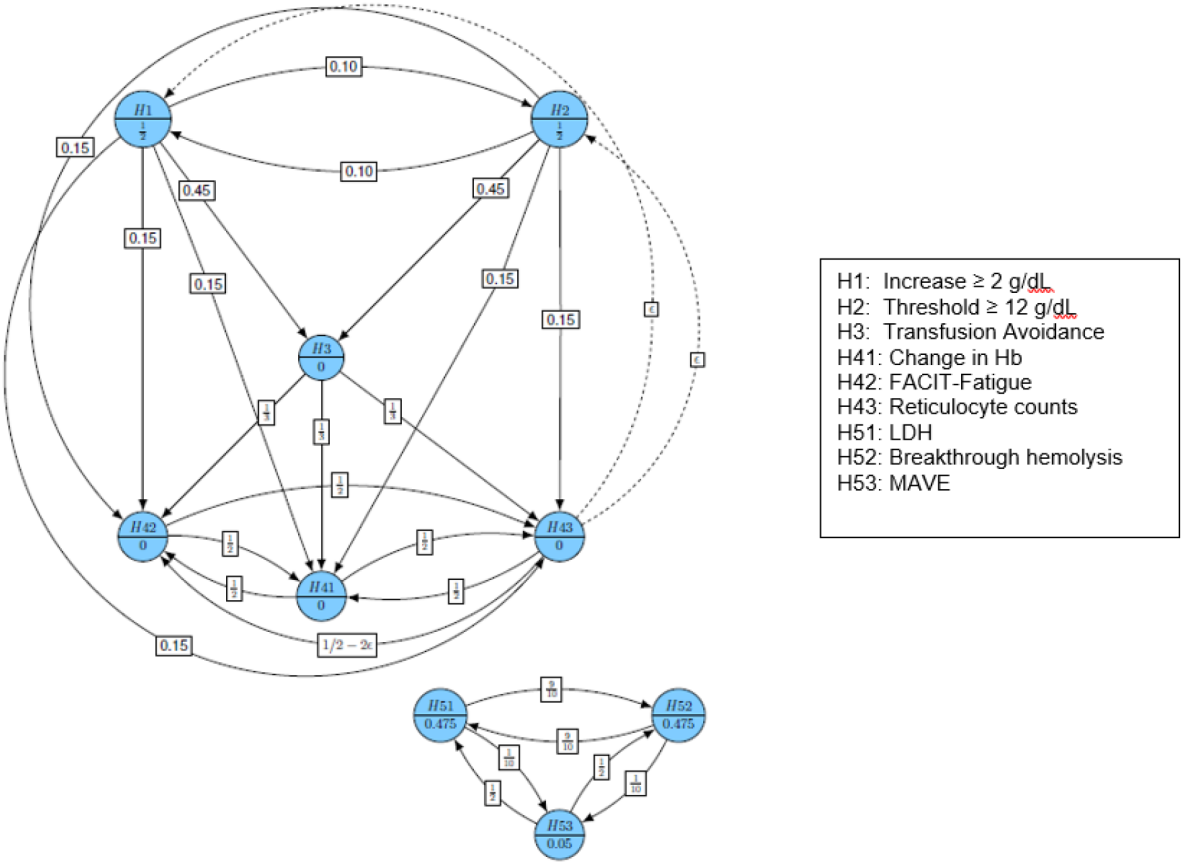
Sensitivity Analyses

Sensitivity analyses were performed where missing central lab data were replaced by available local lab data collected at the same visit.

Multiplicity Adjustment

A graphical approach was applied to control the study wise type I error of 0.05, as shown in Figure 4.

Figure 4. Graphical Display of Multiple Testing Procedure, Study CLNP023C12302



Source: The Applicant's statistical analysis plan.
Abbreviations: FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event

The two primary endpoints were tested first with equal weights. If one or both primary endpoints were rejected, the local alpha was passed on to the set of four secondary endpoints of transfusion avoidance, change in hemoglobin, FACIT-Fatigue, and reticulocyte counts. The remaining three endpoints of LDH, BTH, and MAVE were tested only after successful rejection of the hypotheses of all previous endpoints.

Statistical Reviewer Comment:

During the pre-NDA meeting dated December 14, 2022, the Agency asked the Applicant to justify the weights for all endpoints included in the graphic approach. In the response, the Applicant stated that the sequence of tests in the testing strategy and rationale for weights were based on medical judgement and study design considerations (e.g., lower ranking provided to MAVEs considering the low frequency of events expected based on studies of similar duration with anti-C5 treatment and on the number of subjects randomized into the study).

Interim Analysis

No formal interim analyses of efficacy were planned in this study.

6.2.1.4. Results of Analyses, Study CLNP023C12302 (APPLY-PNH)

Data Quality and Integrity

Data were provided electronically in standard data format with a study data tabulation model and analysis data model. Statistical analysis software programs used to create key efficacy and safety outputs for the study were submitted along with the data of the NDA. The Applicant also provided a clear definition file for datasets and detailed analysis programs for assisting review. The links to the data from the pivotal Study CLNP023C12302 are: \\CDSESUB1\evsprod\NDA218276\0000\m5\datasets\clnp023c12302 and \\CDSESUB1\evsprod\NDA218276\0041\m5\datasets\clnp023c12302

Statistical Reviewer Comment:

The APPLY-PNH (CLNP023C12302) clinical study data with a data cutoff of September 26, 2022, was used for the planned primary efficacy and safety analyses.

On October 24, 2023, the Applicant submitted updated datasets and analyses, reporting that an RBC transfusion administered during the 24-week randomized treatment period to a subject in the iptacopan treatment arm (subject (b) (6)) had been captured in source data, but it was not included in the database or datasets in the NDA due to an error at the site. This resulted in the unlocking and correction of the affected data in the final study database.

Following the correction of the dataset (i.e., inclusion of the transfusion for subject (b) (6)), the subject, who was originally considered to meet the transfusion avoidance endpoint, became a failure. This additional RBC transfusion also resulted in small numerical changes to the results of analyses that applied multiple imputation for the two primary endpoints and the key secondary endpoint of "change from baseline hemoglobin."

In addition, the updated datasets and analyses reflected a correction of an error in the visit labeling of one subject's central laboratory samples (at one visit), which resulted in modifications to the central lab results at this one time point, including LDH and absolute reticulocyte count. This update resulted in minor changes in two of the key secondary endpoints results: ratio to baseline of LDH and change from baseline in reticulocyte counts.

Furthermore, a few corrections were applied by the sites in the update, which altered a few baseline characteristics. Changes included the following:

- *An update of a partial date to a full date, which changed the calculation of the disease duration for one subject*
- *The reporting of a subject with a MAVE in the MAVE history*
- *Reporting of additional transfusions during the screening period for two subjects*

The analyses presented in this review are based on the updated datasets.

Following the update, the Agency requested clarification from the Applicant regarding the steps taken to ensure that results were accurately captured in their datasets. The Applicant provided the following clarifications:

- *The Novartis Quality Management System is a structured and documented approach describing Novartis standards with regards to GxP requirements and other relevant standards and guidelines to ensure quality of all products. All Novartis clinical studies follow well-established standard operating procedures/processes for data collection, monitoring, and data review governed by the Novartis Quality Management System. Annually, a unified quality audit plan is prepared. Areas in scope of the unified quality audit plan are audits of internal Novartis clinical quality systems and processes subject to GxP regulations. To ensure that clinical data were recorded, analyzed, and accurately reported according to the protocol, the sponsor's standard operating procedures, good clinical practice (GCP), and the applicable regulatory requirement(s), an audit target risk assessment and planning occurs on an annual basis for implementation of the coming year.*
- *Novartis processes were applied to the execution of the APPLY-PNH study, including all activities involved in quality assurance and quality control, to ensure compliance with written standard operating procedures as well as applicable global/local GCP regulations and International Council for Harmonization guidelines.*
- *Routine monitoring visits were performed per the study-specific monitoring plan, which included trial-specific critical data and processes to ensure compliance of all monitoring activities with International Council for Harmonization GCP guidelines, applicable regulatory requirements, Novartis standard operating procedures, working practices, and the trial protocol.*
- *For every Novartis study including the APPLY-PNH study, a data quality plan is developed to ensure that data review is completed on an ongoing basis and discrepancies are queried, tracked, and resolved appropriately following the established standard procedures. Before the database lock milestones, as an additional checkpoint, a database lock checklist and approval form are completed to ensure all outstanding issues are addressed or documented as appropriate per established procedural documents.*
- *Per Novartis standard operating procedures and working practices for clinical data collection and data management activities, following the primary analysis database lock ("interim" database lock), if any changes or updates is identified by a site, clinical research associate, third party, or the Novartis global study team, a risk/impact assessment is performed by the study team to evaluate the impact of these changes on subject safety, data integrity, or data analysis. If a significant change to the previously cleaned data is noted, then necessary steps to provide updated data to health authorities are initiated.*

The Agency checked the Applicant's re-analysis results and determined that the Applicant's responses were acceptable.

Subject Disposition

For this study, the randomized analysis set, full analysis set, and safety analysis set were the same. In these analysis sets, 62 subjects were in the iptacopan group and 35 were in the anti-C5 group.

A total of 96 subjects completed the randomized treatment period on treatment. One subject in the iptacopan group discontinued study treatment due to pregnancy. This subject continued study assessments until the end of the randomized treatment period.

Table 8 shows the disposition of the study.

Table 8. Subject Disposition, Randomized Treatment Period, Study CLNP023C12302

Disposition Outcome	Iptacopan 200 mg	Anti-C5	Overall
Subjects randomized	62 (100.0%)	35 (100.0%)	97 (100.0%)
FAS population	62 (100.0%)	35 (100.0%)	97 (100.0%)
Safety population	62 (100.0%)	35 (100.0%)	97 (100.0%)
Discontinued study drug	1 (1.6%)	0 (0.00%)	1 (1.0%)
Pregnancy	1 (1.6%)	0 (0.00%)	1 (1.0%)
Discontinued study	0 (0.00%)	0 (0.00%)	0 (0.00%)

Source: The Applicant's clinical study report.
Abbreviations: FAS, full analysis set

Demographic Characteristics

Table 9 shows the demographic and baseline characteristics of the study.

Table 9. Demographic and Baseline Characteristics, Study CLNP023C12302–Full Analysis Set

Characteristic	Iptacopan 200 mg (N=62)	Anti-C5 (N=35)	Overall (N=97)
Age (years)			
Mean (SD)	51.7 (16.94)	49.8 (16.69)	51.0 (16.79)
Median [Min, Max]	53.0 [22.0, 84.0]	45.0 [20.0, 82.0]	53.0 [20.0, 84.0]
Age category (years)			
18 - <65 years	44 (71.0%)	27 (77.1%)	71 (73.2%)
65 - <75 years	12 (19.4%)	7 (20.0%)	19 (19.6%)
≥75 years	6 (9.7%)	1 (2.9%)	7 (7.2%)
Sex			
Female	43 (69.4%)	24 (68.6%)	67 (69.1%)
Male	19 (30.6%)	11 (31.4%)	30 (30.9%)
Race			
Asian	12 (19.4%)	7 (20.0%)	19 (19.6%)
Black or African American	2 (3.2%)	2 (5.7%)	4 (4.1%)
White	48 (77.4%)	26 (74.3%)	74 (76.3%)
Ethnicity			
Hispanic or Latino	8 (12.9%)	2 (5.7%)	10 (10.3%)
Not Hispanic or Latino	51 (82.3%)	27 (77.1%)	78 (80.4%)
Not reported	2 (3.2%)	6 (17.1%)	8 (8.2%)
Unknown	1 (1.6%)	0 (0%)	1 (1.0%)

Characteristic	Iptacopan 200 mg (N=62)	Anti-C5 (N=35)	Overall (N=97)
Country or Region			
Brazil	2 (3.2%)	2 (5.7%)	4 (4.1%)
Czech Republic	1 (1.6%)	0 (0%)	1 (1.0%)
Germany	13 (21.0%)	7 (20.0%)	20 (20.6%)
Spain	3 (4.8%)	1 (2.9%)	4 (4.1%)
France	9 (14.5%)	6 (17.1%)	15 (15.5%)
United Kingdom	5 (8.1%)	6 (17.1%)	11 (11.3%)
Italy	12 (19.4%)	5 (14.3%)	17 (17.5%)
Japan	6 (9.7%)	3 (8.6%)	9 (9.3%)
Republic of Korea	1 (1.6%)	0 (0%)	1 (1.0%)
Netherlands	2 (3.2%)	2 (5.7%)	4 (4.1%)
Taiwan	2 (3.2%)	1 (2.9%)	3 (3.1%)
United States	6 (9.7%)	2 (5.7%)	8 (8.2%)
Disease duration (years)			
Mean (SD)	11.9 (9.81)	13.5 (10.94)	12.5 (10.21)
Median [Min, Max]	9.0 [0.7, 40.2]	11.6 [1.5, 42.0]	9.5 [0.7, 42.0]
Anti-C5 medication history - 6 months prior to randomization			
Eculizumab	40 (64.5%)	23 (65.7%)	63 (64.9%)
Ravulizumab	22 (35.5%)	12 (34.3%)	34 (35.1%)
Eculizumab dose administered (mg) during 6 months prior to randomization			
Median [Min, Max]	900 [900, 1200]	900 [900, 1500]	900 [900, 1500]
Ravulizumab dose administered (mg) during 6 months prior to randomization			
Median [Min, Max]	3300 [3000-3600]	3300 [3000-3600]	3300 [3000-3600]
Duration of anti-C5 treatment (years)			
Mean (SD)	3.8 (3.57)	4.2 (3.87)	4.0 (3.67)
Median [Min, Max]	2.6 [0.5, 16.6]	2.7 [0.4, 16.6]	2.6 [0.4, 16.6]
Baseline hemoglobin (g/dL)			
Mean (SD)	8.9 (0.70)	8.9 (0.89)	8.9 (0.77)
Median [Min, Max]	9.0 [6.8, 10.0]	9.0 [6.2, 9.9]	9.0 [6.2, 10.0]
Baseline hemoglobin category			
<9 g/dL	32 (51.6%)	18 (51.4%)	50 (51.5%)
≥9 g/dL	30 (48.4%)	17 (48.6%)	47 (48.5%)
LDH levels at baseline (U/L)			
Mean (SD)	269.1 (70.14)	272.7 (84.80)	270.4 (75.34)
Median [Min, Max]	267.5 [150.0, 539.0]	261.0 [133.0, 562.0]	263.0 [133.0, 562.0]
Baseline LDH category			
≤1.5x ULN	58 (93.5%)	32 (91.4%)	90 (92.8%)
>1.5x ULN	4 (6.5%)	3 (8.6%)	7 (7.2%)
Transfusion - 6 months prior to randomization			
No	27 (43.5%)	14 (40.0%)	41 (42.3%)
Yes	35 (56.5%)	21 (60.0%)	56 (57.7%)

Characteristic	Iptacopan 200 mg (N=62)	Anti-C5 (N=35)	Overall (N=97)
Number of transfusions – 6 months prior to randomization (for subjects who had received ≥1 transfusion within 6 months prior to randomization)			
Mean (SD)	3.1 (2.58)	4.0 (4.34)	3.4 (3.34)
Median [Min, Max]	2.0 [1.0, 13.0]	2.0 [1.0, 19.0]	2.0 [1.0, 19.0]
Baseline Platelets (10^9/L)			
Mean (SD)	160.2 (63.83)	147.3 (77.01)	155.6 (68.77)
Median [Min, Max]	148.0 [33.0, 348.0]	138.0 [39.0, 355.0]	148.0 [33.0, 355.0]
Baseline Reticulocytes (10^9/L)			
Mean (SD)	193.2 (83.64)	190.6 (80.92)	192.3 (82.25)
Median [Min, Max]	176.6 [51.0, 562.8]	159.6 [90.3, 411.6]	173.8 [51.0, 562.8]
Baseline FACIT Fatigue score			
Mean (SD)	34.7 (9.82)	30.8 (11.45)	33.4 (10.52)
Median [Min, Max]	34.8 [11.0, 52.0]	31.5 [10.0, 50.0]	33.0 [10.0, 52.0]
Missing	0 (0%)	2 (5.7%)	2 (2.1%)
History of MAVE Prior to Screening			
No	50 (80.6%)	25 (71.4%)	75(77.3%)
Yes	12 (19.4%)	10 (28.6%)	22 (22.7%)
Total PNH Clone Size[a]			
Mean (SD)	64.6 (27.45)	57.4 (29.73)	62.0 (28.36)
Median [Min, Max]	66.0 (10.6, 99.9)	52.8 (9.8, 99.4)	61.2 (9.8, 99.9)

Source: FDA reviewer generated the table from clinical data submitted by the Applicant.
[a] Total PNH clone size is calculated as sum of percentages of positive Red Blood Cells of Type II and Type III.
Abbreviations: FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; FDA, Food and Drug Administration; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; max, maximum; min, minimum; N, number of subjects; PNH, paroxysmal nocturnal hemoglobinuria; SD, standard deviation; ULN, upper limit of normal

Clinical Reviewer Comment:

Demographics and baseline disease characteristics were generally well balanced between treatment groups. A majority of subjects were <65 years of age, female, and White. Only 8.2% of subjects were from the U.S, however the results are still applicable to the U.S. population as PNH is due to a somatic mutation in the PIG-A gene; therefore, factors such as country of origin or environmental factors are not likely to have a significant impact on response to therapy. The disease presentation and progression are similar regardless of whether patients are from the US or ex-US. Subjects were on anti-C5 therapy for a mean of 4 years, and the mean baseline Hb was 8.9 g/dL. About 58% of subjects had received at least one transfusion in the preceding 6 months (among these subjects, there was a median of 2 transfusions; range 1-19). The median dose of eculizumab and ravulizumab in the previous 6 months prior to randomization was consistent with each drug product's recommended dosage per the USPI.

Efficacy Results of Primary Endpoints

The results of the Applicant's proposed primary analyses (i.e., based on the logistic regression and the permutation test) for the two primary endpoints are shown in Table 10. Because there were zero responders in the anti-C5 antibody group, the prespecified conditional logistic regression model did not converge. Therefore, a prespecified alternative method to cope with

nonconvergence, i.e., the logistic regression model based on the Firth penalized maximum likelihood method, was used for the final analyses.

The p-values from the logistic regression model using Firth correction were <0.0001 for both primary endpoints, which were smaller than the respective 1.25th percentiles (i.e., 0.017 for both primary endpoints) of p-values from permutation distributions. Therefore, the statistical significance was reached for the permutation test.

Table 10. Results of the Applicant's Proposed Primary Analyses for the Two Primary Endpoints, Study CLNP023C12302

Endpoints	Iptacopan (N=62) Number of Responders	Anti-C5 (N=35) Number of Responders	Difference Between Responders (%) (95% CI)	2-Sided P-Value[a]	Stat. Sig.[b]
≥2 g/dL increase in Hb from baseline[c] in the absence of RBC transfusions[d]	51 (82.3%)	0 (0.0%)	80.2 (71.2, 87.6)	<0.0001	Yes
Hb ≥12 g/dL[c] in the absence of RBC transfusions[d]	42 (67.7%)	0 (0.0%)	67.0 (56.4, 76.9)	<0.0001	Yes

Source: The Applicant's clinical study report and the updated analyses.
[a] Based on logistic regression model using Firth correction with randomization strata, sex, indicator variable of age ≥45 years, indicator variable of baseline hemoglobin ≥9 g/dL as factors.
[b] Based on the threshold of significance generated from 50,000 permuted realizations of the treatment labels
[c] Between Day 126 and 168 (at least 3 out of 4 scheduled measurements).
[d] Between Day 14 and Day 168. Requiring RBC transfusions refers to any subject receiving transfusions or meeting protocol defined criteria.
Abbreviations: CI, confidence interval, Hb, hemoglobin; N, number of subjects; RBC, red blood cell; Stat. sig; statistical significance

Table 11 shows the results of sensitivity analyses for the two primary endpoints. These exploratory results are consistent with the primary analysis results.

Table 11. Results of Sensitivity Analyses for the Two Primary Endpoints, Study CLNP023C12302

Endpoints	Analysis Description Source	Iptacopan vs. Anti-C5 Treatment Effect (95% CI)
≥2 g/dL increase in Hb from baseline[a] in the absence of RBC transfusions[b]	Tipping point analysis: Imputed hemoglobin values were lowered by a value delta of 2 g/dL in the iptacopan group	76.8 (66.9, 85.4)
	Analysis including local labs: If central lab data missing, include local laboratory data	80.3 (71.2, 87.6)
Hb levels ≥12 g/dL[a] in the absence of RBC transfusions[b]	Tipping point analysis: Imputed hemoglobin values were lowered by a value delta of 2 g/dL in the iptacopan group	64.1 (52.9, 74.0)
	Analysis including local labs: If central lab data missing, include local laboratory data	67.0 (56.4, 76.8)

Source: The Applicant's clinical study report and the updated analyses.
[a] Between Day 126 and 168 (at least 3 out of 4 scheduled measurements).
[b] Between Day 14 and Day 168. Requiring RBC transfusions refers to any subject receiving transfusions or meeting protocol defined criteria.
Abbreviations: CI, confidence interval; Hb, hemoglobin; RBC, red blood cell

A supplementary analysis was performed considering subjects who required rescue therapy as failures for the primary hematological response endpoints. However, because no subject received rescue medications or had rescue procedures during the randomized treatment period, the results of the supplementary analysis were identical to the primary analysis results.

Statistical Reviewer Comment:

For all binary endpoints, in the "safe to proceed" letter dated September 28, 2020, the Agency recommended that the primary analysis be based on the stratified CMH test rather than the Applicant's proposed logistic regression under the permutation test because the logistic regression requires certain assumptions. The Agency re-emphasized this recommendation and informed the Applicant during the pre-NDA meeting dated December 14, 2022, that the determination of drug efficacy would be mainly based on the primary analysis of CMH. However, the Applicant did not change the primary analysis method to CMH in their final version of the statistical analysis plan (SAP).

During the review of the NDA submission, as per the Agency's recommendation, the Applicant reconducted the analyses for the primary endpoints based on the CMH test with imputation of missing data as nonresponders using randomization strata as factors. The results were consistent with the Applicant's prespecified analysis results, as shown in Table 12. The Agency recommended reporting the study results based on the CMH analyses in the label.

Note that only two subjects randomized to the iptacopan group had missed central hemoglobin data between Day 126 and Day 168. Therefore, the impact of missing data on the analysis of the primary endpoints is minimal, and the Agency's recommendation of imputing missing data as nonresponders is conservative.

Table 12. Results of the Agency's Recommended Primary Analyses for the Two Primary Endpoints, Study CLNP023C12302

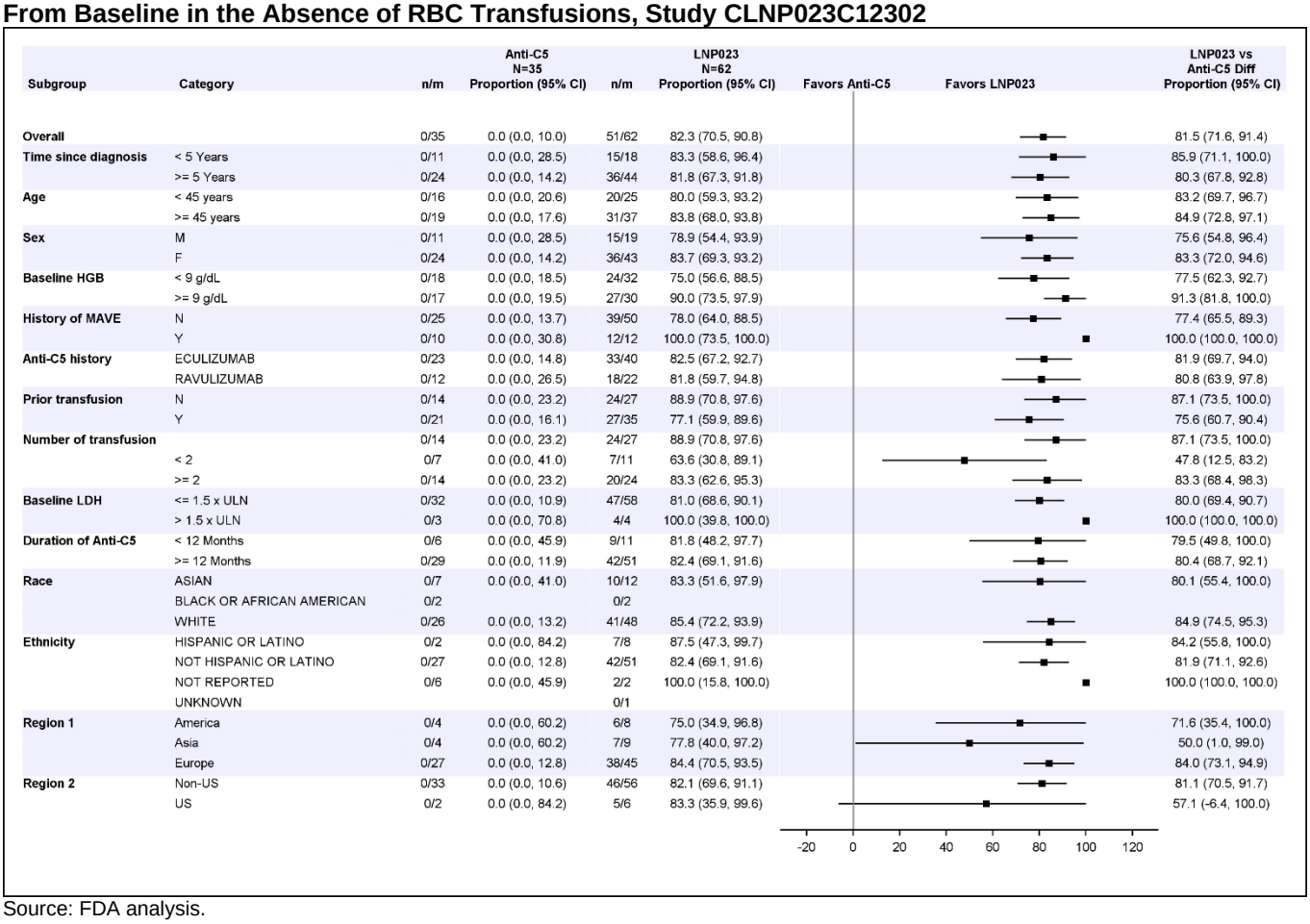
Primary Endpoint	Iptacopan (N=62) Number of Subjects Responding	Anti-C5 (N=35) Number of Subjects Responding	Difference Between Responders (%) (95% CI)[a]
≥2 g/dL increase in Hb from baseline[c] in the absence of RBC transfusions[d]	51 (82.3%)	0 (0.0%)	81.5 (71.6, 91.4)
Hb ≥12 g/dL[b] in the absence of RBC transfusions[c]	42 (67.7%)	0 (0.0%)	66.6 (54.6, 78.6)

Source: The Applicant's responses to the Agency's information requests.
[a] The common rate difference is based on Mantel-Haenszel stratum weights with randomization strata as factors; the 95% CIs are based on the Sato variance estimator.
[b] Between Day 126 and 168 (at least 3 out of 4 scheduled measurements).
[c] Between Day 14 and Day 168. Requiring RBC transfusions refers to any subject receiving transfusions or meeting protocol defined criteria.
Abbreviations: CI, confidence interval; Hb, hemoglobin; N, number; RBC, red blood cell

Subgroup Analyses of the Primary Endpoints

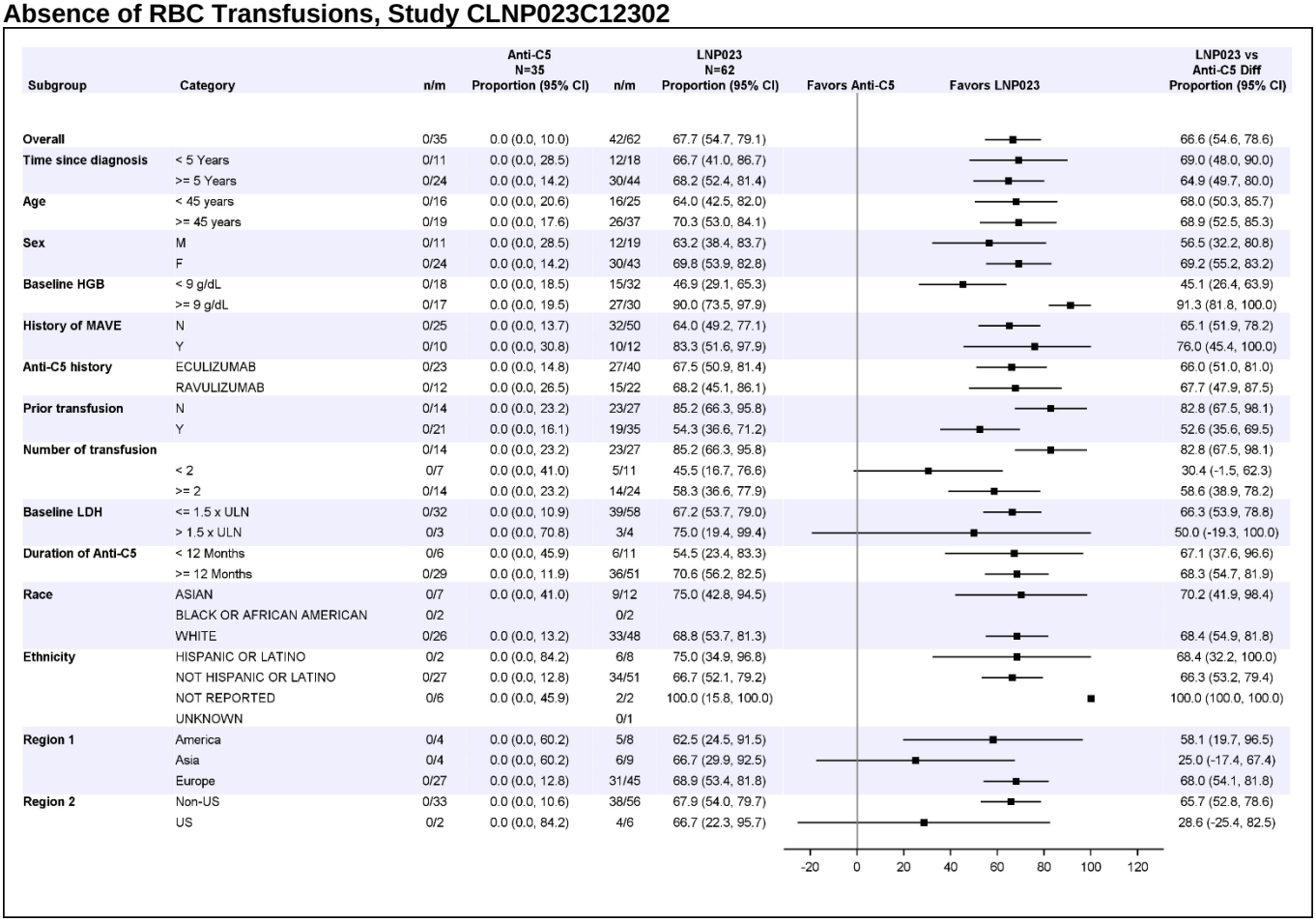
As per the Agency's recommendation, the Applicant reconducted subgroup analyses based on the CMH test to assess the potential for differences in the treatment effect for various demographic and clinical characteristics groups, as shown in Figure 5 and Figure 6. Overall, the treatment effect of iptacopan compared to anti-C5 therapy was consistent across baseline demographics and disease characteristics subgroups that had adequate numbers of subjects. However, these subgroup analyses were limited by the small numbers of subjects, so the results should be interpreted with caution. In particular, the 95% CI of the US subgroup includes zero, while the large variability associated with the estimate appears to be due to the small sample size.

Figure 5. Results of the Subgroup Analyses for the Primary Endpoint of ≥2 g/dL Increase in Hb From Baseline in the Absence of RBC Transfusions, Study CLNP023C12302



Source: FDA analysis.
Note: The common rate difference is based on Mantel-Haenszel stratum weights with randomization strata as factors; the 95% CIs are based on the Sato variance estimator.
Abbreviations: CI, confidence interval; Diff, difference; FDA, Food and Drug Administration; HGB, hemoglobin; LDH, lactate dehydrogenase; LNP023, iptacopan; MAVE, major adverse vascular event; N, number of subjects on the full analysis set; m, number of responders in the subgroup; n, number of subjects in the subgroup; RBC, red blood cell; ULN, upper limit of normal; US, United States; vs, versus

Figure 6. Results of the Subgroup Analyses for the Primary Endpoint of Hb ≥12 g/dL in the Absence of RBC Transfusions, Study CLNP023C12302



Subgroup	Category	Anti-C5 N=35 n/m	Anti-C5 N=35 Proportion (95% CI)	LNP023 N=62 n/m	LNP023 N=62 Proportion (95% CI)	LNP023 vs Anti-C5 Diff Proportion (95% CI)
Overall		0/35	0.0 (0.0, 10.0)	42/62	67.7 (54.7, 79.1)	66.6 (54.6, 78.6)
Time since diagnosis	< 5 Years	0/11	0.0 (0.0, 28.5)	12/18	66.7 (41.0, 86.7)	69.0 (48.0, 90.0)
	>= 5 Years	0/24	0.0 (0.0, 14.2)	30/44	68.2 (52.4, 81.4)	64.9 (49.7, 80.0)
Age	< 45 years	0/16	0.0 (0.0, 20.6)	16/25	64.0 (42.5, 82.0)	68.0 (50.3, 85.7)
	>= 45 years	0/19	0.0 (0.0, 17.6)	26/37	70.3 (53.0, 84.1)	68.9 (52.5, 85.3)
Sex	M	0/11	0.0 (0.0, 28.5)	12/19	63.2 (38.4, 83.7)	56.5 (32.2, 80.8)
	F	0/24	0.0 (0.0, 14.2)	30/43	69.8 (53.9, 82.8)	69.2 (55.2, 83.2)
Baseline HGB	< 9 g/dL	0/18	0.0 (0.0, 18.5)	15/32	46.9 (29.1, 65.3)	45.1 (26.4, 63.9)
	>= 9 g/dL	0/17	0.0 (0.0, 19.5)	27/30	90.0 (73.5, 97.9)	91.3 (81.8, 100.0)
History of MAVE	N	0/25	0.0 (0.0, 13.7)	32/50	64.0 (49.2, 77.1)	65.1 (51.9, 78.2)
	Y	0/10	0.0 (0.0, 30.8)	10/12	83.3 (51.6, 97.9)	76.0 (45.4, 100.0)
Anti-C5 history	ECULIZUMAB	0/23	0.0 (0.0, 14.8)	27/40	67.5 (50.9, 81.4)	66.0 (51.0, 81.0)
	RAVULIZUMAB	0/12	0.0 (0.0, 26.5)	15/22	68.2 (45.1, 86.1)	67.7 (47.9, 87.5)
Prior transfusion	N	0/14	0.0 (0.0, 23.2)	23/27	85.2 (66.3, 95.8)	82.8 (67.5, 98.1)
	Y	0/21	0.0 (0.0, 16.1)	19/35	54.3 (36.6, 71.2)	52.6 (35.6, 69.5)
Number of transfusion		0/14	0.0 (0.0, 23.2)	23/27	85.2 (66.3, 95.8)	82.8 (67.5, 98.1)
	< 2	0/7	0.0 (0.0, 41.0)	5/11	45.5 (16.7, 76.6)	30.4 (-1.5, 62.3)
	>= 2	0/14	0.0 (0.0, 23.2)	14/24	58.3 (36.6, 77.9)	58.6 (38.9, 78.2)
Baseline LDH	<= 1.5 x ULN	0/32	0.0 (0.0, 10.9)	39/58	67.2 (53.7, 79.0)	66.3 (53.9, 78.8)
	> 1.5 x ULN	0/3	0.0 (0.0, 70.8)	3/4	75.0 (19.4, 99.4)	50.0 (-19.3, 100.0)
Duration of Anti-C5	< 12 Months	0/6	0.0 (0.0, 45.9)	6/11	54.5 (23.4, 83.3)	67.1 (37.6, 96.6)
	>= 12 Months	0/29	0.0 (0.0, 11.9)	36/51	70.6 (56.2, 82.5)	68.3 (54.7, 81.9)
Race	ASIAN	0/7	0.0 (0.0, 41.0)	9/12	75.0 (42.8, 94.5)	70.2 (41.9, 98.4)
	BLACK OR AFRICAN AMERICAN	0/2		0/2		
	WHITE	0/26	0.0 (0.0, 13.2)	33/48	68.8 (53.7, 81.3)	68.4 (54.9, 81.8)
Ethnicity	HISPANIC OR LATINO	0/2	0.0 (0.0, 84.2)	6/8	75.0 (34.9, 96.8)	68.4 (32.2, 100.0)
	NOT HISPANIC OR LATINO	0/27	0.0 (0.0, 12.8)	34/51	66.7 (52.1, 79.2)	66.3 (53.2, 79.4)
	NOT REPORTED	0/6	0.0 (0.0, 45.9)	2/2	100.0 (15.8, 100.0)	100.0 (100.0, 100.0)
	UNKNOWN			0/1		
Region 1	America	0/4	0.0 (0.0, 60.2)	5/8	62.5 (24.5, 91.5)	58.1 (19.7, 96.5)
	Asia	0/4	0.0 (0.0, 60.2)	6/9	66.7 (29.9, 92.5)	25.0 (-17.4, 67.4)
	Europe	0/27	0.0 (0.0, 12.8)	31/45	68.9 (53.4, 81.8)	68.0 (54.1, 81.8)
Region 2	Non-US	0/33	0.0 (0.0, 10.6)	38/56	67.9 (54.0, 79.7)	65.7 (52.8, 78.6)
	US	0/2	0.0 (0.0, 84.2)	4/6	66.7 (22.3, 95.7)	28.6 (-25.4, 82.5)

Source: FDA analysis.
Note: The common rate difference is based on Mantel-Haenszel stratum weights with randomization strata as factors; the 95% CIs are based on the Sato variance estimator.
Abbreviations: CI, confidence interval; Diff, difference; FDA, Food and Drug Administration; HGB, hemoglobin; LDH, lactate dehydrogenase; LNP023, iptacopan; MAVE, major adverse vascular event; N, number of subjects on the full analysis set; m, number of responders in the subgroup; n, number of subjects in the subgroup; RBC, red blood cell; ULN, upper limit of normal; US, United States; vs, versus

Clinical Reviewer Comment:

Subgroup analyses in Figures 5 and 6, including by geographic region, suggested similar results favoring LPN023.

Per-Protocol Analyses of the Primary Endpoints

As per the Agency's recommendation, the Applicant conducted the CMH analyses for the primary endpoints based on the per protocol set, which was defined by excluding subjects with major protocol deviations occurring in the screening or randomized treatment periods or before start of the treatment extension period. The results of the per protocol analyses were consistent with the corresponding results on the full analysis set, as shown in Table 13.

Table 13. Results of the Per-Protocol Analyses for the Two Primary Endpoints, Study CLNP023C12302

Endpoints	Iptacopan (N=53) Number of Subjects Responding	Anti-C5 (N=32) Number of Subjects Responding	Difference Between Responders (%) (95% CI)[a]
≥2 g/dL increase in Hb from baseline[c] in the absence of RBC transfusions[d]	45 (84.9%)	0 (0.0%)	84.2 (74.2, 94.3)
Hb ≥12 g/dL[c] in the absence of RBC transfusions[d]	37 (69.8%)	0 (0.0%)	68.2 (55.2, 81.1)

Source: The Applicant's responses to the Agency's information requests.
Note: The analyses are based on the Per-Protocol set which includes subjects without major protocol deviations.
[a] The common rate difference is based on Mantel-Haenszel stratum weights with randomization strata as factors; the 95% CIs are based on the Sato variance estimator.
[b] Based on the Cochran-Mantel-Haenszel test with randomization strata as factors.
[c] Between Day 126 and 168 (at least 3 out of 4 scheduled measurements).
[d] Between Day 14 and Day 168. Requiring RBC transfusions refers to any subject receiving transfusions or meeting protocol defined criteria.
Abbreviations: CI, confidence interval, Hb, hemoglobin; N, number of subjects; RBC, red blood cell

Efficacy Results of Secondary Endpoints

The results of the Applicant's prespecified primary analyses for the key secondary endpoints are shown in Table 14.

Table 14. Results of the Applicant's Prespecified Primary Analyses for Key Secondary Endpoints, Study CLNP023C12302

Endpoints	Iptacopan (N=62)	Anti-C5 (N=35)	Iptacopan vs. Anti-C5 Treatment Effect (95% CI)	2-Sided P-Value	Stat. Sig.
Binary endpoint	Number of subjects responding	Number of subjects responding	Difference between responders (%)		
Transfusion avoidance	59 (95.2%)	14 (40.0%)	68.9 (51.4, 83.9)	<0.0001	Yes
Continuous endpoints	Mean	Mean	Difference between means		
Change in Hb	3.6	-0.1	3.7 (3.2, 4.1)	<0.0001	Yes
Reticulocyte counts	-115.8	0.3	-116.2 (-132.0, -100.3)	<0.0001	Yes
Change in FACIT-Fatigue	8.6	0.3	8.3 (5.3, 11.3)	<0.0001	Yes *

Endpoints	Iptacopan (N=62)	Anti-C5 (N=35)	Iptacopan vs. Anti-C5 Treatment Effect (95% CI)	2-Sided P-Value	Stat. Sig.
Count endpoints	Number of subjects with an event	Number of subjects with an event	Annualized rate ratio		
Clinical BTH rates	2	6	0.10 (0.02, 0.61)	0.012	Yes *
MAVEs	1	0	Not estimable	0.32	No
Continuous endpoint with log transformation	Geom. mean	Geom. mean	Ratio of geom. Means		
LDH	0.96	0.98	0.99 (0.89, 1.10)	0.84	No

Source: The Applicant's clinical study report and the updated analyses.
* Due to the open label design of the study, the change in FACIT-Fatigue results may be biased. The statistical significance of the endpoint of clinical breakthrough hemolysis rate is also in question due to the multiplicity adjustment (see main text).
Note: The transfusion avoidance endpoint was analyzed using the logistic regression model; The continuous endpoints were analyzed using a Mixed Model for Repeated Measures; Adjusted annual rates of clinical Breakthrough Hemolysis events were from the negative binomial model with treatment as the factor; Adjusted annual rates of Major Adverse Vascular Events were from the Poisson model.
Abbreviations: BTH, breakthrough hemolysis; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy; Geom, geometric; Hb, hemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; N, number of subjects; Stat. sig, statistical significance

A difference of 68.9% in responders was observed for the key secondary endpoint of transfusion avoidance; a difference of 3.7 g/dL between means was observed for the key secondary endpoint of change in hemoglobin; a difference of -116.2×10^9/L between means was observed for the key secondary endpoint of reticulocyte counts; and a difference of 8.3 points between means was observed for the key secondary endpoint of change in FACIT-Fatigue. The p-values for the testing of these endpoints were highly significant. However, the result of the FACIT-Fatigue could be biased due to knowledge of treatment assignment from the open-label design.

For the remaining three endpoints of clinical breakthrough hemolysis rates, MAVE, and LDH, only the result of the clinical breakthrough hemolysis rate appeared significant, with an estimated annualized rate ratio of 0.01. Due to the nonconvergence of the prespecified primary analysis method, the negative binomial model with treatment as a factor was implemented for the clinical breakthrough hemolysis endpoint, and the Poisson model was applied for MAVE.

The Applicant also conducted several sensitivity/supportive analyses, such as using different models and different strategies to handle intercurrent events, and the results were consistent with their corresponding primary analysis results, as shown in Table 15.

Table 15. Results of Sensitivity/Supportive Analyses for Key Secondary Endpoints, Study CLNP023C12302

Endpoints	Analysis Description Source	Iptacopan vs. Anti-C5 Treatment Effect (95% CI)
Difference between means		
Change from baseline in hemoglobin levels	Sensitivity analysis based on both central and local labs	3.7 (3.2, 4.1)
	Supportive analysis Including Transfusion Estimand	3.6 (3.2, 4.0)
Change from baseline in FACIT-Fatigue scores	Supportive analysis based on hypothetical strategy	8.21 (5.03, 11.40)
Change from baseline in absolute reticulocyte count	Sensitivity analysis based on both central and local labs	-115.8 (-131.9, -99.7)
	Supportive analysis based on hypothetical strategy	-123.5 (-139.5, -107.6)
Geometric mean ratio		
Percent change from baseline in LDH	Sensitivity analysis based on both central and local labs	0.99 (0.89, 1.10)
	Supportive analysis based on hypothetical strategy	1.00 (0.89, 1.12)

Source: The Applicant's clinical study report and the updated analyses.
Abbreviations: CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase

Statistical Reviewer Comment:

Refer to Section 6.3.1 for issues related to the transfusion avoidance endpoint.

The Applicant's prespecified analyses for the key secondary continuous endpoints were based on the MMRM model with multiple imputation of missing data. The Agency informed the Applicant that the MMRM should be based on the observed data because missing data were addressed with the MAR assumption. In the label, the Agency recommended using the MMRM method based on the observed data for the key secondary endpoints of change in hemoglobin levels and change in reticulocyte counts. The results are shown in Table 16.

Table 16. Analyses of Key Secondary Endpoints of Change in Hemoglobin Levels and Change in Reticulocyte Counts Based on Observed Data, Study CLNP023C12302

Endpoints	Iptacopan (N=62)	Anti-C5 (N=35)	Difference Between Means
Continuous endpoints	Mean	Mean	
Change in Hb	3.6	-0.1	3.7 (3.2, 4.1)
Reticulocytes counts	-115.9	0.3	-116.2 (-132.4, -100)

Source: The FDA analysis.
Note: The endpoints were analyzed using a Mixed Model for Repeated Measures model on observed data.
Abbreviations: FDA, Food and Drug Administration; Hb, hemoglobin; N, number of subjects

Statistical Reviewer Comment:

The Agency did not agree (b) (4) *for the following reasons:*

- *The endpoints of LDH and MAVE did not yield statistically significant results. This is not unexpected. The baseline LDH levels in both study arms at baseline was <1.5x ULN in >90% of subjects, therefore, the magnitude of reduction in LDH would not be large enough to detect a significant difference. Subjects entering the study had an LDH <1.5x ULN because they were on a stable dose of a C5 inhibitor prior to randomization. There were too few MAVE events to detect a significant difference between study arms, this is likely due the duration of the RTP (6 months) and small sample size.*
- *Due to the open-label design of Study APPLY-PNH, the result of the FACIT-Fatigue endpoint could be biased and difficult to interpret. See further considerations below.*
- *According to the prespecified graphical approach for multiplicity adjustment, the endpoints of clinical breakthrough hemolysis, LDH, and MAVE should be tested only if all first six endpoints (i.e., Hb increase ≥2 g/dL, Hb ≥12 g/dL, transfusion avoidance, change in Hb, reticulocyte count, FACIT-Fatigue) reached statistical significance. Although the graphical approach was used to control type I error, the observed statistical significance of FACIT-Fatigue could be impacted if it is a biased estimate due to the open label design. Unless there is a clear statistical significance for the FACIT-Fatigue endpoint, any endpoints after it, including the breakthrough hemolysis, LDH, and MAVE should not be further tested.*
- *There were very few events for the clinical breakthrough hemolysis (2-6) and MAVE (1-0) endpoints so their estimates could be unreliable.*

Clinical Reviewer Comment:

- *The Division of Clinical Outcome Assessment (DCOA) was consulted* (b) (4) *Per the DCOA review (finalized in DARRTS on October 20, 2023), the Applicant submitted an evidence dossier for the FACIT-Fatigue and patient-reported outcome reports. This instrument had previously been accepted* (b) (4) *for the context of PNH. Therefore, this instrument was not reviewed for content validity and other measurement properties. The data from APPLY-PNH demonstrated that iptacopan had statistically significant improvement in FACIT-Fatigue scores compared to anti-C5 treatment (active comparator) between baseline and mean of visits between Day 126 and 168. Despite achievement of statistical significance in the FACIT-Fatigue score, the data were difficult to interpret due to the open-label trial design,*

where subjects' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is currently unknown.

DCOA Reviewer Comment:

- *The Applicant has not adequately addressed the potential impact of bias from knowledge assignment on study results. While we agree that fatigue is an important and relevant concept to patients with PNH, it is difficult to interpret results of the FACIT-Fatigue data given the open-label design of the study and small sample size. In particular, there is insufficient evidence to support that DCOA responses were not influenced by subjects' knowledge of treatment assignment.*

Exploratory endpoint results are described in Section 16.1.

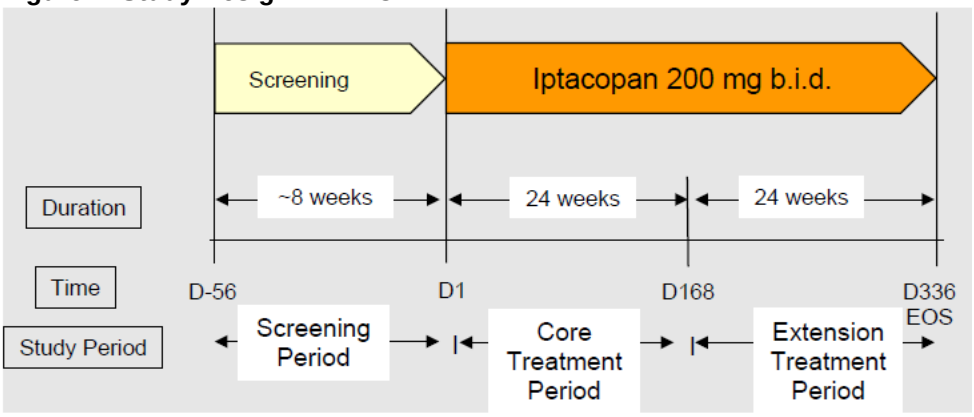
6.2.2. Study CLNP023C12301 (APPOINT-PNH)

6.2.2.1. Design, Study CLNP023C12301 (APPOINT-PNH)

Results from APPOINT-PNH serves as the second adequate and well controlled trial for the benefit evaluation. For more complete details of the study design, see the protocol synopsis included in Section 15.2.

APPOINT-PNH was a multicenter, single-arm, open-label trial in adult subjects with PNH who were naïve to complement inhibitor therapy and had hemolytic anemia (hemoglobin <10 g/dL and LDH >1.5 ULN). The trial design is shown in Figure 7. The study consisted of a 24-week single arm, open-label core treatment period for the primary efficacy and safety analysis. Subsequently, subjects were eligible to enroll in a 24-week treatment extension period and continue to receive iptacopan, followed by a separate long-term extension study.

Figure 7. Study Design – APPOINT-PNH



Source: Applicant's Clinical Trial Protocol for APPOINT-PNH
Abbreviations: b.i.d, twice daily; D, day; EOS, end of study; PNH, paroxysmal nocturnal hemoglobinuria

6.2.2.2. Eligibility Criteria, Study CLNP023C12301 (APPOINT-PNH)

Key eligibility criteria are summarized in this section, and the full criteria are available in Section 15.2.

Inclusion Criteria

1. Male and female participants ≥18 years of age with a diagnosis of PNH confirmed by high sensitivity flow cytometry with RBC and white blood cell (granulocyte/monocyte) clone size ≥10%.
2. Mean hemoglobin level <10 g/dL.
3. LDH >1.5x ULN on at least two central laboratory measurements 2 to 8 weeks apart during the screening period.
4. Vaccination against *Neisseria meningitidis* infection was required and was recommended at least 2 weeks prior to initiation of iptacopan treatment. However, administration of these vaccines less than 2 weeks prior to the start of iptacopan treatment or up to 2 weeks (up to Day 14) after iptacopan initiation was at the discretion of the investigator. If iptacopan treatment was started less than 2 weeks postvaccination or before a specific vaccination is given, the participant must be given prophylactic antibiotics at the start of iptacopan and for at least 2 weeks after vaccination.
5. If not received previously, vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* should be given (if available and according to local/national regulations) and were recommended at least 2 weeks prior to initiation of iptacopan treatment. However, administration of these vaccines less than 2 weeks prior to the start of iptacopan treatment or up to 2 weeks (up to Day 14) after iptacopan initiation was at the discretion of the investigator. If iptacopan treatment was started less than 2 weeks postvaccination or before a specific vaccination is given, the participant must be given prophylactic antibiotics at the start of iptacopan and for at least 2 weeks after vaccination.

Exclusion Criteria

1. Prior treatment with a complement inhibitor, including anti-C5 antibody.
2. History of hypersensitivity to iptacopan or any of its excipients or to drugs of similar chemical classes.
3. Known or suspected hereditary complement deficiency.
4. History of hematopoietic stem cell transplantation.
5. Subjects with laboratory evidence of bone marrow failure (reticulocytes $<100\times10^9$/L, platelets $<30\times10^9$/L, neutrophils $<0.5\times10^9$/L).
6. Active systemic bacterial, viral (including COVID-19) or fungal infection within 14 days prior to study drug administration.
7. History of recurrent invasive infections caused by encapsulated organisms, e.g., meningococcus or pneumococcus.

8. Major concurrent comorbidities, including but not limited to severe kidney disease (e.g., eGFR <30 mL/min/1.73 m^2, dialysis); advanced cardiac disease (e.g., New York Heart Association class IV heart failure); severe pulmonary disease (e.g., severe pulmonary hypertension (World Health Organization class IV)); or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participation in the study.
9. Liver disease, such as active hepatitis B virus or hepatitis C virus infection defined as hepatitis B surface antigen–positive or hepatitis C virus RNA–positive, or liver injury as indicated by abnormal liver function tests at screening:
    a. Any single parameter of ALT, gamma-glutamyl transferase, alkaline phosphatase must not exceed 3x ULN.

6.2.2.3. Statistical Analysis Plan, Study CLNP023C12301 (APPOINT-PNH)

Study Endpoints

Primary Endpoint

- Proportion of participants achieving a sustained increase from baseline in hemoglobin levels of ≥2 g/dL assessed in the absence of red blood cell transfusions.

The need for administration of red blood cell transfusion was defined as follows:

- Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and/or symptoms of sufficient severity to warrant a transfusion.
- Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms.

Analysis Population

- The FAS comprised all participants with confirmed eligibility to whom study treatment has been assigned. This was the dataset used for analysis of all efficacy endpoints.
- The SAF included all participants who received at least one dose of study treatment.

Statistical Reviewer Comment:

For a single-arm study, the population of interest is the treated subjects. The intent-to-treat principal does not apply because there is no control arm. Therefore, the SAF analysis population should be used as the primary analysis population for all efficacy and safety analyses.

***Clinical Reviewer Comment**:*

The study was open-label and, therefore, there is a concern that bias may have been introduced given the nature of the trial design. Bias may have been introduced when determining the need for red blood cell transfusions. The Applicant decreased the risk of bias by including guidelines for when a subject should receive a transfusion, this included a hemoglobin <7g/dL or a hemoglobin level of ≤ 9 g/dL with signs and/or symptoms to warrant a transfusion. In the protocol, the Applicant describes the signs and symptoms that would warrant a transfusion,

which included severe or worsening of fatigue, severe or worsening dyspnea, palpitation/angina and change in mental status (syncope, light-headedness, confusion, stroke, transient ischemic attack). In clinical practice, patients are often transfused when symptomatic from anemia. The guidelines for transfusions were reasonable and the risk of bias for transfusion endpoint is likely minimized.

Sample Size

The sample size was calculated based on the half-width (the margin of error in the estimate) of a two-sided 95% CI for the proportion of subjects reaching the status of responder (primary endpoint). The proposed sample size of 40 subjects was sufficient to achieve a target absolute margin of error not larger than 0.155.

Analysis of the Primary Efficacy Endpoint

The primary analysis of the primary endpoint was a logistic regression to estimate the response probability. The covariates included sex, age (indicator of age ≥45 years), an indicator variable of baseline hemoglobin ≥8 g/dL, and an indicator of transfusion dependence (i.e., whether the subject had any transfusion in the last 6 months prior to starting study treatment).

The primary analysis of the primary endpoint was the assessment of the proportion of subjects reaching the status of responder. The lower bound of the two-sided 95% confidence interval of the response rate obtained from the primary analysis was compared to a threshold of 15%.

Statistical Reviewer Comment:

The Agency had concerns with the prespecified logistic regression method because it requires many model assumptions, e.g., a minimum of 10 cases with the least frequent outcome for each independent variable in the model. Refer to Section 6.2.2.4 and 6.3 for the detailed review issues.

Derivation of the Threshold

This 15% threshold for the primary analysis comparison was derived by indirectly estimating hemoglobin response in two studies with eculizumab: Study ALXN1210-PNH-301 (Brodsky et al. 2021; Committee for Medicinal Products for Human Use 2019; Lee et al. 2019), which included a treatment-naïve population and randomized subjects to either eculizumab or ravulizumab, and the pivotal eculizumab study, TRIUMPH (Dmytrijuk et al. 2008; Hillmen et al. 2006), which included a treatment-naïve population and randomized subjects to either eculizumab or placebo.

The assumptions used for simulation based on the eculizumab arm in ALXN1210-301 data are summarized below:

- Mean hemoglobin level at baseline was 9.6 g/dL from Brodsky et al. (Brodsky et al. 2021)
- Mean hemoglobin level at Week 26 was 10.0 g/dL from Figure 20 of Ultomiris CHMP Assessment Report 2019 (Committee for Medicinal Products for Human Use 2019)
- Standard deviations of hemoglobin at baseline (Brodsky et al. 2021) and Week 26 were assumed to be equal, and the value was 1.70 g/dL

The assumptions used for simulation based on the eculizumab arm in TRIUMPH (Hillmen et al. 2006) data are summarized below:

- Mean hemoglobin level at baseline was 10.0 g/dL
- Mean hemoglobin level at Week 26 was 10.1 g/dL
- Standard deviation of hemoglobin at baseline and Week 26 was assumed to be equal
- The value was calculated as $0.2\sqrt{43}$ =1.31 g/dL, where 0.2 g/dL was the standard error of the mean

The correlation value between hemoglobin level at baseline and at Week 26 was not available from published historical studies. This value was derived based on Hillmen et al. (Hillmen et al. 2006), which published hemoglobin levels before 12 months of eculizumab treatment and after 3 months of eculizumab treatment for 11 subjects with PNH. The correlation was 0.87 for these 11 subjects with PNH. Considering the same sample size and different treatment periods, for simulation purposes, correlation values were drawn from a uniform distribution Unif (0.3, 0.85).

Ten thousand simulation runs indicated that the probability of being a responder (i.e., achieving a hemoglobin increase from baseline ≥2 g/dL) is 14.7% (95% CI: 5.0% - 21.1%) for ALXN1210-301 and 4.5% (95% CI: 0.5% - 11.0%) for TRIUMPH.

The 15% threshold was chosen in order to be above the estimated hemoglobin increases for both historical studies of eculizumab. Thus, exceeding this threshold was sufficient to demonstrate that iptacopan improved the hematological response in subjects with PNH who had hemolysis and anemia in the absence of transfusions.

Statistical Reviewer Comment:

The Agency agreed with the 15% threshold and determined that the methodology for calculating the threshold was acceptable.

Handling of Missing Values

For the primary response definitions, an RBC transfusion qualified the participant as a nonresponder. Missing hemoglobin data due to withdrawal from the study in the core treatment period were imputed by using the multiple imputation method if a participant did not have a prior RBC transfusion.

- For participants withdrawing from the study after discontinuation of iptacopan, their pretreatment levels of Hb were used in the analysis throughout of the study via the copy-reference method)
- For participants with intermittent missing data, their missing data were imputed using a missing-at-random approach.

For subjects with missing hemoglobin data, the need for transfusion was derived from the multiple imputation method with imputed Hb values of ≤9 g/dL (≤8 g/dL for Chinese population) considered sufficient to warrant a transfusion.

Sensitivity Analyses

Sensitivity analysis on the primary endpoint was performed where missing central lab hemoglobin data were replaced by available local lab data collected at the same visit.

Additional sensitivity analyses on the primary analysis were performed:

- Among subjects who did not actually receive a transfusion and had missing Hb data, those with multiple imputed Hb between 7 and 9 g/dL (between 6 g/dL and 8 g/dL for Chinese subjects) were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion.
- Determined the status of "absence of transfusion" in the definition of a responder for the primary endpoint based on actual transfusions received.

Supplementary Analysis

A supplementary estimand considered the use of rescue therapy under intercurrent events as a treatment failure. The logistic regression model that was used for the primary efficacy analysis was also used for this sensitivity analysis.

Interim Analysis

No interim analyses of efficacy were performed for this study.

6.2.2.4. Results of Analyses, Study CLNP023C12301 (APPOINT-PNH)

Data Quality and Integrity

Data were provided electronically in standard data format, with a study data tabulation model and analysis data model. Statistical analysis software programs used to create key efficacy and safety outputs for the study were submitted along with the data. The Applicant also provided clear definition files for datasets and detailed analysis programs to assist the review. The link to the data from study CLNP023C12301 is:
\\CDSESUB1\evsprod\NDA218276\0000\m5\datasets\clnp023c12301

Subject Disposition

Table 17 shows the disposition of the study participants. All 40 subjects enrolled in the study completed the core treatment period. No subject discontinued the study drug or discontinued the study during the core treatment period.

Table 17. Subject Disposition, Study CLNP023C12301–Full Analysis Set

Subject Disposition	Iptacopan Core Treatment Period
FAS population	40 (100.0%)
Safety population	40 (100.0%)
Discontinued study drug	0 (0.00%)
Discontinued study	0 (0.00%)

Source: The Applicant's clinical study report.
Abbreviations: FAS, full analysis set

Statistical Reviewer Comment:

For a single-arm study, the SAF analysis population should be used as the primary analysis population for all efficacy and safety analyses. Because the FAS and SAF were identical, either could be used for the efficacy evaluation in this case.

Demographic Characteristics

In total, 20 of the 40 subjects in the full analysis set were from China. The other 20 subjects were from France (n=4), Germany (n=4), Italy (n=2), Malaysia (n=3), Republic of Korea (n=2), Singapore (n=1), and United Kingdom (n=4).

Table 18 shows the demographic and baseline characteristics of the study.

Table 18. Demographic and Baseline Characteristics, Study CLNP023C12301–Full Analysis Set

Demographic and Baseline Characteristics	Iptacopan 200 mg (N=40)
Age (years)	
Mean (SD)	42.1 (15.85)
Median [Min, Max]	38.5 [18.0, 81.0]
Age category (years)	
18 - <65 years	37 (92.5%)
65 - <75 years	2 (5.0%)
≥75 years	1 (2.5%)
Sex	
Female	17 (42.5%)
Male	23 (57.5%)
Race	
Asian	27 (67.5%)
Black or African American	1 (2.5%)
White	12 (30.0%)
Ethnicity	
Hispanic or Latino	2 (5.0%)
Not Hispanic or Latino	35 (87.5%)
Not reported	2 (5.0%)
Unknown	1 (2.5%)
Disease duration (years)	
Mean (SD)	4.7 (5.54)
Median [Min, Max]	3.6 [0.01, 23.2]
Baseline hemoglobin (g/dL)	
Mean (SD)	8.2 (1.09)
Median [Min, Max]	8.1 [5.8, 10.0]
LDH levels at baseline (U/L)	
Mean (SD)	1698.8 (683.33)
Median [Min, Max]	1581.5 [522.0, 3244.0]
Transfusion - 6 months prior to randomization	
No	12 (30.0%)
Yes	28 (70.0%)

Demographic and Baseline Characteristics	Iptacopan 200 mg (N=40)
Number of transfusions – 6 months prior to randomization (for subjects who had received at least 1 transfusion within 6 months prior to randomization)	
Mean (SD)	3.1 (2.09)
Median [Min, Max]	2.0 [1.0, 8.0]
Baseline Platelets (10^9/L)	
Mean (SD)	159.4 (61.09)
Median [Min, Max]	150.5 [35.0, 316.0]
Baseline Reticulocytes (10^9/L)	
Mean (SD)	154.3 (63.67)
Median [Min, Max]	139.2 [59.4, 324.8]
Baseline FACIT Fatigue score	
Mean (SD)	32.8 (10.17)
Median [Min, Max]	34.3 [13.0, 50.5]
History of MAVE Prior to Screening	
No	35 (87.5%)
Yes	5 (12.5%)
Total PNH RBC Clone Size[a]	
Mean (SD)	42.7 (21.23)
Median [Min, Max]	40.3 (9.0, 92.9)

Source: FDA reviewer generated the table from clinical data submitted by the Applicant.
[a] Total PNH clone size is calculated as sum of percentages of positive Red Blood Cells of Type II and Type III.
Abbreviations: FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; FDA, Food and Drug Administration; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; max, maximum; min, minimum; N, number of subjects; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SD, standard deviation

Clinical Reviewer Comment:

There were no U.S. subjects in the APPOINT-PNH study, which is expected because it is standard of care in the United States to receive a complement inhibitor for PNH. However, the results are still applicable to the U.S. population as PNH is due to a somatic mutation in the PIG-A gene; therefore, factors such as country of origin or environmental factors are not likely to have a significant impact on response to therapy. Also the disease presentation and progression are expected to be similar regardless of whether patients are from the United States or ex-United States. In addition, exposure differences between Asians and other races are not clinically significant (see Section 8.1 for further details). A majority of subjects were <65 years of age, male, and Asian. The mean baseline Hb was 8.2 g/dL. About 70% of subjects had received at least one transfusion in the preceding 6 months (among these subjects, there was a median of 2 transfusions; range 1-8.)

Efficacy Results of Primary Endpoints

Thirty-three subjects (82.5%) had evaluable, nonmissing data. Of the 33 subjects with sufficient central lab data collected to unequivocally determine the response status for the primary endpoint (evaluable subjects), 31 subjects achieved a sustained increase in Hb levels ≥2 g/dL from baseline in absence of RBC transfusions.

The results of the Applicant's prespecified analyses for the primary endpoint are shown in Table 19. For the primary analysis, the lower bound of the two-sided 95% confidence interval of the response rate obtained from the primary analysis (i.e., 82.5%) was well above the prespecified threshold of 15%. The sensitivity analysis results were consistent with the primary analysis result.

Based on the natural history of the disease, spontaneous remissions rarely occur in PNH. In a natural history study, which included 80 patients followed for up to 48 years, 15% of patients with PNH achieved a spontaneous remission, although remissions occurred 10-20 years after diagnosis of PNH (Hillmen et al. 1995). Of note, the median duration of PNH in subjects in APPOINT-PNH was 3.6 years, therefore spontaneous remissions are unlikely in this patient population. Further, in a randomized, placebo-controlled trial in 87 subjects with PNH, randomized 1:1 to placebo or eculizumab. No subject in the placebo arm achieved hemoglobin stabilization or transfusion avoidance (Alexion Pharmaceuticals 2020).

Table 19. Analysis Results for the Primary Endpoint, Study CLNP023C12301

Endpoint	Analysis Description Source	Treatment	n/M	Marginal Proportion (95% CI)[1]
≥2 g/dL increase in Hb from baseline[a] in the absence of RBC transfusions[b]	Primary analysis: Only central lab data included. Missing Hb was imputed via multiple imputation and an assumption was made that subjects had signs and/or symptoms at missed visits for determining transfusion avoidance	Iptacopan 200 mg BID N=40	31/33	92.2 (82.5, 100.0)
	Sensitivity analysis 1: If central lab data missing, include local laboratory data	Iptacopan 200 mg BID N=40	35/37	94.1 (85.0, 100.0)
	Sensitivity analysis 2: Multiple imputed Hb between 7 and 9 g/dL (between 6 g/dL and 8 g/dL for Chinese subjects) were considered by default as not having signs and/or symptoms and therefore not meeting the criteria for transfusion	Iptacopan 200 mg BID N=40	31/33	94.6 (87.5, 100.0)
	Sensitivity analysis 3: Determining transfusion avoidance without imputation	Iptacopan 200 mg BID N=40	31/33	94.6 (87.5, 100.0)
	Supplementary analysis: Subjects requiring rescue therapy were considered as failures for the primary hematological response endpoint	Iptacopan 200 mg BID N=40	31/33	92.2 (82.5, 100.0)

Source: The Applicant's clinical study report.
[1] The marginal proportion of responders was computed using simple proportion. The 95% CI was obtained using the bootstrap method.
[a] between Day 126 and 168 (at least 3 out of 4 scheduled measurements).
[b] between Day 14 and Day 168. Requiring RBC transfusion refers to any subject receiving transfusions or meeting protocol defined criteria or imputed hemoglobin values ≤9 g/dL (≤8 g/dL for Chinese population).
Abbreviations: BID, twice daily; CI, confidence interval; Hb, hemoglobin; M, the number of subjects with response variable defined based on non-missing data (evaluable subjects); N, total number of subjects included in the model (without missing covariates); n, the number of subjects who responded based on non-missing data; RBC, red blood cell

Statistical Reviewer Comment:

The Agency had concerns with the prespecified logistic regression method because it requires many model assumptions, e.g., a minimum of 10 cases with the least frequent outcome for each independent variable in the model.

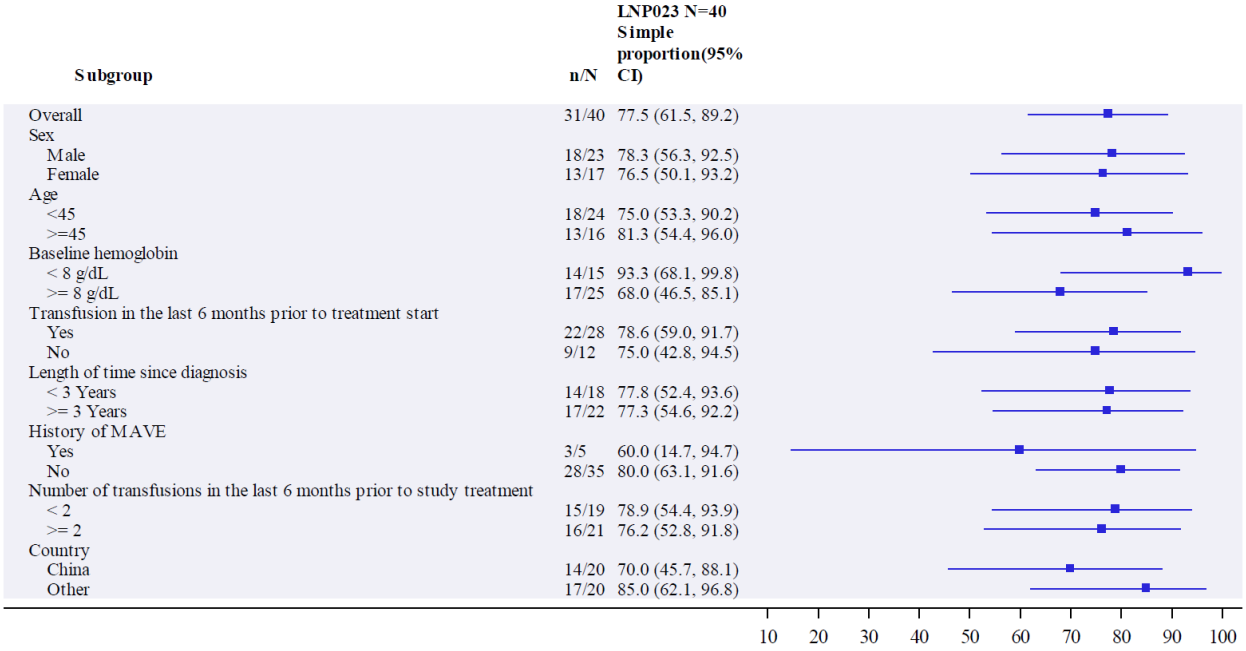
As per the Agency's recommendation, the Applicant computed the following analyses to understand the impact of applying different criteria for need for transfusion.

- *Perform unadjusted analyses based on multiple imputation of missing Hb values with the MAR assumption, where imputed hemoglobin ≤7 g/dL is considered to meet criteria for transfusion.*
- *Perform unadjusted analyses based on multiple imputation of missing Hb values with the MAR assumption, where imputed hemoglobin ≤9 g/dL is considered to meet criteria for transfusion.*

The unadjusted proportions obtained from the above two analyses are 94.1% (95% CI: 76.3%, 99.4%) and 90.7% (95% CI: 70.2%, 98.4%), respectively, where the lower bounds are both substantially >15% even though the use of a higher criterion for need for transfusion would result in a lower response rate of the primary endpoint.

In addition, as per the Agency's recommendation, the Applicant computed unadjusted overall and subgroup proportions based on the observed responders without missing data (N=31) on the full analysis set (N=40) and the 95% CIs based on the Clopper-Pearson method, as shown in Figure 8. Note that the analyses based on observed responders are conservative because cases with missing data are considered nonresponders. For the overall analysis, the lower bound of the two-sided 95% confidence interval of the response rate (i.e., 61.5%) is still considerably higher than the prespecified threshold of 15%. The results of subgroup analyses are, in general, consistent with the overall analysis result. Due to small sample sizes for the subgroups, the estimated CIs are wide and, hence, results should be interpreted with caution. However, the majority of the lower CIs are well above 15%.

Figure 8. Results of the Overall and Subgroup Analyses for the Primary Endpoint Based on the Observed Responders Without Missing Data on the Full Analysis Set, Study CLNP023C12301



Source: The Applicant's responses to the Agency's information requests.
Notes: The age subgroups did not use a cut off of 65 as only 3 subjects were order than or equal to 65 years. The proportions are based on the observed responders without missing data on the Full Analysis Set (N=40) and the 95% CIs are based on the Clopper-Pearson method.
Abbreviations: CI, confidence interval; LNP023, iptacopan; MAVE, major adverse vascular event; N, number of subjects on the full analysis set; n, number of subjects in the subgroup

The Agency recommended the Applicant report the analysis result of the primary endpoint based on the observed responders without missing data on the FAS in the label. Secondary endpoint analyses were considered exploratory, and therefore will not be included in the label. See exploratory analyses in Section 16.2.

Clinical Reviewer Comment:

The primary efficacy endpoint analysis was based on central laboratory values, as prespecified in the SAP. However, due to the COVID-19 pandemic some subjects were unable to attend scheduled visits and therefore obtained local labs. The Applicant proposed to include a sensitivity analysis in the USPI that included local laboratory values. The proposed language is, "In a sensitivity analysis, 87.5% (95% CI: 73.2%, 95.8%) of patients (35/40) achieved a sustained increase (between Day 126 and Day 168) in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions, including local laboratory hemoglobin values when central laboratory hemoglobin values were not available." The clinical team agreed with the inclusion of the sensitivity analysis in the label, as it is reasonable that subjects would be unable to attend visits given isolation recommendations during the COVID-19 pandemic. Further, local hemoglobin laboratory values are not expected to be meaningfully different than central hemoglobin laboratory values.

6.3. Key Efficacy Review Issues

6.3.1. Analyses of the Key Secondary Endpoint of Transfusion Avoidance in APPLY-PNH

Issue

The Agency did not agree with the prespecified primary analysis method for transfusion avoidance in the APPLY-PNH study.

Background

In the SAP, the TA endpoint classified subjects as a failure if they met either of the following:

1. Received an RBC transfusion between Days 14 and 168
2. Met one of the predefined criteria for transfusion between Days 14 and 168:
    a. Hemoglobin ≤9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion
    b. Hemoglobin ≤7 g/dL, regardless of presence of clinical signs and/or symptoms

For component (1) of the endpoint, all subjects were evaluable by definition. For component (2) of the endpoint, some subjects had sparse missing hemoglobin (related to missed visits or technical reason) and were therefore only partly evaluable. For these subjects, the handling of missing data could influence the outcome.

The Applicant's prespecified primary endpoint for the TA endpoint analysis was logistic regression with multiple imputation of missing hemoglobin. If imputed hemoglobin was between 7 and 9 g/dL, then the signs and symptoms information played a role in determining the criterion. In this case, the Applicant considered the subject as meeting the criteria for transfusion, as they assumed that subjects with missing data were presenting symptoms.

For all binary endpoints, in the "safe to proceed" letter dated September 28, 2020, the Agency recommended that the primary analysis be based on the stratified CMH test. However, the Applicant did not change the primary analysis method to CMH in their final version of the SAP. In addition, the Agency did not agree with the Applicant's prespecified method of handling missing data for the TA endpoint.

Assessment

Based on the Applicant's prespecified analysis method (i.e., "Not being TA" includes subjects who received transfusion or met transfusion criteria in case report forms or had imputed Hb values ≤9 g/dL), a difference of 68.9% in responders was observed for the TA endpoint. However, the Applicant's post hoc sensitivity analysis using the same method but considering imputed Hb values ≤7 g/dL as meeting the transfusion criteria showed a difference of 55.7%. Note that according to the Applicant's definition of the TA endpoint, if imputed hemoglobin was between 7 and 9 g/dL, then the signs and symptoms information played a role in determining the criterion. Therefore, considering imputed Hb values ≤9 g/dL as meeting the transfusion criteria is equivalent to assuming the presence of signs/symptoms for imputed Hb between 7 and 9 g/dL,

whereas considering imputed Hb values <7 g/dL as meeting the transfusion criteria is equivalent to assuming the absence of signs/symptoms for imputed Hb between 7 and 9 g/dL. The CMH analyses with the 9 g/dL and 7 g/dL criteria gave similar results of 68.1% and 55.7%, respectively. The discrepancy between results based on the two criteria was due to the fact that subjects randomized to anti-C5 typically had on-study measured Hb values around 9 g/dL and the missing Hb levels were often imputed to values in the range of 7 to 9 g/dL, and therefore, more subjects in the anti-C5 group were considered to meet the transfusion criteria (i.e., non-responders for TA) with the 9 g/dL threshold. As a result, a bigger treatment difference was observed with the 9 g/dL threshold.

In addition to analyses based on imputed Hb values, the Applicant conducted analyses based on observed data. The logistic regression and CMH analyses based on observed data that classified subjects who received a transfusion or met transfusion criteria in case report forms as failures showed a difference of 55.3%. The CMH analysis based on observed data considering only subjects who received a transfusion as failures showed a difference of 49.5%. Note that all of these analyses considered missing Hb data as TA responders, which the Applicant claimed was more appropriate to reflect the extent of information, given that missing hemoglobin were sparse, and that actual transfusions were the main driver for failure on transfusion avoidance.

All of these aforementioned analyses are summarized in Table 20. Note that only randomization strata were used as factors in the CMH analyses.

Table 20. Analyses of the Transfusion Avoidance Endpoint, Study CLNP023C12302

	Transfusion Avoidance %		Transfusion Avoidance Difference % (95% CI)	P-Value
Analysis Description	**Iptacopan**	**Anti-C5**		
Analyses using multiple imputation				
Prespecified analysis[1] * (Failures: Transfusion received + Transfusion based on meeting criteria in CRF + Transfusion based on imputed Hb values ≤9 g/dL)	94.8	25.9	68.9 (51.4, 83.9)	<0.0001
Post-hoc sensitivity analysis[2] * (Failures: Transfusion received + Transfusion based on meeting criteria in CRF+ Transfusion based on imputed Hb values ≤7g/dL)	95.0	39.3	55.7 (37.6, 72.6)	<0.0001
New analysis[1] using CMH test ** (Failures: Transfusion received + Transfusion based on meeting criteria in CRF + Transfusion based on imputed Hb values ≤9 g/dL)	95.1	27.3	68.1 (52.2, 84.0)	<0.0001
New analysis[2] using CMH test ** (Failures: Transfusion received + Transfusion based on meeting criteria in CRF + Transfusion based on imputed Hb values ≤7 g/dL)	95.2	39.6	55.7 (38.8, 72.6)	<0.0001

Analysis Description	Transfusion Avoidance %		Transfusion Avoidance Difference % (95% CI)	P-Value
	Iptacopan	Anti-C5		
Analyses using observed Hb data without multiple imputation				
Analysis on observed data[3] * (Failures: Transfusion received + Transfusion based on meeting criteria in CRF)	95.0	39.7	55.3 (37.2, 72.0)	<0.0001
Analysis on observed data - using CMH test[3] ** (Failures: Transfusion received + Transfusion based on meeting criteria in CRF)	95.2	40.0	55.3 (38.4, 72.1)	<0.0001
Analysis on transfusion received - using CMH test[4] ** (Failures: Transfusion received)	95.2	45.7	49.5 (32.5, 66.6)	<0.0001

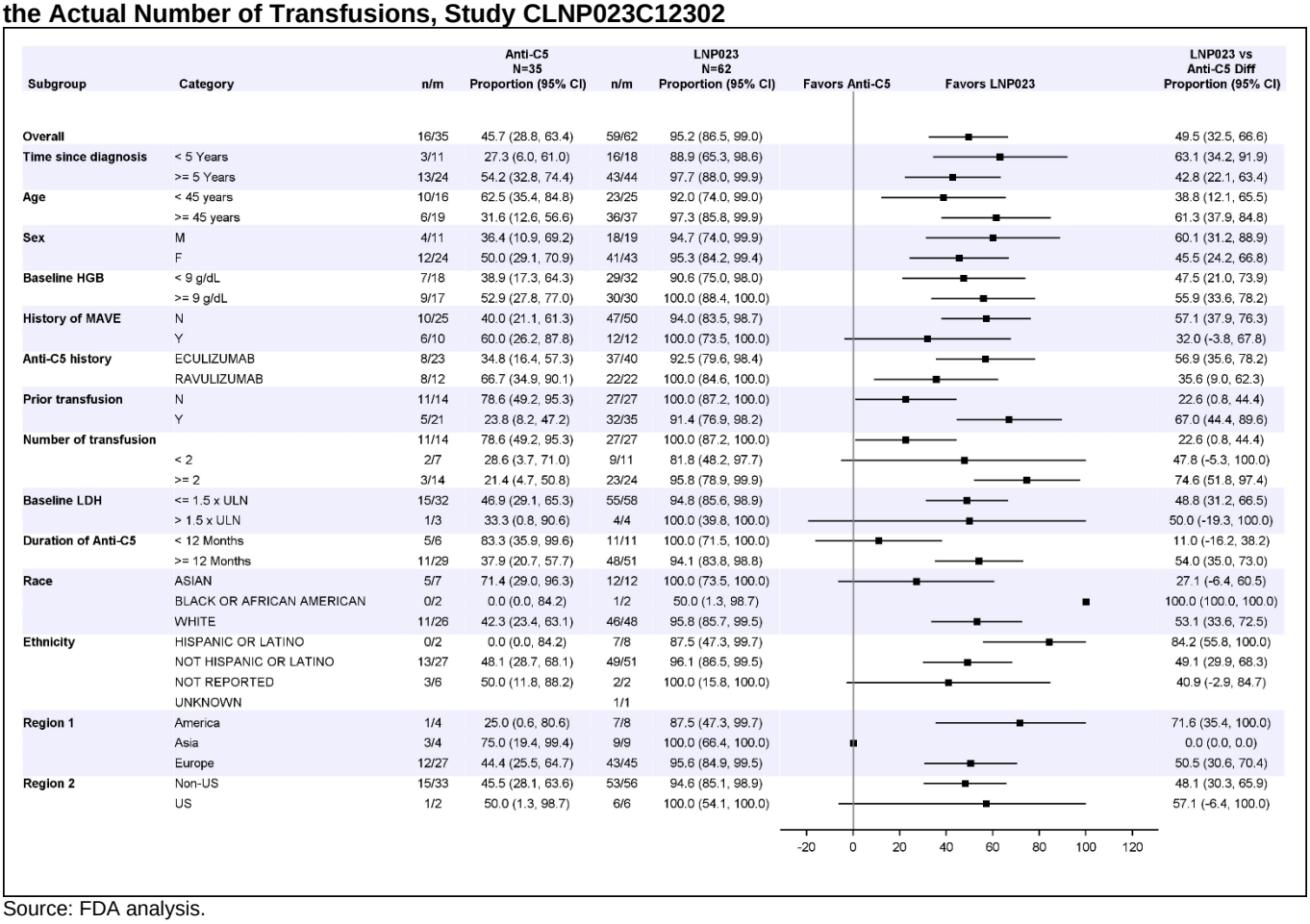
Source: Adapted from the Applicant's responses to the Agency's information requests.
Note: Except for the pre-specified primary analysis, these results should be considered exploratory only and p-values are nominal.
[1] Use multiple imputation for missing Hb data, considering imputed Hb values ≤9 g/dL as meeting the transfusion criteria.
[2] Use multiple imputation for missing Hb data, considering imputed Hb values ≤7 g/dL as meeting the transfusion criteria.
[3] Endpoint is established on observed data.
[4] Endpoint is based on transfusion actually received only.
* Marginal proportions and p-value are obtained from logistic regression and conditional logistic regression respectively.
** Estimated proportions and common rate differences are based on Mantel-Haenszel stratum weights and 95% CIs are based on the Sato variance estimator. P-values are obtained from the CMH test.
Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CRF, case report form; Hb, hemoglobin

To assess the impact of missing data on the statistical significance of the TA endpoint, the Agency performed a CMH analysis based on observed data with the worse-case imputation. In other words, among subjects whose TA status could not be unequivocally determined from the observed data, subjects who had any missing central lab Hb data between Day 14 and Day 168 were considered failures in the iptacopan group and responders in the anti-C5 group. The worst-case analysis showed a difference of 29.6% (95% CI: 10.6%, 48.6%) with a statistically significant p-value of 0.0036. Therefore, the Agency does not have concern about the statistical significance of the TA endpoint.

The Agency considered that the analysis based on the actual number of transfusions was more appropriate because while transfusion thresholds exist in the clinical trial and in clinical practice, the decision to transfuse is based on a multitude of factors (e.g., comorbidities, alloimmunization, risk of allergic reaction, baseline hemoglobin level) in addition to signs and symptoms of anemia. In addition, it may be challenging to differentiate signs and symptoms of anemia and other symptoms of PNH. Also, other approved drugs for PNH have used actual blood transfusion in labeling. Every subject in the iptacopan arm who met the transfusion threshold parameters was transfused. In the C5-inhibitor arm, two subjects who met the transfusion parameters never received a transfusion on study. Both subjects refused the transfusion, but further information was not provided.

The Agency also conducted subgroup analyses for the TA endpoint based on the actual number of transfusions, as shown in Figure 9.

Figure 9. Results of the Subgroup Analyses for the Endpoint of Transfusion Avoidance Based on the Actual Number of Transfusions, Study CLNP023C12302



Source: FDA analysis.
Note: The common rate difference is based on Mantel-Haenszel stratum weights with randomization strata as factors; the 95% CIs are based on the Sato variance estimator.
Abbreviations: CI, confidence interval; Diff, difference; FDA, Food and Drug Administration; HGB, hemoglobin; LDH, lactate dehydrogenase; LNP023, iptacopan; MAVE, major adverse vascular event; N, number of subjects on the full analysis set; m, number of responders in the subgroup; n, number of subjects in the subgroup; RBC, red blood cell; ULN, upper limit of normal; US, United States; vs, versus

The results of subgroup analyses were, in general, consistent with the overall analysis result. Due to low sample sizes for the subgroups, the estimated CIs are wide and, hence, results should be interpreted with caution.

Conclusion

The Applicant's prespecified definition for the TA endpoint took into account both actual transfusions received and if the subject met the prespecified transfusion thresholds based on hemoglobin level and signs/symptoms of anemia. However, the Agency recommends the label only include the CMH analysis based on the actual number of transfusions received to be consistent with clinical practice and labeling for other approved drugs for PNH.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The safety of iptacopan was evaluated in a comprehensive nonclinical program consisting of good laboratory practice compliant toxicology studies in rats and dogs (most sensitive species), a short study in monkeys, reproductive toxicology studies in rats and rabbits, and carcinogenicity assessments in rats and transgenic mice. The doses selected in the chronic toxicology studies produced FB inhibition up to 90%.

A primary concern identified early in product development was a signal for infection. Other systems/organs affected by iptacopan were the heart (dog, monkey), thyroid (rat, dog), and male reproductive organs (rat, dog). An additional safety concern identified was based on a clinical signal for hypercholesterolemia. Each topic is addressed below, followed by an assessment of the potential impact on clinical safety.

Infection Risk

Iptacopan is anticipated to increase the risk of infections due to inhibition of the alternative complement pathway. Iptacopan administered at the high-dose (~10 times the clinical exposure at the maximum recommended human dose [MRHD], based on plasma area under the concentration-time curve [AUC]) resulted in decreased leukocyte parameters in male dogs at the end of the recovery period. One male dog developed a moribund condition during the recovery period in the setting of nonregenerative anemia and elevated fibrinogen, decreased albumin, and elevated liver enzymes. A gene signature analysis revealed expression changes suggesting an acute phase response possibly secondary to infection, although infection was not confirmed by culturing or other methods. This mortality was delayed and occurred in the setting of iptacopan-related body weight loss, immunosuppression, and reduced hepcidin levels, which are established risk factors predicting a poor outcome from infection. The risk of infections related to iptacopan was assessed in clinical trials and will be appropriately addressed in relevant sections of product labeling (e.g., Warnings and Precautions).

Cardiac Risk

Iptacopan treatment resulted in increases in heart rate and shortening of the PR and/or QT interval at doses ≥150 mg/kg in the 13- and 39-week studies in dogs and at 300 mg/kg in a single dose study in monkeys (exposures ≥9 times (dogs) and 18 times (monkeys) the MRHD, based on AUC). At ≥28 times the clinical exposure, cardiomyocyte degeneration/necrosis (graded minimal to mild) was noted in a few animals. When present, necrosis was also characterized by inflammatory cell infiltration, and was noted to occur predominantly in the papillary muscle of the left ventricle.

In a 4-week study in dogs, the Applicant evaluated cardiac biomarkers, cardiac Troponin I (cTnI), N-terminal pro-atrial natriuretic peptide (NTproANP), and N-terminal pro-brain natriuretic peptide (NTproBNP), but there were no drug-related changes in cTnI and NTproANP, and the result of NTproBNP was inconclusive.

To better understand the mechanism(s) leading to cardiac myocyte necrosis, the Applicant conducted a gene expression analysis in heart apex samples collected from 2- and 4-week dog studies. The investigation detected transcriptional changes, including upregulation of cardiac biomarker-associated mRNA (Secreted phosphoprotein 1, Nephronectin, Neuropeptide Y receptor, and Vaso-intestinal peptide receptor 2), and gene signatures associated with heart pacing and cardiomyocyte contraction, and adrenergic and calcium signaling. Blood pressure regulation and relaxin pathway gene signatures, including genes associated with adaptive changes (G protein-coupled receptors: cAMP/cGMP/MAPK/AMPK, RAS/PI3K/AKT, and Wnt pathway, etc.), were downregulated.

The Applicant proposes that dose-related hemodynamic changes/tachycardia eventually led to cardiomyocyte degeneration, which appears to be a reasonable mechanistic explanation. The reassuring safety margins, knowledge of potential mechanisms, and ability to readily monitor hemodynamic changes in subjects supported the safe conduct of clinical trials, and risk was ultimately assessed in clinical trials.

Thyroid Follicular Cell Hypertrophy

Reversible thyroid follicular cell hypertrophy and thyroid organ weight increases were observed at clinically relevant exposures in toxicology studies at doses ≥50 mg/kg/day in the 26-week study in rats and at ≥5 mg/kg/day in the 39-week study in dogs. Transient increases in serum T3 and T4 were also observed in rats in the 13-week study, while decreases in serum T4 were noted in a 4-week study in dogs. Gene expression profiling showed upregulation of thyroid hormone biosynthesis genes and a gene signature suggestive of an overall increase in metabolic activity. The mechanism underlying this phenomenon remains unclear. Based on these findings in animals, thyroid effects were designated as adverse events of special interest in clinical trials. See Section 7.6.3 for further discussion.

Male Reproductive Organ Effects

Male rat and dog reproductive organs, including testis, epididymis, and prostate, were targets of iptacopan. Reversible tubular degeneration in the testes and minimal to slight cell debris in the lumen of tubules of the epididymis, along with decreased testis and epididymis weight, occurred in rats and dogs with chronic dosing. Iptacopan-related changes in hormone levels of the pituitary-testis axis were sporadically observed. Using a primary culture containing Sertoli cells from seminiferous tubules, a direct impact of iptacopan on spermatogenic processes via altered androgen signaling was established. While gene expression profiling failed to demonstrate a significant effect of iptacopan on the transcriptional profile of the testis, evidence suggests that epigenetic changes in genes regulating spermatogenesis in the male reproductive organs are likely involved, based on additional global mapping of transcriptionally active regions of the genome.

In rats in vivo, limited changes in androgen hormones were observed, suggestive of compensatory mechanisms at exposures below 3 times the MRHD, based on AUC. There were no significant effects of iptacopan on sperm morphology, motility, or numbers from the chronic toxicology studies in rats or dedicated male fertility study in rats at exposures of 4 times the clinical exposure. Based on these findings in animals, testicular effects were designated as adverse events of special interest in clinical trials. See Section 7.6.3 for further discussion.

Overall, the risks to fertility based on animal data appear acceptably low, and residual risk can be addressed with appropriate product labeling.

Dyslipidemia Risk

Iptacopan-related increases in low density lipoprotein (LDL)-cholesterol and total cholesterol were observed in phase 3 clinical trial participants (see Section 7.7.2). While no similar signal was noted broadly in animals with iptacopan, total cholesterol levels (analyzed as part of the standard battery of clinical chemistry endpoints in toxicology studies) were re-evaluated. Increases in total cholesterol in animals were limited to the highest iptacopan exposures in female rats for 13 weeks, where an approximate 30% increase in total cholesterol was observed at exposures 3 times the MRHD based on AUC, but no similar findings were observed in nonhuman primates or dogs. Considering the limited increase in cholesterol observed only at the high dose in one sex of rats, the ability of toxicology studies to serve as an investigative model for this human phenomenon with iptacopan is limited. Of interest, higher plasma C3 levels have been associated with a change in lipid profile, including higher VLDL and LDL, in at least one published clinical study (Xin et al. 2021). Serum C3 levels, however, were not measured in studies involving subjects with PNH. Currently, the mechanism by which iptacopan may impact cholesterol levels in humans remains undetermined.

Nonclinical Recommendation

The risks identified in the iptacopan nonclinical program were evaluated in phase 3 trials, are clinically manageable, or can be addressed appropriately in product labeling. There are no nonclinical safety issues that would preclude approvability and no postmarketing requirements (PMRs) are recommended. The Nonclinical Pharmacology/Toxicology team, therefore, supports approval of iptacopan for the treatment of PNH.

Table 21. Safety Margins Provided by the Nonclinical Studies Relative to the Maximum Recommended Clinical Dose of Iptacopan

Study		NOAEL (mg/kg/Day)	C_{max} (ng/kg)	AUC (ng·hr/mL)[b]	Exposure Margins[a] Exposure Multiple AUC
6-month, Rat		150	29000	100000	1.4
9-month, Dog	Male	5	4580	39300	0.5
	Female	30	21000	155000	2.2
Fertility, Rat	Male	750	63900	295000	4.1
	Female[c]	300	22700	123000	1.7
Embryofetal, Rat		1000	36000	278000	3.9
Embryofetal, Rabbit	F0	250	15000	153000	2.1
	F1	450	30600	400000	5.6
Pre/Postnatal, Rat		1000	36000	278000	3.9
Juvenile, Dog	Male	5	5950	50100	0.7
	Female	30	26300	167000	2.3

Source: Reviewer Analysis
[a] Exposure margins based on area under the curve (AUC) of proposed maximum human dose of 200 mg twice a day (71,784 ng.hr/mL)
[b] Rat fertility and pre/postnatal studies had no toxicokinetic (TK) data, therefore, the TK data from toxicology studies were used
[c] Female fertility and early embryonic study
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; NOAEL, no-observed-adverse-effect-level; TK, toxicokinetic

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Potential safety concerns were reviewed based on known information from the approved complement inhibitor therapies and literature on patients with hereditary factor B deficiency.

Approved Complement Inhibitors

Iptacopan is a complement inhibitor and is the first factor B inhibitor. In total, three other complement inhibitors have been approved for PNH, including pegcetacoplan (C3 inhibitor), ravulizumab (C5 inhibitor) and eculizumab (C5 inhibitor). All the complement inhibitors have a boxed warning and REMS with elements to assure safe use (ETASU) for serious infections. Specifically, the C3 inhibitor has a box warning and ETASU REMS for serious infections caused by encapsulated organisms and the C5 inhibitors for serious meningococcal infections. As stated in the pegcetacoplan interdisciplinary review (finalized May 14, 2021), *C3 inhibitors result in proximal inhibition of the complement system, which creates an increased risk of serious infections caused by encapsulated bacteria, including S. pneumoniae, H. influenzae, and N. meningitidis. These associations are based on the review of manifestations of inherited C3 deficiencies, which have shown recurrent and severe infections involving the respiratory system, meninges, and bloodstream by the above-mentioned encapsulated bacteria. These infections are serious, life-threatening, and often require hospitalization and significant medical management* (Figueroa and Densen 1991; Risitano et al. 2014). This is in contrast to approved C5 inhibitor therapies, which lead to terminal complement system inhibition and thereby are associated with a risk of invasive and disseminated N. meningitidis infection (Ram et al. 2010).

All complement inhibitors also carry a warning for monitoring of disease manifestations with drug discontinuation due to risk of reoccurrence of hemolysis.

Similarly, iptacopan will also have a boxed warning and ETASU REMS for serious infections caused by encapsulated organisms. See Section 7.7.1 for further details. The risk of disease manifestations reoccurring with discontinuation of iptacopan is also a concern and will be described in the iptacopan label as a warning.

Literature Review for Hereditary Factor B Deficiency

As iptacopan is a novel factor B inhibitor, the clinical team also reviewed the literature for cases of hereditary factor B deficiency to assess if inhibiting factor B may lead to additional safety concerns that were not observed in clinical trials. There were two case reports in the literature, both of which were notable for encapsulated organism infections, including pneumococcal and meningococcal infections (Gauthier et al. 2021; Slade et al. 2013). No other clinical manifestations were described (i.e., autoimmune disease). The risks of encapsulated organisms will be described in the label.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. Iptacopan is not commercially available or approved in any country.

7.4. FDA Approach to the Safety Review

The safety review of iptacopan 200 mg BID was primarily based on the active-control phase 3 study, APPLY-PNH, in subjects with PNH who had residual anemia despite treatment with anti-C5 therapy, and the phase 3 study, APPOINT-PNH, in subjects with PNH who were naïve to complement inhibition therapy. For further details on the clinical trial design for APPLY-PNH and APPOINT PNH, see Sections 6.2.1 and 6.2.2, respectively.

To support the analysis of safety, six other studies in the development program were also reviewed. The Integrated Summary of Safety (ISS) or all subject population, which included APPLY-PNH, APPOINT-PNH, and the studies listed below, included 223 subjects exposed to at least one dose of iptacopan 200 mg BID. In total, 170 subjects with PNH received at least one dose of iptacopan (PNH pool); 154 of these subjects received iptacopan as monotherapy. An additional 53 subjects from renal studies (renal pool) received at least one dose of iptacopan.

Safety results from supportive studies were only described when applicable. A brief description of each study is listed below.

PNH Studies

- APPLY-PNH and APPOINT-PNH are described above.
- Two additional open-label phase 2 PNH studies (CLNP023X2201, hereafter referred to as Study X2201, in subjects who were anti-C5 experienced, and CLNP023X2204, hereafter referred to as Study X2204, in subjects who were complement inhibitor naïve) with a total of 26 subjects who received iptacopan 200 mg BID treatment during the phase 2 study and/or the PNH roll-over extension program (REP) study treatment period.
- Study CLNP023C12001B (hereafter referred to as Study C12001B or PNH REP), an ongoing REP in subjects who completed PNH phase 2 and phase 3 studies with iptacopan includes 94 subjects.
- Treatment period 4 of Study CLFG316X2201, an open-label study in adult subjects with PNH, who were naïve to complement inhibitors (or experienced at least an 8-week washout period), which included nine subjects.

Renal Studies

- Study CLNP023X2203, hereafter referred to as Study X2203, a completed phase 2, double-blind, randomized, placebo-controlled, dose-ranging study of iptacopan in subjects with IgAN.
- Study CLNP023X2202, hereafter referred to as Study X2202, a completed phase 2, open-label, nonrandomized study of iptacopan in a native kidney and post-transplant population with recurrence of C3 glomerulopathy.
- Study CLNP023B12001B, hereafter referred to as Study B12001B or C3G REP, an ongoing, open-label, nonrandomized, roll-over extension study of iptacopan in subjects with C3 glomerulopathy.

Adverse events of special interests identified by the Applicant were infections caused by encapsulated bacteria, hemolysis and thrombosis, decreased platelets, testicular effects, and thyroid changes.

The 120-day safety update provided additional safety data collected from ongoing studies. Findings from the safety update were incorporated into the safety assessment when applicable.

No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. There were no major identified issues with respect to recording, coding, and categorizing adverse events (AEs). The Applicant's translations of verbatim terms to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for the events reported in trials APPLY-PNH and APPOINT-PNH were reviewed and found to be acceptable. Treatment-emergent AEs (TEAEs) were defined as any adverse event after receiving a dose of the study drug. All AEs in the reviewed trials were graded by investigators using the terms mild (usually transient in nature and generally not interfering with normal activities), moderate (sufficiently discomforting to interfere with normal activities), and severe (prevents normal activities).

7.5. Adequacy of the Clinical Safety Database

In the APPLY-PNH RTP, the median duration of exposure to study treatment was the same for both the treatment groups: 24.1 weeks (range: 24 to 24.1) for the iptacopan group, and 24.1 weeks (range: 24 to 24.2) for the anti-C5 treatment group. The median duration of the RTP + the extension period in the 62 subjects who received iptacopan was 47.9 weeks (range: 36.2 to 48.3), with 31 subjects having at least 48 weeks of exposure. Table 22 and Table 23 summarize the duration of exposure during the randomized treatment period and extension period in APPLY-PNH, respectively. Subject demographics for APPLY-PNH can be found in Table 9.

The median duration of exposure to iptacopan 200 mg BID in the APPOINT-PNH study was 24.1 weeks (range: 24.1 to 24.3) for the core treatment period and 45.4 weeks (range: 43.3 to 47.1) for the core and extension periods. Table 24 summarizes the overall duration of iptacopan exposure for all subjects in APPOINT-PNH. Subject demographics for APPOINT-PNH can be found in Table 18.

The exposure of the entire safety database, which includes the PNH and renal studies, is shown in Table 25.

Table 22. Duration of Exposure, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Parameter	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)
Duration of treatment, weeks		
Mean (SD)	24 (0.5)	24.3 (0.6)
Median (Q1, Q3)	24.1 (24, 24.1)	24.1 (24.1, 24.2)
Min, max	20.1, 24.4	23.7, 26.9
Total exposure (person years)	29	16

Parameter	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)
Subjects treated, by duration, n (%)		
<20 weeks	0	0
≥20 to <22 weeks	1 (1.6)	0
≥22 to <24 weeks	7 (11.3)	2 (5.7)
≥24 to <26 weeks	54 (87.1)	31 (88.6)
≥26 to <28 weeks	0	2 (5.7)
≥28 weeks	0	0

Source: adex.xpt and adsl.xpt; Software: R
Duration is 24 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PNH, paroxysmal nocturnal hemoglobinuria; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 23. Duration of Exposure, Safety Population, Trial APPLY-PNH and Roll-over Extension Period

Parameter	Iptacopan (RTP) to Iptacopan (Ext.) Ext. Period Only N=61 n (%)	Anti-C5 (RTP) to Iptacopan (Ext.) Ext. Period Only N=33 n (%)	Iptacopan (RTP) to Iptacopan (Ext.) RTP + Ext. Period N=62 n (%)
Duration of treatment, weeks			
Mean (SD)	18.9 (7.6)	20.5 (5.4)	42.6 (8.1)
Median (Q1, Q3)	24 (13.9, 24.1)	23.7 (18.6, 24)	47.9 (36.2, 48.3)
Min, max	2.4, 25	4, 24.1	20.1, 49.1
Total exposure (person years)	22	13	51
Subjects treated, by duration, n (%)			
<12 weeks	15 (24.6)	4 (12.1)	0
≥12 to <24 weeks	15 (24.6)	18 (54.5)	1 (1.6)
≥24 to <48 weeks	31 (50.8)	11 (33.3)	30 (48.4)
≥48 to <72 weeks	0	0	31 (50.0)

Source: adex.xpt and adsl.xpt; Software: R
Duration of the RTP is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the RTP + Ext. period is 48 weeks.
Abbreviations: Ext., extension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PNH, paroxysmal nocturnal hemoglobinuria; Q1, first quartile; Q3, third quartile; RTP, randomized treatment period; SD, standard deviation

Table 24. Duration of Exposure, Safety Population, Trial APPOINT-PNH

Parameter	Iptacopan Core Period N=40	Iptacopan Core + Ext. Period N=40
Duration of treatment, weeks		
Mean (SD)	24.2 (0.2)	42.9 (6.6)
Median (Q1, Q3)	24.1 (24.1, 24.3)	45.4 (43.3, 47.1)
Min, max	23.6, 25	24.3, 48.4
Total exposure (person years)	19	33
Subjects treated, by duration, n (%)		
<24 weeks	3 (7.5)	0
≥24 to <36 weeks	37 (92.5)	7 (17.5)
≥36 to <48 weeks	0	27 (67.5)
≥48 to <72 weeks	0	6 (15.0)
≥72 weeks	0	0

Source: adex.xpt and adsl.xpt; Software: R
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Abbreviations: Ext., extension; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PNH, paroxysmal nocturnal hemoglobinuria; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 25. Duration of Exposure to Study Treatment, Pooled PNH Studies and Pooled Renal Studies, Safety Population

	APPLY-PNH RTP		PNH studies	Renal studies
	LNP023 200mg b.i.d. N=62	Anti-C5 N=35	LNP023 200mg b.i.d. N=170	LNP023 200mg b.i.d. N=53
Total number of patients receiving study treatment-n (%)	62 (100)	35 (100)	170 (100)	53 (100)
Duration of exposure (months)				
Mean (SD)	5.5 (0.12)	5.6 (0.15)	13.1 (9.71)	12.3 (9.89)
Median	5.6	5.6	10.6	5.9
Q1-Q3	5.5-5.6	5.6-5.6	7.8-13.8	3.0-22.6
Min-Max	4.6-5.6	5.5-6.2	0.9-51.9	1.0-30.0
Duration of exposure categories - n (%)				
>= 1 day	62 (100)	35 (100)	170 (100)	53 (100)
>= 7 day	62 (100)	35 (100)	170 (100)	53 (100)
>= 1 month	62 (100)	35 (100)	169 (99.4)	52 (98.1)
>= 3 months	62 (100)	35 (100)	166 (97.6)	39 (73.6)
>= 6 months	0	2 (5.7)	150 (88.2)	25 (47.2)
>= 9 months	0	0	118 (69.4)	25 (47.2)
>= 12 months	0	0	57 (33.5)	23 (43.4)
>= 18 months	0	0	21 (12.4)	17 (32.1)
>= 24 months	0	0	18 (10.6)	10 (18.9)
>= 30 months	0	0	14 (8.2)	0
>= 36 months	0	0	8 (4.7)	0
>= 4 years	0	0	4 (2.4)	0
>= 5 years	0	0	0	0
patient-time (years)	28.6	16.3	185.1	54.5

Source: Applicant's Summary of Clinical Safety, p. 23 and verified by CDS.
Duration of exposure in months is defined as days on exposure/(365.25/12) and duration of exposure in years is days on exposure/365.25, where days on exposure is derived as (last dose date in the corresponding treatment period – first dose date + 1 – days on temporary treatment interruptions). Patient-time is the sum of each patient's treatment exposure in year.
Abbreviations: b.i.d, twice a day; CDS, clinical data scientist; LNP023, iptacopan; Max, maximum; Min, minimum; N, number of subjects; n, number of subjects receiving study treatment; PNH, paroxysmal nocturnal hemoglobinuria; Q1, quarter 1; Q3, quarter 3; RTP, randomized treatment period; SD, standard deviation

Clinical Reviewer Comment:

In subjects with PNH, 170 subjects received at least one dose of iptacopan 200 mg BID (the proposed dose for marketing), 57 of whom received iptacopan for at least 12 months. There are an additional 53 subjects in the renal studies who received at least one dose of iptacopan 200 mg BID, 23 of whom received iptacopan for at least 12 months, providing supportive safety data. This safety database is reasonable and sufficient to support approval in the context of this rare, serious disease. PNH is a chronic disease and, therefore, treatment with a complement inhibitor is usually expected to be lifelong. Similar to other approved complement inhibitors for PNH, the review team is recommending PMRs to further assess the long-term safety of iptacopan. See Section 24 for a description of PMRs.

7.6. Safety Results

Overall, iptacopan was well tolerated with a safety profile generally consistent with other approved complement inhibitors, with the exception of lipid abnormalities and thrombocytopenia, which were clinically relevant adverse reactions. Safety analysis showed iptacopan to have an acceptable safety profile in both subjects who were complement inhibitor naïve and in subjects previously treated with a C5 inhibitor. No new safety concerns were identified in the APPLY-PNH and APPOINT-PNH extension periods, although additional long-term safety data are needed given the small database and limited longer exposure times. No additional safety concerns emerged from an analysis of the larger ISS population, more specifically the PNH pool, that were not identified in the primary safety analysis (see Section 17 for a description of safety findings from the PNH pool). No new safety concerns were identified in the 120-day safety update. A brief overview of the key safety findings from the APPLY-PNH RTP and APPOINT-PNH core treatment periods is provided below.

Deaths

No deaths occurred in APPLY-PNH and APPOINT-PNH. One death occurred due to an encapsulated organism infection in an iptacopan-treated subject in the rollover extension study.

Serious Adverse Reactions

Overall, the rates of serious adverse reactions were similar in the APPLY-PNH and APPOINT-PNH core periods. In APPLY-PNH, the frequency of serious adverse events (SAEs) was lower in the iptacopan arm than in the anti-C5 arm (9.7% versus 14.3%, respectively). Serious adverse reactions occurred in 3% of subjects in the APPLY-PNH RCP; this included pyelonephritis, urinary tract infection, and COVID-19. In APPOINT-PNH, serious adverse reactions were reported in 2 (5%) subjects in the core treatment period, including COVID-19 and bacterial pneumonia.

AEs Leading to Drug Discontinuation

No AEs leading to drug discontinuation or modification occurred in APPLY-PNH and APPOINT-PNH.

Common Adverse Reactions

Overall, the most common adverse reactions (>10%) in APPLY-PNH and APPOINT-PNH were headache, nasopharyngitis, viral infection, abdominal pain, diarrhea, rash, and bacterial infection. In APPLY-PNH, the proportion of subjects in the iptacopan arm who experienced a treatment-emergent adverse event (TEAE) was similar to that in subjects who received anti-C5 therapy (82% versus 80%, respectively).

7.6.1. Safety Results, Trial APPLY-PNH

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Trial APPLY-PNH

Table 26 and Table 27 provide a summary of TEAEs reported in the RTP and extension periods of APPLY-PNH, respectively. Overall, iptacopan was well tolerated. No subject discontinued or modified the dose of iptacopan during the RTP and extension periods. Compared to C5 inhibitor therapy, iptacopan had fewer SAEs and severe TEAEs.

Table 26. Overview of Treatment-Emergent Adverse Events,[1] Safety Population, Trial APPLY-PNH Randomized Treatment Period

Event Category	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
SAE	6 (9.7)	5 (14.3)	-4.6 (-18.3, 9.1)
SAEs with fatal outcome	0	0	0 (0, 0)
Life-threatening SAEs	1 (1.6)	0	1.6 (-1.5, 4.7)
AE leading to permanent discontinuation of study drug	0	0	0 (0, 0)
AE leading to dose modification of study drug	0	0	0 (0, 0)
AE leading to interruption of study drug	0	0	0 (0, 0)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)
Other	0	0	0 (0, 0)
Any AE	51 (82.3)	28 (80.0)	2.3 (-14.1, 18.6)
Severe and worse	3 (4.8)	3 (8.6)	-3.7 (-14.4, 7.0)
Moderate	28 (45.2)	12 (34.3)	10.9 (-9.1, 30.9)
Mild	20 (32.3)	13 (37.1)	-4.9 (-24.7, 14.9)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier. The on-treatment period for Anti-C5 is from the fist dose date until one day before the next planned dose or the analysis cut-off date, whichever is earlier.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event

Table 27. Overview of Adverse Events, Safety Population, Trial APPLY-PNH

Event Category	Iptacopan (RTP) to Iptacopan (Ext.) Ext. Period N=61 n (%)	Anti-C5 (RTP) to Iptaopan (Ext.) Ext. Period N=33 n (%)
SAE	3 (4.9)	3 (9.1)
SAEs with fatal outcome	0	0
Life-threatening SAEs	0	0
AE leading to permanent discontinuation of study drug	0	0

Event Category	Iptacopan (RTP) to Iptacopan (Ext.) Ext. Period N=61 n (%)	Anti-C5 (RTP) to Iptaopan (Ext.) Ext. Period N=33 n (%)
AE leading to dose modification of study drug	0	0
AE leading to interruption of study drug	0	0
AE leading to reduction of study drug	0	0
AE leading to dose delay of study drug	0	0
Other	0	0
Any AE	35 (57.4)	21 (63.6)
Severe and worse	3 (4.9)	2 (6.1)
Moderate	13 (21.3)	4 (12.1)
Mild	19 (31.1)	15 (45.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Duration of the RTP is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the RTP + Ext. period is 48 weeks.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with at least one event; PNH, paroxysmal nocturnal hemoglobinuria; RTP, randomized treatment period; SAE, serious adverse event

7.6.1.2. Deaths, Trial APPLY-PNH

No deaths occurred in the RTP.

In the safety update, it was reported there was one death in the extension period. Subject (b) (6) was a 69-year-old female who died due to sepsis and cardiopulmonary compromise on day 592 of the study. In brief, on Day 567 the subject was hospitalized due to bacteremia (organism identified as *Streptococcus gallolyticus).* The subject's central venous catheter was removed, and antibiotics were initiated. Despite interventions the subject died of sepsis and multiorgan failure.

Clinical Reviewer Comment:

Serious infections caused by encapsulated organisms will be a boxed warning in the USPI. See Section 7.7.1 for further discussion.

7.6.1.3. Serious Treatment-Emergent Adverse Events, APPLY-PNH

The frequency of SAEs was lower in the iptacopan arm than in the anti-C5 arm (9.7% versus 14.3%, respectively). Serious adverse reactions included pyelonephritis, urinary tract infection, and COVID-19. See Section 7.7.1 for a discussion of serious infections.

Table 28. Subjects With Serious Treatment-Emergent Adverse Events[1] by System Organ Class and Preferred Term, Safety Population, Trial APPLY-PNH Randomized Treatment Period

System Organ Class Preferred Term	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan Versus Anti-C5 Risk Difference (%) (95% CI)
Any SAE	6 (9.7)	5 (14.3)	-4.6 (-18.3, 9.1)
Blood and lymphatic system disorders (SOC)	0	2 (5.7)	-5.7 (-13.4, 2.0)
Breakthrough hemolysis	0	1 (2.9)	-2.9 (-8.4, 2.7)
Extravascular hemolysis	0	1 (2.9)	-2.9 (-8.4, 2.7)
Cardiac disorders (SOC)	1 (1.6)	0	1.6 (-1.5, 4.7)
Sinus node dysfunction	1 (1.6)	0	1.6 (-1.5, 4.7)
Hepatobiliary disorders (SOC)	0	1 (2.9)	-2.9 (-8.4, 2.7)
Jaundice	0	1 (2.9)	-2.9 (-8.4, 2.7)
Infections and infestations (SOC)	2 (3.2)	3 (8.6)	-5.3 (-15.6, 4.9)
Pyelonephritis	1 (1.6)	0	1.6 (-1.5, 4.7)
Urinary tract infection	1 (1.6)	0	1.6 (-1.5, 4.7)
Arthritis bacterial	0	1 (2.9)	-2.9 (-8.4, 2.7)
Intervertebral discitis	0	1 (2.9)	-2.9 (-8.4, 2.7)
Pseudomonas infection	0	1 (2.9)	-2.9 (-8.4, 2.7)
Sepsis	0	1 (2.9)	-2.9 (-8.4, 2.7)
Staphylococcal infection	0	1 (2.9)	-2.9 (-8.4, 2.7)
COVID-19	1 (1.6)	2 (5.7)	-4.1 (-12.4, 4.2)
Investigations (SOC)	1 (1.6)	1 (2.9)	-1.2 (-7.6, 5.1)
Blood creatine phosphokinase increased	1 (1.6)	0	1.6 (-1.5, 4.7)
Influenza A virus test positive	0	1 (2.9)	-2.9 (-8.4, 2.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC)	2 (3.2)	0	3.2 (-1.2, 7.6)
Basal cell carcinoma	1 (1.6)	0	1.6 (-1.5, 4.7)
Myelodysplastic syndrome	1 (1.6)	0	1.6 (-1.5, 4.7)
Nervous system disorders (SOC)	1 (1.6)	0	1.6 (-1.5, 4.7)
Transient ischemic attack	1 (1.6)	0	1.6 (-1.5, 4.7)
Renal and urinary disorders (SOC)	0	1 (2.9)	-2.9 (-8.4, 2.7)
Acute kidney injury	0	1 (2.9)	-2.9 (-8.4, 2.7)
Bilirubinuria	0	1 (2.9)	-2.9 (-8.4, 2.7)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier. The on-treatment period for Anti-C5 is from the fist dose date until one day before the next planned dose or the analysis cut-off date, whichever is earlier.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Arthritis bacterial replaces: Arthritis bacterial
Intervertebral discitis replaces: Intervertebral discitis
Pseudomonas infection replaces: Arthritis bacterial
Staphylococcal infection replaces: Intervertebral discitis
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event; SOC, system organ class

Subject Narratives for SAEs in RTP (Iptacopan Arm Only)

- Subject (b) (6) was diagnosed with a serious adverse event of basal cell carcinoma on the right lower leg on Day 123. There was a family history of malignancy and, given the size of the carcinoma, it was likely the carcinoma was present prior to the start of study drug treatment. Therefore, the clinical reviewer agrees that this SAE was not related to iptacopan.
- Subject (b) (6) was diagnosed with myelodysplastic syndrome on Day 70. The subject had a monosomy 7 chromosomal abnormality prior to the study entry. The clinical reviewer agrees with the Applicant that the event of myelodysplastic syndrome was unrelated to iptacopan as monosomy 7 is one of the most frequent aneuploidies in myeloid malignancies (Inaba et al. 2018).
- Subject (b) (6), a 62-year-old subject, had serious adverse events of sinus node dysfunction and transient ischemic attack. On Day 132, the subject was hospitalized after an episode of syncope. The subject developed hemiparesis and recovered after treatment and placement of a pacemaker for sinus node dysfunction. The subject's history of atrial fibrillation, dyslipidemia, and arterial hypertension are mostly likely the cause of the SAEs as opposed to iptacopan.
- Subject (b) (6) had an SAE of increase in blood creatine phosphokinase. After exercising at home for a few days, the subject's creatine phosphokinase increased to 16,371 IU/L (normal range: 20 to 200 IU/L). The subject was also taking eltrombopag and cyclosporine, so drug-drug interactions with iptacopan were considered. The subject was hospitalized and treated with intravenous hydration. The subject recovered after eltrombopag and cyclosporine were discontinued, but iptacopan was continued. Cyclosporine is known to increase iptacopan exposure by 40-50% and eltrombopag (being an OATP1B1 inhibitor) also has potential to increase iptacopan exposure. The potential increase in iptacopan exposure level is likely not clinically significant because it is within the range of available clinical experience in which no exposure-dependent change in safety parameters were observed. This SAE is considered not related to iptacopan and more likely related to eltrombopag and/or cyclosporine and/or exercise given that it did not recur despite continued treatment with iptacopan after discontinuation of eltrombopag and cyclosporine.
- Subject (b) (6) was hospitalized with pyelonephritis on Day 36. After being treated with antibiotics, the subject recovered. However, on Day 60, the subject was hospitalized again with a urinary tract infection. Iptacopan is a complement inhibitor and can interfere with the immune system, and therefore, the events are considered related to iptacopan.
- Subject (b) (6) was hospitalized with COVID-19 on Day 15 despite receiving a COVID-19 vaccine. Even though the infection was at the time of the pandemic, a decrease in the functioning of the immune system by iptacopan could have contributed to this serious adverse event.

In the extension period, the proportion of subjects who experienced SAEs was similar to that in the RTP. Serious adverse events related to iptacopan included cellulitis and septic shock. A list of SAEs in the extension period are provided in Table 29 below.

Table 29. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial APPLY-PNH Extension Period

System Organ Class Preferred Term	Iptacopan (RTP) to Iptacopan (Ext.) Ext. Period N=61 n (%)	Anti-C5 (RTP) to Iptacopan (Ext.) Ext. Period N=33 n (%)
Any SAE	3 (4.9)	3 (9.1)
Gastrointestinal disorders (SOC)	0	1 (3.0)
Pancreatolithiasis	0	1 (3.0)
Infections and infestations (SOC)	2 (3.3)	1 (3.0)
Cellulitis	1 (1.6)	0
Septic shock	1 (1.6)	0
Systemic infection	0	1 (3.0)
Investigations (SOC)	0	1 (3.0)
Platelet count decreased	0	1 (3.0)
Reproductive system and breast disorders (SOC)	1 (1.6)	0
Ovarian cyst	1 (1.6)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of the RTP is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the RTP + Ext. period is 48 weeks.
Abbreviations: Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; RTP, randomized treatment period; SAE, serious adverse event; SOC, system organ class

Subject Narratives for SAEs in Extension Period

- Subject (b) (6) developed cellulitis in their left arm after receiving a pneumococcal vaccine on Day 197. The subject was hospitalized and recovered after being treated with vancomycin, meropenem, and amoxicillin-clavulanate. There was no change to the study drug. Although the cellulitis appeared with the initiating factor of the vaccine injection, iptacopan inhibits the complement system, which is a central component of the innate immune system; therefore, iptacopan likely contributed to the infectious event.
- Subject (b) (6) was diagnosed with septic shock and hospitalized on Day 190. At the time, the subject was positive for COVID-19 and developed pneumonia. A causal relationship between iptacopan and septic shock is likely because of the complement inhibitor's effect on the immune system.
- Subject (b) (6) presented with abdominal pain on Day 236 of the study and was ultimately diagnosed with an ovarian cyst. The ovarian cyst was unlikely due to iptacopan.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Trial APPLY-PNH

No AEs leading to treatment discontinuation occurred in the core or extension periods of APPLY-PNH.

7.6.1.5. Treatment-Emergent Adverse Events, Trial APPLY-PNH

The proportion of subjects in the iptacopan arm who experienced a TEAE (82%) was similar to that in the anti-C5 therapy arm (80%). The most common (>5%) adverse reactions with iptacopan that occurred in the APPLY-PNH RCP, based on preferred terms, were headache, diarrhea, nasopharyngitis, nausea, arthralgia, urinary tract infection, dizziness, and abdominal pain. While LDH increase occurred in 7% of subjects in the iptacopan arm, this finding was considered related to the underlying disease and was, therefore, not considered a common adverse reaction.

Table 31 shows common adverse reactions based on FDA Medical Queries, which group related preferred terms into medical concepts. This approach also identified bacterial infection, thrombocytopenia, hypertension, hepatic injury, and lipid disorder as common adverse events (>5% incidence in the iptacopan arm). See Sections 7.6.3 and 7.7 for further discussion on infections, lipid disorder, and thrombocytopenia. “Hepatic injury” was considered not related to iptacopan as the liver enzyme elevations were transient (single timepoint) and improved with continued iptacopan treatment.

Table 30. Subjects With Common Treatment-Emergent Adverse Events[1] Occurring at ≥2% Frequency, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Preferred Term	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Any AE	51 (82.3)	28 (80.0)	2.3 (-14.1, 18.6)
Headache	10 (16.1)	1 (2.9)	13.3 (2.6, 24.0) *
Diarrhea	9 (14.5)	2 (5.7)	8.8 (-2.9, 20.5)
Nasopharyngitis	7 (11.3)	2 (5.7)	5.6 (-5.4, 16.6)
Nausea	6 (9.7)	1 (2.9)	6.8 (-2.4, 16.0)
Arthralgia	5 (8.1)	1 (2.9)	5.2 (-3.5, 13.9)
Urinary tract infection	5 (8.1)	1 (2.9)	5.2 (-3.5, 13.9)
COVID-19	5 (8.1)	9 (25.7)	-17.6 (-33.6, -1.7) *
Blood lactate dehydrogenase increased	4 (6.5)	3 (8.6)	-2.1 (-13.2, 9.0)
Dizziness	4 (6.5)	0	6.5 (0.3, 12.6) *
Abdominal pain	4 (6.5)	1 (2.9)	3.6 (-4.6, 11.8)
Abdominal pain upper	3 (4.8)	0	4.8 (-0.5, 10.2)
Bronchitis	3 (4.8)	0	4.8 (-0.5, 10.2)
Hypertension	3 (4.8)	0	4.8 (-0.5, 10.2)
Insomnia	3 (4.8)	0	4.8 (-0.5, 10.2)
Thrombocytopenia	3 (4.8)	0	4.8 (-0.5, 10.2)
Toothache	3 (4.8)	0	4.8 (-0.5, 10.2)
Alanine aminotransferase increased	3 (4.8)	1 (2.9)	2.0 (-5.7, 9.7)
Oedema peripheral	3 (4.8)	1 (2.9)	2.0 (-5.7, 9.7)
Back pain	3 (4.8)	2 (5.7)	-0.9 (-10.2, 8.5)
Blood creatine phosphokinase increased	2 (3.2)	0	3.2 (-1.2, 7.6)
Chromaturia	2 (3.2)	0	3.2 (-1.2, 7.6)
Cough	2 (3.2)	0	3.2 (-1.2, 7.6)
Dyslipidemia	2 (3.2)	0	3.2 (-1.2, 7.6)
Hematuria	2 (3.2)	0	3.2 (-1.2, 7.6)
Hot flush	2 (3.2)	0	3.2 (-1.2, 7.6)
Muscle spasms	2 (3.2)	0	3.2 (-1.2, 7.6)
Peripheral sensory neuropathy	2 (3.2)	0	3.2 (-1.2, 7.6)

Preferred Term	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Rash erythematous	2 (3.2)	0	3.2 (-1.2, 7.6)
Rhinorrhea	2 (3.2)	0	3.2 (-1.2, 7.6)
Palpitations	2 (3.2)	1 (2.9)	0.4 (-6.7, 7.4)
Vomiting	2 (3.2)	1 (2.9)	0.4 (-6.7, 7.4)
Breakthrough haemolysis	2 (3.2)	6 (17.1)	-13.9 (-27.2, -0.7) *
Pyrexia	2 (3.2)	3 (8.6)	-5.3 (-15.6, 4.9)
Sinusitis	2 (3.2)	3 (8.6)	-5.3 (-15.6, 4.9)
Upper respiratory tract infection	2 (3.2)	3 (8.6)	-5.3 (-15.6, 4.9)
Fatigue	1 (1.6)	1 (2.9)	-1.2 (-7.6, 5.1)
Immunization reaction	1 (1.6)	1 (2.9)	-1.2 (-7.6, 5.1)
Neutropenia	1 (1.6)	1 (2.9)	-1.2 (-7.6, 5.1)
Odynophagia	1 (1.6)	1 (2.9)	-1.2 (-7.6, 5.1)
Pneumonia	1 (1.6)	1 (2.9)	-1.2 (-7.6, 5.1)
Post vaccination syndrome	1 (1.6)	1 (2.9)	-1.2 (-7.6, 5.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier. The on-treatment period for Anti-C5 is from the fist dose date until one day before the next planned dose or the analysis cut-off date, whichever is earlier.
Duration is 24 weeks.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Arthritis bacterial replaces: Arthritis bacterial
Intervertebral discitis replaces: Intervertebral discitis
Pseudomonas infection replaces: Arthritis bacterial
Staphylococcal infection replaces: Intervertebral discitis
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary of Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria

Table 31. Subjects With Treatment-Emergent Adverse Events[1] by System Organ Class and FDA Medical Query (Narrow) Occurring at ≥2% Frequency, Safety Population, Trial APPLY-PNH Randomized Treatment Period

System Organ Class FMQ (Narrow)	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)			
Thrombocytopenia	4 (6.5)	0	6.5 (0.3, 12.6) *
Anemia	1 (1.6)	0	1.6 (-1.5, 4.7)
Leukopenia	1 (1.6)	0	1.6 (-1.5, 4.7)
Cardiac disorders (SOC)			
Systemic hypertension	4 (6.5)	0	6.5 (0.3, 12.6) *
Arrhythmia	2 (3.2)	0	3.2 (-1.2, 7.6)
Cardiac conduction disturbance	1 (1.6)	0	1.6 (-1.5, 4.7)
Palpitations	2 (3.2)	1 (2.9)	0.4 (-6.7, 7.4)

System Organ Class FMQ (Narrow)	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Gastrointestinal disorders (SOC)			
Abdominal pain	9 (14.5)	1 (2.9)	11.7 (1.3, 22.0) *
Diarrhea	9 (14.5)	2 (5.7)	8.8 (-2.9, 20.5)
Nausea	6 (9.7)	1 (2.9)	6.8 (-2.4, 16.0)
Dyspepsia	3 (4.8)	1 (2.9)	2.0 (-5.7, 9.7)
Vomiting	3 (4.8)	1 (2.9)	2.0 (-5.7, 9.7)
General disorders and administration site conditions (SOC)			
Dizziness	4 (6.5)	0	6.5 (0.3, 12.6) *
Peripheral edema	3 (4.8)	1 (2.9)	2.0 (-5.7, 9.7)
Fatigue	2 (3.2)	1 (2.9)	0.4 (-6.7, 7.4)
Pyrexia	3 (4.8)	3 (8.6)	-3.7 (-14.4, 7.0)
Hepatobiliary disorders (SOC)			
Hepatic injury	4 (6.5)	1 (2.9)	3.6 (-4.6, 11.8)
Infections and infestations (SOC)			
Fungal infection	3 (4.8)	0	4.8 (-0.5, 10.2)
Nasopharyngitis	10 (16.1)	5 (14.3)	1.8 (-12.9, 16.6)
Pneumonia	2 (3.2)	1 (2.9)	0.4 (-6.7, 7.4)
Bacterial infection	7 (11.3)	4 (11.4)	-0.1 (-13.3, 13.0)
Viral infection	6 (9.7)	11 (31.4)	-21.8 (-38.8, -4.7) *
Metabolism and nutrition disorders (SOC)			
Lipid disorder	4 (6.5)	0	6.5 (0.3, 12.6) *
Musculoskeletal and connective tissue disorders (SOC)			
Arthralgia	5 (8.1)	1 (2.9)	5.2 (-3.5, 13.9)
Myalgia	1 (1.6)	0	1.6 (-1.5, 4.7)
Fracture	0	1 (2.9)	-2.9 (-8.4, 2.7)
Back pain	3 (4.8)	3 (8.6)	-3.7 (-14.4, 7.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC)			
Malignancy	1 (1.6)	0	1.6 (-1.5, 4.7)
Nervous system disorders (SOC)			
Headache	11 (17.7)	1 (2.9)	14.9 (3.9, 25.9) *
Paresthesia	2 (3.2)	0	3.2 (-1.2, 7.6)
Stroke and TIA	1 (1.6)	0	1.6 (-1.5, 4.7)
Tremor	1 (1.6)	0	1.6 (-1.5, 4.7)
Psychiatric disorders (SOC)			
Insomnia	3 (4.8)	0	4.8 (-0.5, 10.2)
Anxiety	1 (1.6)	0	1.6 (-1.5, 4.7)
Depression	1 (1.6)	0	1.6 (-1.5, 4.7)
Renal and urinary disorders (SOC)			
Renal & urinary tract infection	5 (8.1)	1 (2.9)	5.2 (-3.5, 13.9)
Reproductive system and breast disorders (SOC)			
Abnormal uterine bleeding	1 (1.6)	0	1.6 (-1.5, 4.7)
Excessive menstrual bleeding	1 (1.6)	0	1.6 (-1.5, 4.7)
Respiratory, thoracic and mediastinal disorders (SOC)			
Cough	2 (3.2)	1 (2.9)	0.4 (-6.7, 7.4)

System Organ Class FMQ (Narrow)	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Skin and subcutaneous tissue disorders (SOC)			
Erythema	2 (3.2)	0	3.2 (-1.2, 7.6)
Rash	2 (3.2)	0	3.2 (-1.2, 7.6)
Alopecia	1 (1.6)	0	1.6 (-1.5, 4.7)
Vascular disorders (SOC)			
Thrombosis	1 (1.6)	0	1.6 (-1.5, 4.7)
Thrombosis arterial	1 (1.6)	0	1.6 (-1.5, 4.7)
Hemorrhage	3 (4.8)	2 (5.7)	-0.9 (-10.2, 8.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for Iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier. The on-treatment period for Anti-C5 is from the fist dose date until one day before the next planned dose or the analysis cut-off date, whichever is earlier.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
The following preferred terms were combined:
Abdominal Pain contains: Abdominal pain upper, Abdominal discomfort, Abdominal tenderness
Bacterial Infection contains: Pyelonephritis, Urinary tract infection, Bronchitis bacterial, Bronchitis hemophilus, Cholecystitis, Folliculitis, Cellulitis, Arthritis bacterial, Sepsis, Klebsiella infection, Staphylococcal infection, Pseudomonas infection, Hordeolum, Pneumonia bacterial
Headache contains: Vascular headache, Migraine
Hepatic Injury contains: Hepatic function abnormal, ALT increased, aspartate transferase (AST) increased
Hyperglycemia contains: Blood glucose increase
Lipid Disorder contains: Dyslipidemia, Blood cholesterol increased, LDL increased, Hypercholesterolemia, Blood triglycerides increased, Hyperlipidemia
Nasopharyngitis contains: Rhinitis allergic, Upper respiratory tract infection, Pharyngitis, Rhinitis
Rash contains: Dermatitis allergic, Acne, Erythema multiforme, Rash maculo-papular, Rash erythematous
Systemic Hypertension contains: Hypertension, Systolic hypertension
Thrombocytopenia contains: Platelet count decreased
Viral Infection contains: COVID-19, Herpes zoster, Oral herpes, Nasal herpes, Influenza A virus test positive, Influenza
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; PT, preferred term; SOC, system organ class; TIA, transient ischemic attack

Adverse events observed in the extension period were generally similar to those in the RCP. The most common adverse reactions, based on FDA Medical Queries, were viral infection, bacterial infection, nasopharyngitis, and thrombocytopenia.

Table 32. Subjects With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, Trial APPLY-PNH

Preferred Term	Iptacopan (RTP) to Iptacopan (Ext.) Ext. Period N=61 n (%)	Anti-C5 (RTP) to Iptacopan (Ext.) Ext. Period N=33 n (%)
Any AE	35 (57.4)	21 (63.6)
COVID-19	10 (16.4)	7 (21.2)
Arthralgia	3 (4.9)	0
Breakthrough hemolysis	3 (4.9)	1 (3.0)
Myalgia	3 (4.9)	0
Cough	2 (3.3)	1 (3.0)
Headache	2 (3.3)	2 (6.1)
Influenza like illness	2 (3.3)	0
Nasopharyngitis	2 (3.3)	3 (9.1)

Preferred Term	Iptacopan (RTP) to Iptacopan (Ext.) Ext. Period N=61 n (%)	Anti-C5 (RTP) to Iptacopan (Ext.) Ext. Period N=33 n (%)
Non-cardiac chest pain	2 (3.3)	0
Pain in extremity	2 (3.3)	0
Uterine leiomyoma	2 (3.3)	0
Abdominal discomfort	1 (1.6)	1 (3.0)
Diarrhea	1 (1.6)	2 (6.1)
Nausea	1 (1.6)	2 (6.1)
Petechiae	1 (1.6)	1 (3.0)
Pneumonia	1 (1.6)	1 (3.0)
Vaccination complication	1 (1.6)	1 (3.0)
Hypertension	0	2 (6.1)
Platelet count decreased	0	3 (9.1)
Thrombocytopenia	0	2 (6.1)
Vomiting	0	2 (6.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Duration of the RTP is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the RTP + Ext. period is 48 weeks.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; Ext., extension; MedDRA, Medical Dictionary of Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; RTP, randomized treatment period

Table 33. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Occurring in >1 Subject, Safety Population, Trial APPLY-PNH Extension

System Organ Class FMQ (Narrow)	Iptacopan (RTP) to Iptacopan (Ext.) Ext. Period N=61 n (%)	Anti-C5 (RTP) to Iptacopan (Ext.) Ext. Period N=33 n (%)
Blood and lymphatic system disorders (SOC)		
Thrombocytopenia	0	5 (15.2)
Cardiac disorders (SOC)		
Systemic hypertension	0	2 (6.1)
Gastrointestinal disorders (SOC)		
Abdominal pain	2 (3.3)	1 (3.0)
Diarrhea	1 (1.6)	2 (6.1)
Nausea	1 (1.6)	2 (6.1)
Vomiting	0	2 (6.1)
Infections and infestations (SOC)		
Viral infection	10 (16.4)	7 (21.2)
Bacterial infection	6 (9.8)	3 (9.1)
Nasopharyngitis	4 (6.6)	3 (9.1)
Pneumonia	1 (1.6)	1 (3.0)
Musculoskeletal and connective tissue disorders (SOC)		
Arthralgia	3 (4.9)	0
Myalgia	3 (4.9)	0
Nervous system disorders (SOC)		
Headache	2 (3.3)	2 (6.1)

System Organ Class FMQ (Narrow)	Iptacopan (RTP) to Iptacopan (Ext.) Ext. Period N=61 n (%)	Anti-C5 (RTP) to Iptacopan (Ext.) Ext. Period N=33 n (%)
Renal and urinary disorders (SOC)		
Renal & urinary tract infection	1 (1.6)	1 (3.0)
Respiratory, thoracic and mediastinal disorders (SOC)		
Cough	2 (3.3)	1 (3.0)
Dyspnea	1 (1.6)	1 (3.0)
Vascular disorders (SOC)		
Hemorrhage	2 (3.3)	1 (3.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Duration of the RTP is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the RTP + Ext. period is 48 weeks.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: Ext., extension; FDA, Food and Drug Administration; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; PT, preferred term; RTP, randomized treatment period; SOC, system organ class; TIA, transient ischemic attack

7.6.1.6. Laboratory Findings, Trial APPLY-PNH

This section presents a frequency-based analysis of laboratory assessments using the objective laboratory data. Assessment of laboratory assessments based on AE reporting is included in the analysis of adverse events discussed previously. Overall, with the exception of thrombocytopenia (see Section 7.7.3) and elevated CPK (See Section 7.6.1.3), no clinically relevant laboratory findings were identified. Changes in hemoglobin was considered related to the underlying disease or efficacy of the study drug. No additional clinically relevant laboratory findings were identified in the extension period.

Lipid laboratory values are described in Section 7.7.2.

Table 34. Subjects With Chemistry Values Exceeding Specified Levels for General Chemistry, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 2 (<130)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (<125)	0/62 (0)	0/35 (0)	0 (0, 0)
Sodium, high (mEq/L)			
Level 1 (>150)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 2 (>155)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (>160)	0/62 (0)	0/35 (0)	0 (0, 0)
Potassium, low (mEq/L)			
Level 1 (<3.6)	8/62 (12.9)	3/35 (8.6)	4.3 (-8.1, 16.8)
Level 2 (<3.4)	4/62 (6.5)	2/35 (5.7)	0.7 (-9.1, 10.6)
Level 3 (<3)	0/62 (0)	0/35 (0)	0 (0, 0)

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Potassium, high (mEq/L)			
Level 1 (>5.5)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 2 (>6)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (>6.5)	0/62 (0)	0/35 (0)	0 (0, 0)
Chloride, low (mEq/L)			
Level 1 (<95)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 2 (<88)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (<80)	0/62 (0)	0/35 (0)	0 (0, 0)
Chloride, high (mEq/L)			
Level 1 (>108)	3/62 (4.8)	3/35 (8.6)	-3.7 (-14.4, 7.0)
Level 2 (>112)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (>115)	0/62 (0)	0/35 (0)	0 (0, 0)
Glucose, low (mg/dL)			
Level 1 (<70)	4/62 (6.5)	0/35 (0)	6.5 (0.3, 12.6)*
Level 2 (<54)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Level 3 (<40)	0/62 (0)	0/35 (0)	0 (0, 0)
Glucose, random, high (mg/dL)			
Level 2 (≥200)	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)
Level 3 (>250)	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)
Calcium, low (mg/dL)			
Level 1 (<8.4)	0/62 (0)	2/35 (5.7)	-5.7 (-13.4, 2.0)
Level 2 (<8)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (<7.5)	0/62 (0)	0/35 (0)	0 (0, 0)
Calcium, high (mg/dL)			
Level 1 (>10.5)	3/62 (4.8)	2/35 (5.7)	-0.9 (-10.2, 8.5)
Level 2 (>11)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Level 3 (>12)	0/62 (0)	0/35 (0)	0 (0, 0)
Magnesium, low (mg/dL)			
Level 1 (<1.5)	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)
Level 2 (<1.2)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (<0.9)	0/62 (0)	0/35 (0)	0 (0, 0)
Magnesium, high (mg/dL)			
Level 1 (>2.3)	6/62 (9.7)	6/35 (17.1)	-7.5 (-22.0, 7.0)
Level 2 (>4)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (>7)	0/62 (0)	0/35 (0)	0 (0, 0)
Phosphate, low (mg/dL)			
Level 1 (<2.5)	11/62 (17.7)	5/35 (14.3)	3.5 (-11.5, 18.5)
Level 2 (<2)	1/62 (1.6)	1/35 (2.9)	1.2 (7.6, 5.1)
Level 3 (<1.4)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Protein, total, low (g/dL)			
Level 1 (<6)	3/62 (4.8)	3/35 (8.6)	-3.7 (-14.4, 7.0)
Level 2 (<5.4)	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)
Level 3 (<5)	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)
Albumin, low (g/dL)			
Level 1 (<3.1)	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)
Level 2 (<2.5)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (<2)	0/62 (0)	0/35 (0)	0 (0, 0)

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
CPK, high (U/L)			
Level 1 (>3X ULN)	2/61 (3.3)	0/35 (0)	3.3 (-1.2, 7.7)
Level 2 (>5X ULN)	2/61 (3.3)	0/35 (0)	3.3 (-1.2, 7.7)
Level 3 (>10X ULN)	2/61 (3.3)	0/35 (0)	3.3 (-1.2, 7.7)
Amylase, high (U/L)			
Level 1 (>1.1X ULN)	7/62 (11.3)	3/35 (8.6)	2.7 (-9.4, 14.9)
Level 2 (>1.5X ULN)	1/62 (1.6)	2/35 (5.7)	-4.1 (-12.4, 4.2)
Level 3 (>3X ULN)	0/62 (0)	0/35 (0)	0 (0, 0)
Lipase, high (U/L)			
Level 1 (>1.1X ULN)	5/62 (8.1)	4/35 (11.4)	-3.4 (-15.9, 9.2)
Level 2 (>1.5X ULN)	2/62 (3.2)	1/35 (2.9)	0.4 (-6.7, 7.4)
Level 3 (>3X ULN)	0/62 (0)	0/35 (0)	0 (0, 0)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	12/62 (19.4)	14/35 (40.0)	-20.6 (-39.6, -1.7)*
Level 2 (>27)	6/62 (9.7)	10/35 (28.6)	-18.9 (-35.6, -2.2)*
Level 3 (>31)	4/62 (6.5)	5/35 (14.3)	-7.8 (-20.9, 5.3)
Lactate dehydrogenase, high (U/L), Serum			
Level 1 (≥1000)	2/62 (3.2)	3/35 (8.6)	-5.3 (-15.6, 4.9)
Level 2 (≥2000)	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)
Level 3 (≥3000)	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)

Source: ad b.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal

Clinical Reviewer Comment:

Several trends in laboratory values identified in APPLY-PNH are discussed below.

Low Potassium

Low potassium values, <3.6 mEq/L and <3.4 mEq/L, occurred in 12.9% and 6.5% of subjects in the iptacopan arm, respectively. In the C5 inhibitor arm, low potassium values, <3.6 mEq/L and <3.4 mEq/L, occurred in 8.6% and 5.7% of subjects, respectively. All subjects in the iptacopan arm had a potassium level of grade 0 at baseline (per CTCAE v4.03), two subjects shifted to a grade 2. No subject had a potassium level below 3.2 mmol/L. The majority of low potassium values were transient or were similar to baseline values.

The mean baseline potassium level in the iptacopan arm was 4.01 mmol/L (SD 0.31), the mean change from baseline at week 24 was -0.01 mmol/L (SD 0.306). The mean baseline potassium level in the C5 inhibitor arm was 4.11 mmol/L (SD 0.33) with a mean change of +0.01 (0.41).

The changes in potassium level do not appear clinically significant.

Low Glucose

Low glucose values, <70 mg/dL and <54 mg/dL, occurred in 4 subjects (6.5%) and 1 subject (1.6%) in the iptacopan arm, respectively. No subject in the C5 inhibitor arm had low glucose levels.

Two subjects in the iptacopan arm had a single occurrence of low glucose level to 68 mg/dL, which resolved without change to iptacopan. One subject (subject (b) (6)) had multiple occurrences of low glucose levels, with a range between 49-65 mg/dL between days 56-168 of the RCP. The subject's glucose was within the normal range at baseline, and the subject was not on any medications to lower the glucose level. The subject continued iptacopan in the extension period and no interventions were noted. One subject ((b) (6)) had a normal glucose level at baseline and subsequently developed two occurrences with low glucose level to 63 mg/dL on days 56 and 168 while receiving iptacopan. All other glucose values were within normal limits. The subject was not on any concomitant medications to lower glucose levels.

For the iptacopan arm, the mean glucose level at baseline was 89 mg/dL (SD 12.4), with a mean change of +2 mg/dL (SD 18.1) at Day 168. In the C5 inhibitor arm, the mean glucose level at baseline was 105 mg/dL (SD 40.7), with a mean change of 3 mg/dL (SD 20.9).

In summary, while two subjects developed lower blood glucose on more than one occasion, there does not appear to be any clinically significant trends in glucose levels overall. The etiology of the lower blood glucose is not clear in these two subjects.

High Calcium

High calcium levels, >10.5 mg/dL and >11 mg/dL, occurred in 4.8% and 1.6% of subjects in the iptacopan arm, respectively. In the C5 inhibitor arm, 5.7% of subjects had a calcium level of >10.5 mg/dL.

Three subjects in the iptacopan arm had calcium levels >10.5 mg/dL. One subject (Subject (b) (6)) had a transient increase to 10.8 mg/dL on Day 57 with levels returning to normal (10.2 mg/dL) at the following laboratory testing on Day 112. The other subject (Subject (b) (6)) had a single elevated calcium level of 10.5 mg/dL on Day 169, which returned to normal in the extension period. The subject (Subject (b) (6)) who had a calcium level > 11 mg/dL, had a transient increase to 11.02 mg/dL which returned to the normal range (10.2 mg/dL) by Day 169.

Elevated calcium levels were all transient and normalized without intervention, therefore, high calcium levels were likely not related to iptacopan.

Low Phosphate

Low phosphate levels, <2.5 mg/dL, <2 mg/dL, and <1.4 mg/dL occurred in 17.5%, 1.6% and 1.6% of subjects in the iptacopan arm, respectively. In the C5 inhibitor arm, low phosphate levels, <2.5 mg/dL and <2 mg/dL occurred in 14.3% and 2.9% of subjects, respectively.

Eleven subjects in the iptacopan arm had phosphate levels <2.5mg/dL. The majority of subjects (9 subjects) had a single low phosphate level. Two patients had low phosphate level on more than one occasion. Subject (b) (6) had a normal phosphate level at baseline but developed phosphate levels between 2.2 mg/dL to 2.3 mg/dL from days 56 to 168 of the study. The subject did not have a history of hypophosphatemia and was not taking any medications to lower phosphate levels. The subject's calcium levels on the study were normal. Subject (b) (6) had a

low phosphate level of 2.2 mg/dL on Day 56 of the study, which then normalized. The same subject developed a phosphate level of 1.3 mg/dL on day 168 of the study. The subject had normal phosphate levels in the extension period. The etiology of the hypophosphatemia was likely the concomitant medication of ferric carboxymaltose, which has a warning in the USPI for hypophosphatemia.

Low phosphate levels were mostly transient or confounded by concomitant medications.

CPK Increase

In total, two subjects had elevated CPK increase. One subject (Subject (b) (6)) had an increased CPK after exercise that did not recur despite continued iptacopan treatment, see further discussion in Section 7.6.1.3. The other subject ((b) (6)) had an increase in CPK to 2728 IU/L (reference range 39-308 U/L). The increase was noted at one study visit and resolved at the following visit without intervention. There was no change in iptacopan treatment. The subject stated that she went to the gym, and engaged in muscle activity, prior to the increase in CPK.

Table 35. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Laboratory Parameter	APPLY-PNH N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	APPLY-PNH vs. Anti-C5 Risk Difference (%) (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5X baseline)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Level 2 (≥2X baseline)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (≥3X baseline)	0/62 (0)	0/35 (0)	0 (0, 0)
eGFR, low (mL/min/1.73 m^2)			
Level 1 (≥25% decrease)	8/62 (12.9)	4/35 (11.4)	1.5 (-12.0, 14.9)
Level 2 (≥50% decrease)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (≥75% decrease)	0/62 (0)	0/35 (0)	0 (0, 0)

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

Clinical Reviewer Comment: In total, 13% and 11% of subjects in the iptacopan arm and anti-C5 arm had ≥25% decrease in eGFR, respectively. For all subjects in the iptacopan arm with a ≥25% decrease in eGFR, the decrease was resolved at the end of the study. The mean eGFR at baseline in the iptacopan arm was 93.4 mL/min (SD 23.4) and the mean change at day 168 was -1.2 mL/min (SD 9.2). The mean eGFR at baseline in the anti-C5 arm was 90.3 mL/min (SD 29.2) and the mean change at day 168 was -1.5 mL/min (10.2).

Overall, decreases in eGFR appear to be transient. Results are also confounded by the underlying disease, as patients with PNH are at risk for renal insufficiency due to hemolysis or thrombotic events.

Table 36. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Complete Blood Count			
WBC, low (cells/uL)			
Level 1 (<3500)	32/62 (51.6)	25/35 (71.4)	-19.8 (-39.3, -0.4) *
Level 2 (<3000)	21/62 (33.9)	18/35 (51.4)	-17.6 (-37.9, 2.8)
Level 3 (<1000)	0/62 (0)	0/35 (0)	0 (0, 0)
WBC, high (cells/uL)			
Level 1 (>10800)	3/62 (4.8)	0/35 (0)	4.8 (-0.5, 10.2)
Level 2 (>13000)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Level 3 (>15000)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	1/62 (1.6)	14/35 (40.0)	-38.4 (-54.9, -21.9) *
Level 3 (>2 g/dL dec. from baseline)	1/62 (1.6)	7/35 (20.0)	-18.4 (-32.0, -4.8) *
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	60/62 (96.8)	6/35 (17.1)	79.6 (66.4, 92.9) *
Level 3 (>3 g/dL inc. from baseline)	59/62 (95.2)	2/35 (5.7)	89.4 (80.1, 98.8) *
Platelets, low (cells/uL)			
Level 1 (<140000)	41/62 (66.1)	23/35 (65.7)	0.4 (-19.2, 20.1)
Level 2 (<125000)	33/62 (53.2)	20/35 (57.1)	-3.9 (-24.5, 16.7)
Level 3 (<100000)	15/62 (24.2)	13/35 (37.1)	-12.9 (-32.2, 6.3)
WBC Differential			
Lymphocytes, low (cells/uL)			
Level 1 (<1000)	29/62 (46.8)	21/35 (60.0)	-13.2 (-33.7, 7.2)
Level 2 (<750)	14/62 (22.6)	14/35 (40.0)	-17.4 (-36.7, 1.9)
Level 3 (<500)	4/62 (6.5)	4/35 (11.4)	-5.0 (-17.2, 7.2)
Lymphocytes, high (cells/uL)			
Level 1 (>4000)	3/62 (4.8)	0/35 (0)	4.8 (-0.5, 10.2)
Level 2 (>10000)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (>20000)	0/62 (0)	0/35 (0)	0 (0, 0)
Neutrophils, low (cells/uL)			
Level 1 (<2000)	36/62 (58.1)	25/35 (71.4)	-13.4 (-32.7, 6.0)
Level 2 (<1000)	5/62 (8.1)	7/35 (20.0)	-11.9 (-26.8, 2.9)
Level 3 (<500)	1/62 (1.6)	2/35 (5.7)	-4.1 (-12.4, 4.2)
Eosinophils, high (cells/uL)			
Level 1 (>650)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 2 (>1500)	0/62 (0)	0/35 (0)	0 (0, 0)
Level 3 (>5000)	0/62 (0)	0/35 (0)	0 (0, 0)
Coagulation Studies			
PT, high (sec)			
Level 1 (>1.1X ULN)	14/62 (22.6)	13/35 (37.1)	-14.6 (-33.7, 4.5)
Level 2 (>1.3X ULN)	11/62 (17.7)	6/35 (17.1)	0.6 (-15.1, 16.3)
Level 3 (>1.5X ULN)	10/62 (16.1)	4/35 (11.4)	4.7 (-9.3, 18.7)

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Complete Blood Count			
PTT, high (sec)			
Level 1 (>1X ULN)	27/62 (43.5)	11/35 (31.4)	12.1 (-7.6, 31.8)
Level 2 (>1.21X ULN)	12/62 (19.4)	8/35 (22.9)	-3.5 (-20.5, 13.5)
Level 3 (>1.41X ULN)	9/62 (14.5)	5/35 (14.3)	0.2 (-14.3, 14.8)

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; dec., decrease; inc., increase; Iptacopan; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; sec, second; ULN, upper limit of normal; WBC, White blood cells

Clinical Reviewer Comment:

Elevated PT/PTT

Subjects in the iptacopan arm had elevated PT and PTT, this was not unexpected as many subjects were on anticoagulants during the clinical trial due to a history or risk of thrombosis. In the iptacopan arm, 13% of subjects were on vitamin K antagonists, 6.5% of subjects were on direct factor Xa inhibitors, and 6.5% of subjects were on low molecular weight heparin.

Low WBC

Thirty-four percent of subjects in the iptacopan arm and 51% of subjects in the anti-C5 arm had a WBC <3000 cells/uL. Of the 21 subjects with low WBCs in the iptacopan arm, 7 had a low WBC count at baseline. The mean WBC at baseline in the iptacopan arm was 3.8 cells/uL (1.6) and the mean change was +0.8 cells/uL (SD 2.1). The mean baseline WBC at baseline in the anti-C5 arm was 3.9 cells/uL (SD 1.6) and the mean change was -0.2 cells/uL (SD 1.1). Overall, there does not appear to be a trend in decrease WBC in subjects exposed to iptacopan. Further, PNH is associated with bone marrow failure, therefore patients may have neutropenia, thrombocytopenia, anemia and leukopenia. In total, 14.4% of subjects included in APPLY-PNH had a history of aplastic anemia.

Low Lymphocytes

Seven percent of subjects in the iptacopan arm and 11% of subjects in the anti-C5 arm had a lymphocyte count of <500 cells/uL. All four patients in the iptacopan arm with lymphocytes below 500 cells/uL had low lymphocytes at baseline (<600 cells/uL). In addition, of the 14 subjects with low lymphocytes, <750 cells/uL, 13 had low lymphocytes at baseline (<1000 cells/uL). The one subject (Subject (b) (6)) who had >1000 cells/uL at baseline had a level of 1090 cells/uL. In summary, low lymphocyte values were consistent with baseline values.

7.6.1.7. Assessment of Drug-Induced Liver Injury, Trial APPLY-PNH

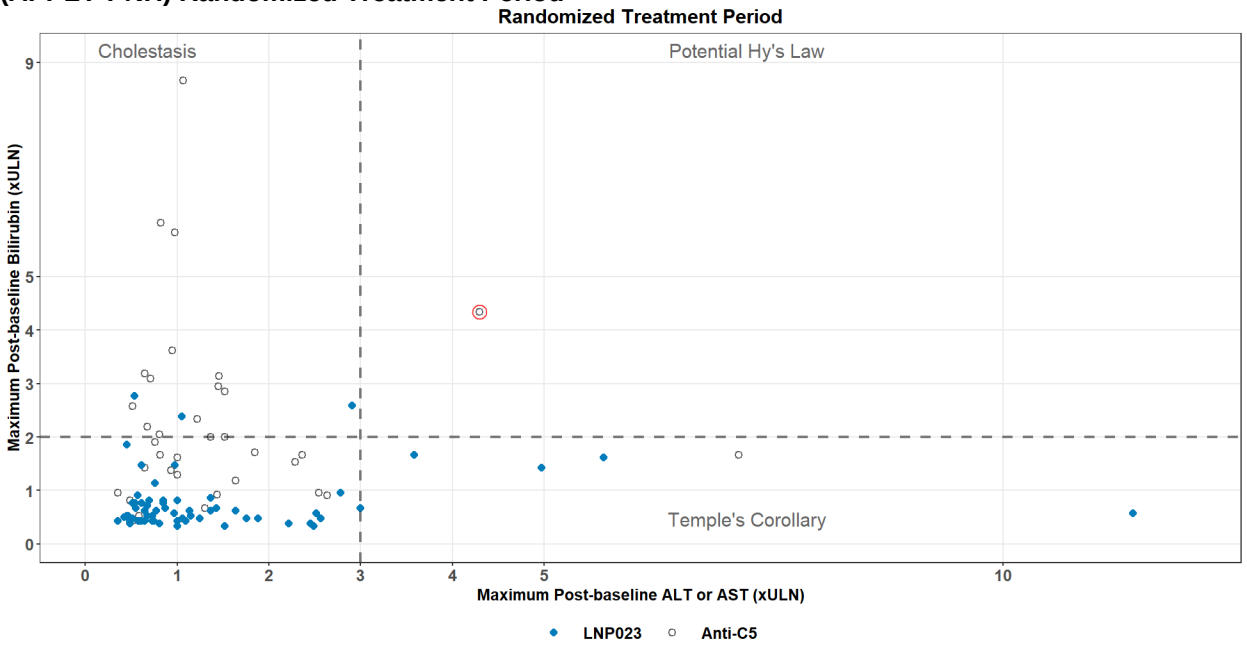
Table 37 shows the incidence of elevated liver enzymes. Figure 1 and Table 38 show the data for Hy's Law and Temple's Corollary.

Table 37. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan Versus Anti-C5 Risk Difference (%) (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	4/62 (6.5)	2/35 (5.7)	0.7 (-9.1, 10.6)
Level 2 (>2X ULN)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Level 3 (>3X ULN)	0/62 (0)	0/35 (0)	0 (0, 0)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	3/62 (4.8)	1/35 (2.9)	2.0 (-5.7, 9.7)
Level 2 (>5X ULN)	1/62 (1.6)	1/35 (2.9)	-1.2 (-7.6, 5.1)
Level 3 (>10X ULN)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	1/62 (1.6)	2/35 (5.7)	-4.1 (-12.4, 4.2)
Level 2 (>5X ULN)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Level 3 (>10X ULN)	0/62 (0)	0/35 (0)	0 (0, 0)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	6/62 (9.7)	23/35 (65.7)	-56.0 (-73.4, -38.7) *
Level 2 (>2X ULN)	3/62 (4.8)	14/35 (40.0)	-35.2 (-52.2, -18.1) *
Level 3 (>3X ULN)	0/62 (0)	8/35 (22.9)	-22.9 (-36.8, -8.9) *

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal

Figure 1. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial C12302 (APPLY-PNH) Randomized Treatment Period



Source: ad b.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled).
All subjects with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LNP023, iptacopan; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal

Table 38. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Quadrant	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)
Potential Hy's law (right upper)	0/62 (0)	1/35 (2.9)
Cholestasis (left upper)	3/62 (4.8)	15/35 (42.9)
Temple's corollary (right lower)	5/62 (8.1)	1/35 (2.9)
Total	8/62 (12.9)	17/35 (48.6)

Source: ad b.xpt; Software: R
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

Reviewer Comment:

In the APPLY-PNH study, no subjects in the iptacopan arm and one subject in the anti-C5 arm met Hy's Law. The subject (Subject (b) (6)*) in the anti-C5 arm who met Hy's law, had an upper respiratory infection which likely triggered a case of serious breakthrough hemolysis leading to an increase in AST and bilirubin. This case is likely not DILI as the study drug was unchanged during the event. The subject recovered and laboratory values returned to normal. The subject received two units of blood to treat the anemia due to breakthrough hemolysis. The majority of hepatic laboratory abnormalities were confounded by concomitant hemolysis due to PNH, which increases indirect bilirubin (and thus total bilirubin) and AST.*

Two subjects in the iptacopan arm met the threshold for 5 times the upper limit for serum transaminases (see Table 37). One subject (Subject (b) (6)) had an elevated ALT and met the threshold of 5 times and 10 times the ULN. There was a transient increase in ALT of 468 U/L, which returned to normal (19 U/L) by the next study visit with no change to the study drug. Lactate dehydrogenase was mildly increased (279 U/L) at the time of the ALT elevation. As iptacopan was continued and the ALT decreased to normal by the next study visit without intervention, this event is considered unlikely to be related to iptacopan. The second subject (Subject (b) (6)) met the threshold of 5 times the ULN of AST. This event occurred at the time of rhabdomyolysis that was not attributed to iptacopan. See Section 7.6.1.3 for the subject narrative. All five subjects who met Temple's corollary returned to baseline levels without a change in the dose of iptacopan.

7.6.1.8. Vital Signs' Analyses, Trial APPLY-PNH

Overall, baseline and change from baseline in systolic blood pressure (SBP) was similar between treatment arms. See Table 39 below.

Table 39. Change in Systolic Blood Pressure, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Visit	Iptacopan N=62	Anti-C5 N=35
Mean (SD) baseline systolic blood pressure (mmHg)	122 (12)	123 (15)
Mean (SD) Day 168 systolic blood pressure (mmHg)	125 (15)	119 (13)
Change	3 (11)	-5 (16)

Source: Applicant's Clinical Study Report, Table 14.3-3.1a
Abbreviations: N, number of subjects; SD, standard deviation

In the RCP, more subjects in the iptacopan arm had elevated cuff blood pressures than in the anti-C5 arm. Systemic hypertension will be described as a common adverse reaction in the label. Of note, the Applicant stated the effect on blood pressure is considered to be related to improvement of anemia and consequent to an increase in hemoglobin in patients with PNH treated with iptacopan; however, insufficient evidence was provided by the Applicant to make this claim. No other clinically relevant vital sign abnormalities occurred in APPLY-PNH.

Table 40. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Systolic Blood Pressure (mm Hg)	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
<90	0/62 (0)	0/35 (0)	0 (0, 0)
≥90	62/62 (100)	35/35 (100)	0 (0, 0)
≥120	57/62 (91.9)	33/35 (94.3)	-2.4 (-12.6, 7.9)
≥140	29/62 (46.8)	14/35 (40.0)	6.8 (-13.7, 27.2)
≥160	5/62 (8.1)	1/35 (2.9)	5.2 (-3.5, 13.9)
≥180	0/62 (0)	0/35 (0)	0 (0, 0)

Source: advs.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

Clinical Reviewer Comment: Systolic blood pressures (SBPs) at baseline for subjects in both the iptacopan and anti-C5 arm were similar. The majority of subjects with elevated SBPs did not have elevated SBPs at baseline. In total, six of 29 subjects in the iptacopan arm, and three of 14 subjects in the anti-C5 arm had a baseline SBP ≥ 140 mmHg.

Table 41. Percentage of Subjects With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Trial APPLY-PNH Randomized Treatment Period

Diastolic Blood Pressure (mm Hg)	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
<60	0/62 (0)	1/35 (2.9)	-2.9 (-8.4, 2.7)
≥60	62/62 (100)	34/35 (97.1)	2.9 (-2.7, 8.4)
≥90	16/62 (25.8)	6/35 (17.1)	8.7 (-7.9, 25.2)
≥110	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
≥120	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)

Source: advs.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

7.6.1.9. Subgroup Analyses, Trial APPLY-PNH

An overview of TEAEs by demographic subgroup is summarized in Table 42. Results should be interpreted with caution given the small sample sizes.

Table 42. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial C12302 (APPLY-PNH) Randomized Treatment Period

Characteristic	Iptacopan N=62 n/N_s (%)	Anti-C5 N=35 n/N_s (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Sex, n (%)			
Female	35/43 (81.4)	19/24 (79.2)	2.2 (-17.8, 22.2)
Male	16/19 (84.2)	9/11 (81.8)	2.4 (-25.7, 30.5)
Age group, years, n (%)			
<45	21/25 (84.0)	14/16 (87.5)	-3.5 (-25.2, 18.2)
≥45	30/37 (81.1)	14/19 (73.7)	7.4 (-16.1, 30.9)
Age group ≥65, years, n (%)			
≥65	15/18 (83.3)	5/8 (62.5)	20.8 (-16.9, 58.5)
Age group ≥75, years, n (%)			
≥75	6/6 (100)	1/1 (100)	0 (0, 0)
Race, n (%)			
Asian	10/12 (83.3)	6/7 (85.7)	-2.4 (-35.8, 31.0)
Black or African American	1/2 (50.0)	2/2 (100)	-50.0 (-119.3, 19.3)
White	40/48 (83.3)	20/26 (76.9)	6.4 (-12.9, 25.7)
Ethnicity, n (%)			
Hispanic or Latino	5/8 (62.5)	2/2 (100)	-37.5 (-71.0, -4.0) *
Not Hispanic or Latino	44/51 (86.3)	21/27 (77.8)	8.5 (-9.8, 26.8)
Not reported	1/2 (50.0)	5/6 (83.3)	-33.3 (-108.8, 42.1)
Unknown	1/1 (100)	0/0 (NA)	NA

Characteristic	Iptacopan N=62 n/N_s (%)	Anti-C5 N=35 n/N_s (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Is in United States, n (%)			
United States	6/6 (100)	2/2 (100)	0 (0, 0)
Non-United States	45/56 (80.4)	26/33 (78.8)	1.6 (-15.8, 19.0)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
* indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; PNH, paroxysmal nocturnal hemoglobinuria

7.6.2. Safety Results, Trial APPOINT-PNH (C12301)

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial APPOINT-PNH

Table 43 provides a summary of TEAEs reported in the core and extension periods of APPOINT-PNH. Overall, iptacopan was well tolerated. No subject discontinued or modified the dose of iptacopan during the core and extension periods. The majority of TEAEs were mild.

Table 43. Overview of Treatment-Emergent Adverse Events Safety Population, Trial APPOINT-PNH

Event Category	Iptacopan Core Period N=40 n (%)	Iptacopan Core + Ext. Period N=40 n (%)
SAE	4 (10.0)	6 (15.0)
SAEs with fatal outcome	0	0
Life-threatening SAEs	0	1 (2.5)
AE leading to permanent discontinuation of study drug	0	0
AE leading to dose modification of study drug	0	0
AE leading to interruption of study drug	0	0
AE leading to reduction of study drug	0	0
AE leading to dose delay of study drug	0	0
Other	0	0
Any AE	37 (92.5)	37 (92.5)
Severe and worse	1 (2.5)	3 (7.5)
Moderate	10 (25.0)	10 (25.0)
Mild	26 (65.0)	24 (60.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with at least one event; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event

7.6.2.2. Deaths, Trial APPOINT-PNH

At the data cutoff date, no deaths were reported in the overall study period.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Trial APPOINT-PNH

Serious adverse events occurred in 4 (10%) subjects in the iptacopan core treatment period, Serious adverse reactions included COVID-19 and bacterial pneumonia. Infections are considered related to iptacopan, see further discussion in Section 7.7.1. The events of cataract and diabetes were not related to iptacopan, as subjects had symptoms or a diagnosis prior to iptacopan exposure. Additional adverse reactions of COVID-19 and pneumonia occurred in the extension period.

Table 44. Subjects With Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Population, APPOINT-PNH

System Organ Class Preferred Term	Iptacopan Core Period N=40 n (%)	Iptacopan Core + Ext. Period N=40 n (%)
Any SAE	4 (10.0)	6 (15.0)
Blood and lymphatic system disorders (SOC)	0	1 (2.5)
Breakthrough hemolysis	0	1 (2.5)
Eye disorders (SOC)	1 (2.5)	1 (2.5)
Cataract	1 (2.5)	1 (2.5)
Infections and infestations (SOC)	2 (5.0)	4 (10.0)
COVID-19	1 (2.5)	2 (5.0)
Pneumonia	0	1 (2.5)
Pneumonia bacterial	1 (2.5)	1 (2.5)
Metabolism and nutrition disorders (SOC)	1 (2.5)	1 (2.5)
Type 2 diabetes mellitus	1 (2.5)	1 (2.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Abbreviations: COVID-19, coronavirus disease 2019; Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event; SOC, system organ class

7.6.2.4. Adverse Events Leading to Treatment Discontinuation, Trial APPOINT-PNH

No TEAE led to treatment discontinuation.

7.6.2.5. Treatment-Emergent Adverse Events, Trial APPOINT-PNH

The most common (>10%) adverse reactions that occurred in the core treatment period, based on preferred terms, were headache, COVID-19, and upper respiratory tract infection. Based on FDA Medical Queries, the most common adverse reactions were headache, viral infection, nasopharyngitis, and rash. No new safety signals occurred during the extension period. See Section 7.7.1 for further discussion on infection risk.

Table 45. Subjects With Common Treatment-Emergent Adverse Events Occurring at ≥2% Frequency, Safety Population, APPOINT-PNH

Preferred Term	Iptacopan Core Period N=40 n (%)	Iptacopan Core + Ext. Period N=40 n (%)
Any AE	37 (92.5)	37 (92.5)
Headache	11 (27.5)	12 (30.0)
COVID-19	6 (15.0)	7 (17.5)
Upper respiratory tract infection	5 (12.5)	6 (15.0)
Diarrhea	3 (7.5)	5 (12.5)
Iron deficiency	3 (7.5)	5 (12.5)
Pyrexia	2 (5.0)	3 (7.5)
Vomiting	2 (5.0)	3 (7.5)
Abdominal pain	2 (5.0)	2 (5.0)
Blood glucose increased	2 (5.0)	2 (5.0)
Cataract	2 (5.0)	2 (5.0)
Conjunctivitis	2 (5.0)	2 (5.0)
Constipation	2 (5.0)	2 (5.0)
Dermatitis allergic	2 (5.0)	2 (5.0)
Epistaxis	2 (5.0)	2 (5.0)
Hyperlipidemia	2 (5.0)	2 (5.0)
Nasal congestion	2 (5.0)	2 (5.0)
Nausea	2 (5.0)	2 (5.0)
Periarthritis	2 (5.0)	2 (5.0)
Renal impairment	2 (5.0)	2 (5.0)
Amylase increased	1 (2.5)	2 (5.0)
Asthenia	1 (2.5)	2 (5.0)
C-reactive protein increased	1 (2.5)	2 (5.0)
Chest pain	1 (2.5)	2 (5.0)
Contusion	1 (2.5)	2 (5.0)
Heavy menstrual bleeding	1 (2.5)	2 (5.0)
Lipids abnormal	1 (2.5)	2 (5.0)
Vision blurred	1 (2.5)	2 (5.0)
Abdominal pain upper	1 (2.5)	1 (2.5)
Acne	1 (2.5)	1 (2.5)
Bipolar disorder	1 (2.5)	1 (2.5)
Blood creatine phosphokinase increased	1 (2.5)	1 (2.5)
Blood creatinine increased	1 (2.5)	1 (2.5)
Blood follicle stimulating hormone increased	1 (2.5)	1 (2.5)
Blood magnesium decreased	1 (2.5)	1 (2.5)
Blood triglycerides increased	1 (2.5)	1 (2.5)
Blood uric acid increased	1 (2.5)	1 (2.5)
Chronic gastritis	1 (2.5)	1 (2.5)
Dihydrotestosterone decreased	1 (2.5)	1 (2.5)
Dizziness	1 (2.5)	1 (2.5)
Dysmenorrhea	1 (2.5)	1 (2.5)
Dyspepsia	1 (2.5)	1 (2.5)
Erythema multiforme	1 (2.5)	1 (2.5)
Fatigue	1 (2.5)	1 (2.5)
Fibrin D dimer increased	1 (2.5)	1 (2.5)
Gastritis	1 (2.5)	1 (2.5)
Gastrointestinal infection	1 (2.5)	1 (2.5)
Gastroesophageal reflux disease	1 (2.5)	1 (2.5)
Hemorrhage subcutaneous	1 (2.5)	1 (2.5)
Hemorrhoidal hemorrhage	1 (2.5)	1 (2.5)

Preferred Term	Iptacopan Core Period N=40 n (%)	Iptacopan Core + Ext. Period N=40 n (%)
Hepatic function abnormal	1 (2.5)	1 (2.5)
Hordeolum	1 (2.5)	1 (2.5)
Hyperglycemia	1 (2.5)	1 (2.5)
Hypomagnesaemia	1 (2.5)	1 (2.5)
Immunosuppressant drug level increased	1 (2.5)	1 (2.5)
Influenza	1 (2.5)	1 (2.5)
Influenza-like illness	1 (2.5)	1 (2.5)
Insomnia	1 (2.5)	1 (2.5)
Ligament sprain	1 (2.5)	1 (2.5)
Memory impairment	1 (2.5)	1 (2.5)
Menstrual disorder	1 (2.5)	1 (2.5)
Mucosal infection	1 (2.5)	1 (2.5)
Nasal dryness	1 (2.5)	1 (2.5)
Neutropenia	1 (2.5)	1 (2.5)
Oropharyngeal pain	1 (2.5)	1 (2.5)
Osteoporosis	1 (2.5)	1 (2.5)
Pain in extremity	1 (2.5)	1 (2.5)
Peripheral swelling	1 (2.5)	1 (2.5)
Pneumonia bacterial	1 (2.5)	1 (2.5)
Protein urine present	1 (2.5)	1 (2.5)
Proteinuria	1 (2.5)	1 (2.5)
Pruritus	1 (2.5)	1 (2.5)
Rash maculo-papular	1 (2.5)	1 (2.5)
Renal disorder	1 (2.5)	1 (2.5)
Renal injury	1 (2.5)	1 (2.5)
Reverse triiodothyronine increased	1 (2.5)	1 (2.5)
Rhinitis	1 (2.5)	1 (2.5)
Sinus bradycardia	1 (2.5)	1 (2.5)
Skin discoloration	1 (2.5)	1 (2.5)
Sneezing	1 (2.5)	1 (2.5)
Tachycardia	1 (2.5)	1 (2.5)
Type 2 diabetes mellitus	1 (2.5)	1 (2.5)
Vaccination complication	1 (2.5)	1 (2.5)
Weight increased	1 (2.5)	1 (2.5)
White blood cell count increased	1 (2.5)	1 (2.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; Ext., extension; MedDRA, Medical Dictionary of Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria

Table 46. Subjects With Treatment-Emergent Adverse Events by System Organ Class and FDA Medical Query (Narrow) Occurring at ≥2% Frequency, Safety Population, APPOINT-PNH

System Organ Class FMQ (Narrow)	Iptacopan Core Period N=40 n (%)	Iptacopan Core + Ext. Period N=40 n (%)
Cardiac disorders (SOC)		
Arrhythmia	2 (5.0)	2 (5.0)
Tachycardia	1 (2.5)	1 (2.5)
Endocrine disorders (SOC)		
Hyperglycemia	4 (10.0)	4 (10.0)
Gastrointestinal disorders (SOC)		
Diarrhea	3 (7.5)	5 (12.5)
Abdominal pain	3 (7.5)	3 (7.5)
Vomiting	2 (5.0)	3 (7.5)
Constipation	2 (5.0)	2 (5.0)
Dyspepsia	2 (5.0)	2 (5.0)
Nausea	2 (5.0)	2 (5.0)
General disorders and administration site conditions (SOC)		
Fatigue	2 (5.0)	3 (7.5)
Pyrexia	2 (5.0)	3 (7.5)
Dizziness	1 (2.5)	1 (2.5)
Peripheral edema	1 (2.5)	1 (2.5)
Hepatobiliary disorders (SOC)		
Hepatic injury	1 (2.5)	1 (2.5)
Infections and infestations (SOC)		
Viral infection	7 (17.5)	8 (20.0)
Nasopharyngitis	6 (15.0)	7 (17.5)
Bacterial infection	2 (5.0)	3 (7.5)
Pneumonia	1 (2.5)	2 (5.0)
Metabolism and nutrition disorders (SOC)		
Lipid disorder	3 (7.5)	4 (10.0)
Musculoskeletal and connective tissue disorders (SOC)		
Arthritis	2 (5.0)	2 (5.0)
Osteoporosis	1 (2.5)	1 (2.5)
Nervous system disorders (SOC)		
Headache	11 (27.5)	12 (30.0)
Psychiatric disorders (SOC)		
Insomnia	1 (2.5)	1 (2.5)
Mania	1 (2.5)	1 (2.5)
Renal and urinary disorders (SOC)		
Acute kidney injury	1 (2.5)	1 (2.5)
Reproductive system and breast disorders (SOC)		
Abnormal uterine bleeding	1 (2.5)	2 (5.0)
Excessive menstrual bleeding	1 (2.5)	2 (5.0)
Skin and subcutaneous tissue disorders (SOC)		
Rash	4 (10.0)	5 (12.5)
Pruritus	1 (2.5)	1 (2.5)

System Organ Class FMQ (Narrow)	Iptacopan Core Period N=40 n (%)	Iptacopan Core + Ext. Period N=40 n (%)
Vascular disorders (SOC)		
Hemorrhage	4 (10.0)	5 (12.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: Ext., extension; FDA, Food and Drug Administration; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; PT, preferred term; SOC, system organ class

Clinical Reviewer Comment:

Attribution of TEAEs was challenging given the lack of a control arm. Hyperglycemia was not considered a common AR as elevated glucose levels were transient (i.e., on a single visit) and confounded by underlying conditions such as diabetes. Iron deficiency, which occurred in 7.5% of subjects in the iptacopan arm was also not considered a common AR. Hemolysis is a hallmark of PNH and anemia is a common clinical manifestation. Red blood cells contain iron and, therefore, patients can develop iron deficiency due to intravascular hemolysis, which leads to urinary iron loss. In total, 7.5% of subjects had iron deficiency at baseline. Hemorrhage was also not considered a common AR. Preferred terms included for hemorrhage were contusion, epistaxis, blood urine present, hemorrhage subcutaneous, hemorrhage urinary tract and hemorrhoidal hemorrhage. These adverse reactions are unlikely to be caused by iptacopan. In particular, blood urine present and urinary tract hemorrhage are likely related to the underlying disease as hemoglobinuria occurs in the setting of hemolysis from PNH.

7.6.2.6. Laboratory Findings, Trial APPOINT-PNH

This section presents a frequency-based analysis of the objective laboratory assessments. Assessment of AE reporting based on laboratory assessments is included in analysis of adverse events in the sections above. Overall, no clinically relevant laboratory findings were identified with the exception of thrombocytopenia (see discussion in Section 7.7.3). Changes in hemoglobin and LDH were considered related to the underlying disease or efficacy of the study drug. No additional clinically relevant laboratory findings were identified in the extension period.

Lipid laboratory values are described in Section 7.7.2.

Table 47. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial APPOINT-PNH

Laboratory Parameter	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
Sodium, low (mEq/L)		
Level 1 (<132)	0/40 (0)	0/40 (0)
Level 2 (<130)	0/40 (0)	0/40 (0)
Level 3 (<125)	0/40 (0)	0/40 (0)
Sodium, high (mEq/L)		
Level 1 (>150)	0/40 (0)	0/40 (0)
Level 2 (>155)	0/40 (0)	0/40 (0)
Level 3 (>160)	0/40 (0)	0/40 (0)
Potassium, low (mEq/L)		
Level 1 (<3.6)	6/40 (15.0)	7/40 (17.5)
Level 2 (<3.4)	2/40 (5.0)	3/40 (7.5)
Level 3 (<3)	0/40 (0)	0/40 (0)
Potassium, high (mEq/L)		
Level 1 (>5.5)	0/40 (0)	0/40 (0)
Level 2 (>6)	0/40 (0)	0/40 (0)
Level 3 (>6.5)	0/40 (0)	0/40 (0)
Chloride, low (mEq/L)		
Level 1 (<95)	1/40 (2.5)	1/40 (2.5)
Level 2 (<88)	0/40 (0)	0/40 (0)
Level 3 (<80)	0/40 (0)	0/40 (0)
Chloride, high (mEq/L)		
Level 1 (>108)	1/40 (2.5)	1/40 (2.5)
Level 2 (>112)	0/40 (0)	0/40 (0)
Level 3 (>115)	0/40 (0)	0/40 (0)
Glucose, low (mg/dL)		
Level 1 (<70)	0/40 (0)	0/40 (0)
Level 2 (<54)	0/40 (0)	0/40 (0)
Level 3 (<40)	0/40 (0)	0/40 (0)
Glucose, random, high (mg/dL)		
Level 2 (≥200)	1/40 (2.5)	2/40 (5.0)
Level 3 (>250)	1/40 (2.5)	1/40 (2.5)
Calcium, low (mg/dL)		
Level 1 (<8.4)	0/40 (0)	0/40 (0)
Level 2 (<8)	0/40 (0)	0/40 (0)
Level 3 (<7.5)	0/40 (0)	0/40 (0)
Calcium, high (mg/dL)		
Level 1 (>10.5)	0/40 (0)	0/40 (0)
Level 2 (>11)	0/40 (0)	0/40 (0)
Level 3 (>12)	0/40 (0)	0/40 (0)
Magnesium, low (mg/dL)		
Level 1 (<1.5)	1/40 (2.5)	1/40 (2.5)
Level 2 (<1.2)	0/40 (0)	0/40 (0)
Level 3 (<0.9)	0/40 (0)	0/40 (0)
Magnesium, high (mg/dL)		
Level 1 (>2.3)	2/40 (5.0)	3/40 (7.5)
Level 2 (>4)	0/40 (0)	0/40 (0)
Level 3 (>7)	0/40 (0)	0/40 (0)

Laboratory Parameter	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
Phosphate, low (mg/dL)		
Level 1 (<2.5)	2/40 (5.0)	5/40 (12.5)
Level 2 (<2)	0/40 (0)	2/40 (5.0)
Level 3 (<1.4)	0/40 (0)	1/40 (2.5)
Protein, total, low (g/dL)		
Level 1 (<6)	2/40 (5.0)	2/40 (5.0)
Level 2 (<5.4)	2/40 (5.0)	2/40 (5.0)
Level 3 (<5)	1/40 (2.5)	1/40 (2.5)
Albumin, low (g/dL)		
Level 1 (<3.1)	0/40 (0)	0/40 (0)
Level 2 (<2.5)	0/40 (0)	0/40 (0)
Level 3 (<2)	0/40 (0)	0/40 (0)
CPK, high (U/L)		
Level 1 (>3X ULN)	0/40 (0)	0/40 (0)
Level 2 (>5X ULN)	0/40 (0)	0/40 (0)
Level 3 (>10X ULN)	0/40 (0)	0/40 (0)
Amylase, high (U/L)		
Level 1 (>1.1X ULN)	10/40 (25.0)	11/40 (27.5)
Level 2 (>1.5X ULN)	1/40 (2.5)	1/40 (2.5)
Level 3 (>3X ULN)	0/40 (0)	0/40 (0)
Lipase, high (U/L)		
Level 1 (>1.1X ULN)	9/40 (22.5)	9/40 (22.5)
Level 2 (>1.5X ULN)	3/40 (7.5)	5/40 (12.5)
Level 3 (>3X ULN)	0/40 (0)	1/40 (2.5)
Blood urea nitrogen, high (mg/dL)		
Level 1 (>23)	8/40 (20.0)	8/40 (20.0)
Level 2 (>27)	6/40 (15.0)	6/40 (15.0)
Level 3 (>31)	4/40 (10.0)	4/40 (10.0)
Lactate dehydrogenase, high (U/L), Serum		
Level 1 (≥1000)	0/40 (0)	1/40 (2.5)
Level 2 (≥2000)	0/40 (0)	1/40 (2.5)
Level 3 (≥3000)	0/40 (0)	1/40 (2.5)

Source: ad b.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Abbreviations: CPK, creatine phosphokinase; Ext., extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal

Table 48. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial APPOINT-PNH

Laboratory Parameter	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
Creatinine, high (mg/dL)		
Level 1 (≥1.5X baseline)	2/40 (5.0)	2/40 (5.0)
Level 2 (≥2X baseline)	0/40 (0)	0/40 (0)
Level 3 (≥3X baseline)	0/40 (0)	0/40 (0)
eGFR, low (mL/min/1.73 m^2)		
Level 1 (≥25% decrease)	3/40 (7.5)	3/40 (7.5)
Level 2 (≥50% decrease)	1/40 (2.5)	1/40 (2.5)
Level 3 (≥75% decrease)	0/40 (0)	0/40 (0)

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Abbreviations: eGFR, estimated glomerular filtration rate; Ext., extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

Table 49. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial C12301

Laboratory Parameter	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
Complete blood count		
WBC, low (cells/uL)		
Level 1 (<3500)	24/40 (60.0)	24/40 (60.0)
Level 2 (<3000)	13/40 (32.5)	13/40 (32.5)
Level 3 (<1000)	0/40 (0)	0/40 (0)
WBC, high (cells/uL)		
Level 1 (>10800)	4/40 (10.0)	5/40 (12.5)
Level 2 (>13000)	0/40 (0)	0/40 (0)
Level 3 (>15000)	0/40 (0)	0/40 (0)
Hemoglobin, low (g/dL)		
Level 2 (>1.5 g/dL dec. from baseline)	3/40 (7.5)	4/40 (10.0)
Level 3 (>2 g/dL dec. from baseline)	0/40 (0)	1/40 (2.5)
Hemoglobin, high (g/dL)		
Level 2 (>2 g/dL inc. from baseline)	38/40 (95.0)	40/40 (100)
Level 3 (>3 g/dL inc. from baseline)	36/40 (90.0)	38/40 (95.0)
Platelets, low (cells/uL)		
Level 1 (<140000)	27/40 (67.5)	28/40 (70.0)
Level 2 (<125000)	19/40 (47.5)	22/40 (55.0)
Level 3 (<100000)	9/40 (22.5)	13/40 (32.5)
WBC differential		
Lymphocytes, low (cells/uL)		
Level 1 (<1000)	17/40 (42.5)	19/40 (47.5)
Level 2 (<750)	8/40 (20.0)	10/40 (25.0)
Level 3 (<500)	1/40 (2.5)	2/40 (5.0)
Lymphocytes, high (cells/uL)		
Level 1 (>4000)	0/40 (0)	0/40 (0)
Level 2 (>10000)	0/40 (0)	0/40 (0)
Level 3 (>20000)	0/40 (0)	0/40 (0)

Laboratory Parameter	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
Neutrophils, low (cells/uL)		
Level 1 (<2000)	27/40 (67.5)	29/40 (72.5)
Level 2 (<1000)	4/40 (10.0)	4/40 (10.0)
Level 3 (<500)	1/40 (2.5)	1/40 (2.5)
Eosinophils, high (cells/uL)		
Level 1 (>650)	0/40 (0)	0/40 (0)
Level 2 (>1500)	0/40 (0)	0/40 (0)
Level 3 (>5000)	0/40 (0)	0/40 (0)
Coagulation studies		
PT, high (sec)		
Level 1 (>1.1X ULN)	4/40 (10.0)	5/40 (12.5)
Level 2 (>1.3X ULN)	3/40 (7.5)	3/40 (7.5)
Level 3 (>1.5X ULN)	1/40 (2.5)	1/40 (2.5)
PTT, high (sec)		
Level 1 (>1X ULN)	7/40 (17.5)	9/40 (22.5)
Level 2 (>1.21X ULN)	2/40 (5.0)	2/40 (5.0)
Level 3 (>1.41X ULN)	0/40 (0)	1/40 (2.5)

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Abbreviations: dec., decrease; Ext., extension; inc., increase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; sec, second; ULN, upper limit of normal; WBC, White blood cells

Clinical Reviewer Comment:

One subject had a neutrophil count of <500 cells/uL while on the study; however, the subject had a history of neutropenia, which required intermittent treatment with prophylactic granulocyte colony-stimulating factor and, therefore, was unlikely related to iptacopan.

7.6.2.7. Assessment of Drug-Induced Liver Injury, Trial APPOINT-PNH

Table 50 shows elevated liver enzymes. No cases of drug-induced liver injury (DILI) occurred in APPOINT-PNH. One subject met criteria for potential Hy's law, ultimately this was not considered related to iptacopan and is discussed in the clinical reviewer comment below.

Table 50. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial APPOINT-PNH

Laboratory Parameter	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
Alkaline phosphatase, high (U/L)		
Level 1 (>1.5X ULN)	3/40 (7.5)	4/40 (10.0)
Level 2 (>2X ULN)	1/40 (2.5)	1/40 (2.5)
Level 3 (>3X ULN)	1/40 (2.5)	1/40 (2.5)

Laboratory Parameter	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
Alanine aminotransferase, high (U/L)		
Level 1 (>3X ULN)	1/40 (2.5)	1/40 (2.5)
Level 2 (>5X ULN)	1/40 (2.5)	1/40 (2.5)
Level 3 (>10X ULN)	0/40 (0)	0/40 (0)
Aspartate aminotransferase, high (U/L)		
Level 1 (>3X ULN)	1/40 (2.5)	2/40 (5.0)
Level 2 (>5X ULN)	0/40 (0)	1/40 (2.5)
Level 3 (>10X ULN)	0/40 (0)	0/40 (0)
Bilirubin, total, high (mg/dL)		
Level 1 (>1.5X ULN)	0/40 (0)	4/40 (10.0)
Level 2 (>2X ULN)	0/40 (0)	1/40 (2.5)
Level 3 (>3X ULN)	0/40 (0)	1/40 (2.5)

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Abbreviations: Ext., extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal

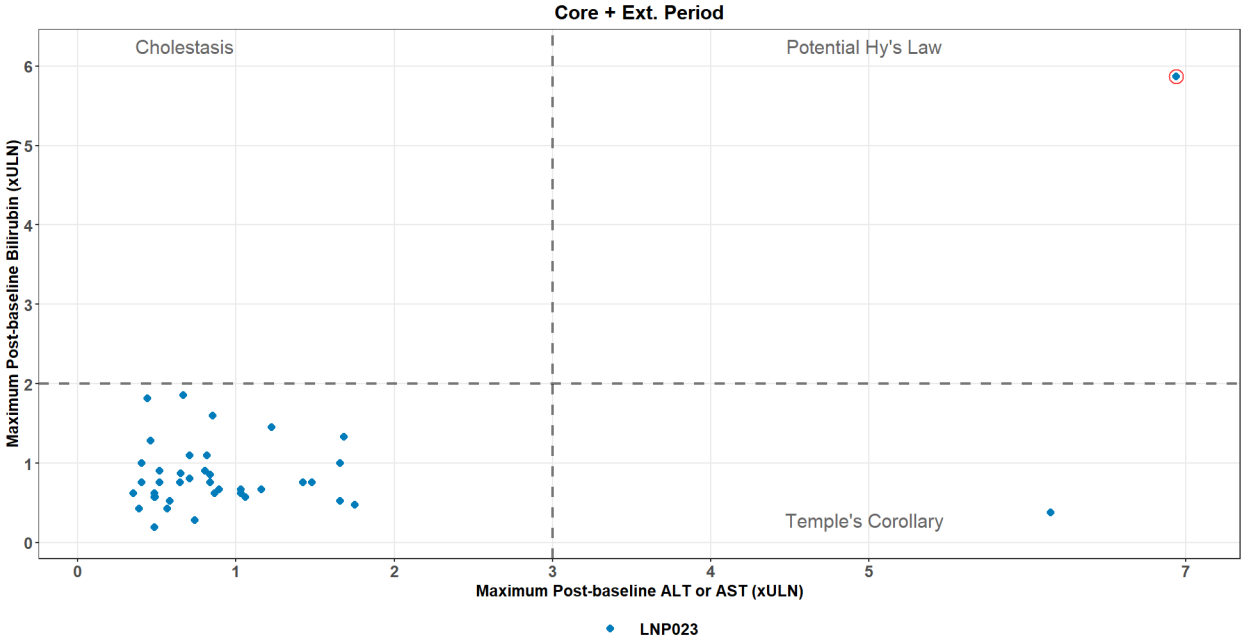
Table 51. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial APPOINT-PNH

Quadrant	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
Potential Hy's law (right upper)	0/40 (0)	1/40 (2.5)
Cholestasis (left upper)	0/40 (0)	0/40 (0)
Temple's corollary (right lower)	1/40 (2.5)	1/40 (2.5)
Total	1/40 (2.5)	2/40 (5)

Source: ad b.xpt; Software: R
Abbreviations: DILI, drug-induced liver injury; Ext., extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

Figure 2 shows a screening assessment for potential cases of serious DILI.

Figure 2. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, APPOINT-PNH



Source: ad b.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled).
All subjects with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ext., extension; LNP023, iptacopan; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal

Clinical Reviewer Comment:

In trial APPOINT-PNH, one subject receiving iptacopan met potential Hy's Law in the extension period. This subject ((b) (6) *) had concurrent adverse events of breakthrough hemolysis with LDH levels >1.5 times the ULN. The Applicant stated that this subject's liver enzyme and bilirubin increases were related to concurrent breakthrough hemolysis and not indicative of potential hepatocellular DILI. The clinical reviewer agreed with the Applicant's assessment. On Day 141, the ALT levels increased by >6 times the ULN (252 U/L) and the AST levels increased by >3 times the ULN (133 U/L). This subject also had increased AST levels at baseline (57 U/L, 1.5 times the ULN). Both ALT and AST levels returned to normal values on Day 154 with continuation of iptacopan and remained normal until the data cutoff date.*

7.6.2.8. Vital Signs' Analyses, Trial APPOINT-PNH

Elevated blood pressure occurred in APPOINT-PNH. Hypertension will be described as an adverse reaction in the label as this was a common AR. No other clinically relevant vital sign abnormalities occurred in APPOINT-PNH.

Table 52. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Trial APPOINT-PNH

Systolic Blood Pressure (mm Hg)	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
<90	0/40 (0)	0/40 (0)
≥90	40/40 (100)	40/40 (100)
≥120	38/40 (95.0)	39/40 (97.5)
≥140	13/40 (32.5)	14/40 (35.0)
≥160	3/40 (7.5)	3/40 (7.5)
≥180	0/40 (0)	1/40 (2.5)

Source: advs.xpt; Software: R
Abbreviations: Ext., extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

Clinical Reviewer Comment:

Less than half of subjects had elevated SBP at baseline. Overall, there did not appear to be an increase in SBP from baseline to Day 168, based on mean data, as shown in the table below, however, conclusions are limited due to the uncontrolled data.

Table 53. Change in Systolic Blood Pressure, Safety Population, Trial APPOINT-PNH

Visit	Iptacopan N=40
Mean (SD) Baseline Systolic Blood Pressure (mmHg)	127 (13)
Mean (SD) Day 168 Systolic Blood Pressure (mmHg)	121 (13)
Change	-5.4 (15.7)

Source: Applicant's Clinical Study Report, Table 14.3-3.1a
Abbreviations: N, number of subjects; SD, standard deviation

Table 54. Percentage of Subjects With Maximum Diastolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Trial APPOINT-PNH

Diastolic Blood Pressure (mm Hg)	Iptacopan Core Period N=40 n/N_w (%)	Iptacopan Core + Ext. Period N=40 n/N_w (%)
<60	0/40 (0)	0/40 (0)
≥60	40/40 (100)	40/40 (100)
≥90	13/40 (32.5)	14/40 (35.0)
≥110	1/40 (2.5)	2/40 (5.0)
≥120	0/40 (0)	0/40 (0)

Source: advs.xpt; Software: R
Abbreviations: Ext., extension; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

7.6.2.9. Subgroup Analyses, Trial APPOINT-PNH

An overview of TEAEs by demographic subgroup is described in Table 55. Results should be interpreted with caution given the small sample size and lack of a control arm.

Table 55. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial APPOINT-PNH

Characteristic	Iptacopan Core Period N=40 n/N_s (%)	Iptacopan Core + Ext. Period N=40 n/N_s (%)
Sex		
Female	15/17 (88.2)	15/17 (88.2)
Male	22/23 (95.7)	22/23 (95.7)
Age group, years		
<45 years	22/24 (91.7)	22/24 (91.7)
≥45 years	15/16 (93.8)	15/16 (93.8)
Age group ≥65, years		
≥65	3/3 (100)	3/3 (100)
Age group ≥75, years		
≥75	1/1 (100)	1/1 (100)
Race		
White	11/12 (91.7)	11/12 (91.7)
Asian	25/27 (92.6)	25/27 (92.6)
Black or African American	1/1 (100)	1/1 (100)
Ethnicity		
Hispanic or Latino	1/2 (50.0)	1/2 (50.0)
Not Hispanic or Latino	33/35 (94.3)	33/35 (94.3)
Not reported	2/2 (100)	2/2 (100)
Unknown	1/1 (100)	1/1 (100)
Is in United States		
Non-United States	37/40 (92.5)	37/40 (92.5)

Source: adae.xpt; Software: R
Abbreviations: Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; PNH, paroxysmal nocturnal hemoglobinuria

7.6.3. Adverse Events of Special Interest

7.6.3.1. Breakthrough Hemolysis

Breakthrough hemolysis (BH) is a hallmark of PNH but can also be triggered after discontinuation of a drug to treat the disease. An infection can also be a trigger for hemolysis in patients with PNH. Clinical BH was defined as a decrease in Hb >2 g/dL within 15 days or at the latest assessment, gross hemoglobinuria, pain, dysphagia, or other PNH symptoms, and LDH >1.5x ULN compared to the last two assessments. Of note, intravascular hemolysis releases free hemoglobin into the circulation and the resulting depletion of nitric oxide may cause symptoms of smooth muscle dystonia (i.e., dysphagia, abdominal pain, or erectile dysfunction) (Cançado et al. 2021). Subclinical BH was defined as a decrease in Hb <2 g/dL, moderate hemoglobinuria with no other clinical symptoms, and LDH >1.5x ULN. The rate of BH was lower in the iptacopan arm than in the anti-C5 drug arm, 9/170 (5.3%) subjects in the iptacopan pool and 8/35 (22.9%) subjects on anti-C5 had a TEAE of BH. Five of these nine subjects with BH in the iptacopan pool had an infection. For one subject, the hemoglobin (Hb) decreased to 4 g/dL, but on average for subjects in the iptacopan arm, Hb did not decline below 9 g/dL. The highest value of LDH was 4,444 U/L, but on average, the increase was to 800 U/L from a normal level of 140 to 280 U/L.

Three subjects in APPLY-PNH who discontinued iptacopan had decreases in hemoglobin (≥2 g/dL), but only one had an increase in LDH to >1.5x ULN. Subject (b) (6) discontinued the study treatment due to pregnancy and was switched to eculizumab. Her hemoglobin decreased from 10.4 to 7.5 g/dL, but the LDH remained in the normal range increasing from 169 to 215 U/L. Subject (b) (6) was also discontinued from treatment due to pregnancy and switched to eculizumab. Her hemoglobin decreased from 13.2 to 10.1 g/dL (for which she required a RBC transfusion), however, LDH increased from 174 to 350 U/L (<1.5x ULN). The subject's course was complicated by a spontaneous abortion. The third subject ((b) (6)) discontinued iptacopan treatment due to the physician's decision. This subject was switched to eculizumab. The subject experienced a 2.8 g/dL decrease in hemoglobin to 7.7 g/dL and an LDH increase from 559 U/L to 608 U/L; the subject did not receive RBC transfusion.

There were six subjects in trials APPLY-PNH and APPOINT-PNH who missed at least one dose of iptacopan, but no AEs or laboratory abnormalities associated with hemolysis were reported. The median number of missed doses in APPLY-PNH was 2.5 days (range: 1-6 days) and the median number of missed doses in APPOINT-PNH was 4 days (range: 1-14 days).

In the safety update, one event of hemolysis was reported in a subject [(b) (6)] one week after discontinuation of iptacopan. This subject, who was diagnosed with myelodysplastic syndrome, completed the parent study (APPLY-PNH) on iptacopan 200 mg BID. The subject was switched back to anti-C5 therapy and had iptacopan dose reduction. The subject experienced a 0.8 g/dL hemoglobin decrease at the end of the iptacopan dose reduction to 11.3 g/dL, and a 3.8 g/dL decrease one week after permanent discontinuation of iptacopan to 8.3 g/dL and required an RBC transfusion. LDH remained below 1.5 times the ULN. This subject's disease course was complicated by MDS.

The discontinuation of iptacopan treatment leaving PNH RBCs unprotected against complement activation increases the risk of hemolysis, which may be severe. As with other complement inhibitors approved for PNH, iptacopan will have a warning in the label to monitor for PNH manifestations after iptacopan discontinuation; this includes signs and symptoms of hemolysis.

7.6.3.2. Thyroid Changes

Due to thyroid hormonal changes seen in nonclinical studies, the Applicant had concerns about possible thyroid effects in the patient population exposed to iptacopan. There were transient changes in thyroid weight and hormone levels observed in the rat and dog toxicity studies (See Section 7.1 for further details).

In APPLY-PNH, thyroid laboratory changes in the iptacopan arm compared to the C5 inhibitor arm are shown in Table 56 below. Overall, a higher proportion of subjects in the iptacopan arm had abnormal thyroid laboratory values. Only one subject initiated treatment for hypothyroidism (described below); however, this subject had a previous diagnosis of hypothyroidism.

An information request was sent to the Applicant regarding abnormal levels of thyroid stimulating hormone level in APPLY-PNH as well as the entire development program. The Applicant reported that in all clinical studies, one female subject with a history of obesity, vitamin D deficiency, and hypothyroidism was diagnosed based on a single high thyroid stimulating hormone level (3.45 µIU/mL; reference range: 0.30 to 3.00 µIU/mL) and was treated with levothyroxine prior to starting treatment with iptacopan. The subject's dose of

levothyroxine was increased due to the increase in TSH level, but she had no worsening of hypothyroid symptoms. The above subject was one of three subjects with a consistently elevated TSH level in Study APPLY-PNH. In addition, there were three subjects with a decreased thyroid stimulating hormone level, compared to baseline. However, per the Applicant no subject had signs or symptoms related to a thyroid disorder and changes in TSH were not accompanied by consistent and persistent changes in thyroid hormones T3 and T4. Two of the three subjects had previous thyroid diagnoses. The first subject's (Subject (b) (6)) baseline labs showed a slightly decreased TSH to 0.49 mIU/L, which was then elevated while on study to 55.6 mIU/L, which decreased to 6.5 mIU/L at the end of study. The second subject (Subject (b) (6)) started the study with a normal TSH level while on levothyroxine for previously diagnosed subclinical hypothyroidism. The subject's TSH increased to 10.7 mIU/L but returned to normal after an increase in levothyroxine dose. No changes were made to iptacopan dosing for these subjects due to their thyroid hormone levels. It is not possible to determine based on the available cases whether iptacopan may cause changes to thyroid levels. For example, Subject (b) (6) may have had silent thyroiditis unrelated to iptacopan, and Subject (b) (6) may have had underlying progression of their hypothyroidism unrelated to iptacopan.

Table 56. Subjects With One or More Blood Hormone Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial APPLY-PNH, Randomized Treatment Period

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Thyrotropin, low (mU/L)			
Level 1 (<0.5)	7/62 (11.3)	2/35 (5.7)	5.6 (-5.4, 16.6)
Thyrotropin, high (mU/L)			
Level 1 (≥5)	8/62 (12.9)	0/35 (0)	12.9 (4.6, 21.2)*
Level 2 (>7)	5/62 (8.1)	0/35 (0)	8.1 (1.3, 14.8)*
Triiodothyronine, low (nmol/L)			
Level 1 (<0.9)	0/62 (0)	2/35 (5.7)	-5.7 (-13.4, 2.0)
Triiodothyronine, high (nmol/L)			
Level 1 (≥2.8)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)
Level 2 (>3.5)	1/62 (1.6)	0/35 (0)	1.6 (-1.5, 4.7)

Source: ad b.xpt; Software: R
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

7.6.3.3. Testicular Effects

The Applicant explored testicular effects of iptacopan in subjects due to findings in nonclinical studies in rats and dogs at doses above the equivalent proposed dose in humans (see Section 7.1 for further details).

There are only limited data in the clinical development program to assess for testicular effects. The Applicant measured follicle stimulating hormone and dihydrotestosterone in both arms of trial APPLY-PNH but did not measure morning serum testosterone levels. The majority of men with abnormal values for the two measured hormones began the study with low or high values, or did not sustain the abnormal value with subsequent laboratory values.

In clinical studies, one subject had two AEs of abnormal reproductive hormone levels. This subject (Subject (b) (6)) in the APPOINT-PNH study had a mild increase of follicle stimulating hormone (FSH) to 19.7 U/L (baseline: 16.1 U/L, reference range:1.4-18.1 U/L) and a mild dihydrotestosterone decrease to 0.238 nmol/L (baseline: 0.376 nmol/L, reference range: 0.239-0.917 nmol/L). Iptacopan was continued with resolution of the increase in FSH but continued decrease of dihydrotestosterone.

The clinical pharmacology team agreed with the Applicant's conclusion based on their mixed model for repeated measures (MMRM) analysis that the safety outcome for testicular effects was not statistically associated with the iptacopan exposure.

Table 57. Male Subjects With One or More Blood Hormone Values With Elevated or Low Values Meeting Specified Levels, Male Safety Population, Trial C12302 Randomized Treatment Period

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Follicle stimulating hormone, low (U/L)			
Level 1 (<1.5)	1/19 (5.3)	0/11 (0)	5.3 (-4.8, 15.3)
Follicle stimulating hormone, high (U/L)			
Level 1 (≥12.4)	6/19 (31.6)	4/11 (36.4)	-4.8 (-40.1, 30.5)
Level 2 (>15)	4/19 (21.1)	2/11 (18.2)	2.9 (-26.4, 32.1)
Dihydrotestosterone, low (nmol/L)			
Level 1 (<0.47)	0/19 (0)	4/11 (36.4)	-36.4 (-64.8, -7.9) *
Dihydrotestosterone, high (nmol/L)			
Level 1 (≥2.65)	4/19 (21.1)	0/11 (0)	21.1 (2.7, 39.4) *
Level 2 (>3)	2/19 (10.5)	0/11 (0)	10.5 (-3.3, 24.3)

Source: ad b.xpt; Software: R
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

7.7. Key Safety Review Issues

7.7.1. Serious Infections

Issue

Iptacopan inhibits the alterative complement pathway, therefore, there is a risk of serious infections in patients exposed to iptacopan, particularly infections with encapsulated bacterial organisms.

Background

Iptacopan binds to factor B and regulates the cleavage of C3 and the generation of downstream effectors of complement activation. The complement system is a key component of the innate immune system. The complement alternative pathway (CAP) includes complement factors D, B, H and I, complement component 3, and properdin. The AP is antibody independent and provides "natural defense" against organisms (Müller-Eberhard 1988). "Complement activation results in

fast neutralization of bacteria by immune cells. Only a few minutes are required between initial detection of invading bacteria and subsequent permeabilization of their membrane by complement components, making complement one of the most rapid ways to kill invading bacteria" (Heesterbeek et al. 2018). All three paths of the complement pathway, classical, alternative and lectin, end by activating C3. The activation of C3 is necessary for the destruction of encapsulated bacteria (i.e., *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae*). Patients with a deficiency of C3 have recurrent infections with encapsulated bacteria.

Given the risk of encapsulated organism infections, all subjects were vaccinated against the encapsulated organisms *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* in clinical trials.

It is also notable that all other complement inhibitors approved for PNH have an ETASU REMS given the risk of serious encapsulated organism infections and meningococcal infections.

Assessment

In the main trial, APPLY-PNH, there was an infection of bronchitis, caused by *Haemophilus influenzae,* an encapsulated bacterial organism, in a subject (Subject ID: (b) (6)) in the iptacopan arm. The subject was previously vaccinated against this bacteria but no antibody titers were collected. The subject was treated with amoxicillin-clavulanate and levofloxacin, and recovered. No changes were made to the study drug. In APPLY-PNH, serious infections occurred at a higher rate in the anti-C5 arm than in the iptacopan arm, although the number of subjects with these events in both arms is low given the size of the trial. See Table 58 below for a complete list of serious infections reported in APPLY-PNH.

Table 58. Subjects With Serious Treatment-Emergent Adverse Event Infections, Safety Population, Trial APPLY-PNH, Randomized Treatment Period

System Organ Class Preferred Term	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Infections and infestations (SOC)	2 (3.2)	3 (8.6)	-5.3 (-15.6, 4.9)
Pyelonephritis	1 (1.6)	0	1.6 (-1.5, 4.7)
Urinary tract infection	1 (1.6)	0	1.6 (-1.5, 4.7)
Arthritis bacterial	0	1 (2.9)	-2.9 (-8.4, 2.7)
Intervertebral discitis	0	1 (2.9)	-2.9 (-8.4, 2.7)
Pseudomonas infection	0	1 (2.9)	-2.9 (-8.4, 2.7)
Sepsis	0	1 (2.9)	-2.9 (-8.4, 2.7)
Staphylococcal infection	0	1 (2.9)	-2.9 (-8.4, 2.7)
COVID-19	1 (1.6)	2 (5.7)	-4.1 (-12.4, 4.2)

System Organ Class Preferred Term	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Investigations (SOC)	1 (1.6)	1 (2.9)	-1.2 (-7.6, 5.1)
Influenza A virus test positive	0	1 (2.9)	-2.9 (-8.4, 2.7)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier. The on-treatment period for Anti-C5 is from the fist dose date until one day before the next planned dose or the analysis cut-off date, whichever is earlier.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Arthritis bacterial replaces: Arthritis bacterial
Intervertebral discitis replaces: Intervertebral discitis
Pseudomonas infection replaces: Arthritis bacterial
Staphylococcal infection replaces: Intervertebral discitis
Abbreviations: CI, confidence interval; COVID-19. Coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; SAE, serious adverse event; SOC, system organ class

In pooled PNH studies, 11 (6.5%) subjects had a serious TEAE of infection while receiving iptacopan. The most common serious infection was COVID-19. See Table 59 below for infections which occurred in at least 2% of subjects in pooled PNH studies. In the pooled PNH studies, there were seven cases of infections caused by or potentially caused by encapsulated organisms: bronchitis hemophilus, bacterial pneumonia (2), erysipelas, furuncle, otitis media, and staphylococcal skin infection. All of the organisms for the aforementioned seven infections were not identified. The Applicant states that the infections were identified as those that could potentially be caused by an encapsulated organism.

In the renal studies, serious infections occurred in 2 (3.8%) subjects. This included pneumonia pneumococcal, pyelonephritis, and septic shock. A pneumococcal pneumonia case with sepsis was reported in a subject with C3 glomerulopathy, but this subject was receiving concomitant immunosuppressants for prophylaxis for rejection of a kidney transplant.

Table 59. Subjects With Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Occurring in at Least 2% of Subjects in Any Arm, Safety Population, ISS Pooled PNH Trials

System Organ Class FMQ (Narrow) Preferred Term	Pooled Monotherapy Studies Iptacopan N=154 n (%)	Pooled Add-on Study Iptacopan N=15 n (%)	All Pooled Studies Iptacopan N=170 n (%)
Infections and infestations (SOC)	9 (5.8)	0	11 (6.5)
Bacterial Infection (FMQ)	3 (1.9)	0	5 (2.9)*
Pneumonia bacterial	1 (0.6)	0	2 (1.2)
Urinary tract infection	1 (0.6)	0	2 (1.2)
Cellulitis	1 (0.6)	0	1 (0.6)
Pyelonephritis	1 (0.6)	0	1 (0.6)
Viral Infection (FMQ)	4 (2.6)	0	4 (2.4)
COVID-19	4 (2.6)	0	4 (2.4)

System Organ Class FMQ (Narrow) Preferred Term	Pooled Monotherapy Studies Iptacopan N=154 n (%)	Pooled Add-on Study Iptacopan N=15 n (%)	All Pooled Studies Iptacopan N=170 n (%)
Pneumonia (FMQ)	2 (1.3)	0	3 (1.8)
Pneumonia bacterial	1 (0.6)	0	2 (1.2)
Pneumonia	1 (0.6)	0	1 (0.6)

Source: adae.xpt; Software R
Treatment-emergent adverse events defined as events that started during the on-treatment period, which is defined as the first dose of iptacopan 200 mg BID up to the earlier date between data cutoff date and the last dose + 7 days.
Pooled Monotherapy Studies includes all treatment-emergent adverse events from C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, and CLNP023C12001B PNH REP.
Pooled Add-on Study includes only treatment-emergent adverse events with a start date while the subject received add-on therapy in CLNP023X2201.
All Pooled Studies includes all treatment-emergent adverse events from C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, CLNP023C12001B PNH REP, and CLNP023X2201.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 48 weeks for C12302 (APPLY-PNH) and C12301 (APPOINT-PNH). Duration is 13 weeks plus up to 3 years for CLNP023X2201. Duration is 12 weeks plus up to 2 years for CLNP023X2204. Duration is up to 21 weeks for CLFG316X2201. Duration is up to 36 months for CLNP023C12001B PNH REP.
Bronchitis bacterial replaces: Bronchitis bacterial
Klebsiella infection replaces: Bronchitis bacterial
* PTs shown only if at least one study arm meets the 2% cutoff.
Abbreviations: BID, twice daily; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; FMQ, FDA medical query; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; PT, preferred term; REP, roll-over extension program; SOC, system organ class

In the safety update, additional events of encapsulated organisms were captured. This included pneumonia bacterial (causative organisms reported as *Streptococcus vestibularis* and *Streptococcus salivarius*) in the pooled PNH studies. In addition, one subject died due to an event of encapsulated organism sepsis (*Streptococcus gallolyticus*), see Section 7.6.1.2 for the subject narrative.

Conclusion

Iptacopan is expected to increase the risk of serious infections based on its mechanism of action. In addition, serious infections caused by encapsulated organisms occurred in the clinical trials, although no meningococcal infections were reported. Serious infections from encapsulated organisms will be described in a boxed warning in the United States prescribing information. In addition, we are requiring an ETASU REMS to mitigate the risk of encapsulated bacterial infections, consistent with the approach used with other complement inhibitors. The REMS for iptacopan requires patients to be vaccinated against infections caused by encapsulated bacteria (*Neisseria meningitidis* serogroups A, C, W, Y, and B; and *Streptococcus pneumoniae*); and *Haemophilus influenzae* type B) prior to starting therapy according to current Advisory Committee on Immunization Practices (ACIP) recommendations and receive antibacterial drug prophylaxis if needed. For a detailed description of the ETASU REMS please see review in DARRTS by Lindsey Crist, PharmD, finalized November 21, 2023. This ETASU REMS differs from the C5 inhibitors REMS which requires vaccination to Neisseria meningitidis only. This difference in the REMS is because iptacopan inhibits Factor B, a key component of the alternative pathway of the complement system and the amplification loop of the lectin and classical pathways. This point of inhibition is higher in the complement cascade compared to C5 inhibitors, and therefore patients are more vulnerable to other encapsulated organism infections.

This is supported by experience in patients with inherited Factor B deficiency, in which patients developed encapsulated organism infections such as streptococcus pneumoniae and Neisseria meningitidis.

In addition, long-term risk of serious infections is also a concern. Therefore, a PMR will be issued at the time of approval for the Applicant to establish or participate in a registry for up to 5 years of follow-up and to submit reports summarizing serious infections with encapsulated organisms. See Section 24 for the PMR language.

7.7.2. Lipid Abnormalities

Issue

Lipid abnormalities occurred in iptacopan clinical trials.

Background

In APPLY-PNH, a higher proportion of subjects in the iptacopan arm (6.5%) had TEAEs of lipid disorders than in the anti-C5 arm (0%). Therefore, the Agency conducted further analysis into the risk of lipid disorders. Of note, the other approved complement inhibitors for PNH do not have a risk for lipid abnormalities.

Assessment

APPLY-PNH

The change in lipid laboratory values from baseline in APPLY-PNH RTP are shown in the table below. For total cholesterol, LDL-cholesterol, and triglycerides there was a mean increase from baseline in the iptacopan arm compared to no change from baseline in the C5 inhibitor arm.

Table 60. Mean Change in Baseline Lipid Values, APPLY-PNH, Randomized Treatment Period

	Iptacopan N=62 Mean (SD)			Anti-C5 N=35 Mean (SD)		
Laboratory Value	Baseline	Day 168	Change From Baseline	Baseline	Day 168	Change From Baseline
Total Cholesterol (mg/dL)	159 (31.4)	195 (39.5)	37 (28.8)	137 (35.6)	139 (32.8)	2 (14.9)
LDL (mg/dL)	81 (24.2)	113 (36.8)	32 (27.4)	67.44 (29.6)	67.63 (29.1)	0.2 (12.3)
Triglycerides (mg/dL)	105 (43.1)	123 (64.7)	18 (47.7)	101 (38.8)	100 (37.7)	-0.5 (24.8)

Source: FDA clinical reviewer
Abbreviations: dL, deciliter; FDA, Food and Drug Administration; LDL, low-density lipoprotein; N, number of subjects; PNH, Paroxysmal Nocturnal Hemoglobinuria; SD, standard deviation

Of the 54 iptacopan-treated subjects who had a normal cholesterol level at baseline in APPLY-PNH, 43% developed Grade 1 hypercholesterolemia during the randomized treatment period. One iptacopan-treated subject experienced increased cholesterol that worsened to Grade 2 from baseline. Of the 52 subjects with normal triglyceride level at baseline in APPLY-PNH, 23%

developed grade 1 elevated triglycerides during the randomized treatment period. Three iptacopan-treated subjects experienced increased triglycerides that increased to grade 2. Of the 41 iptacopan-treated subjects who had a normal LDL level at baseline, 33% developed elevated LDL levels. The shift table for LDL laboratory values are shown in the table below (CTCAE v4.03 does not included elevated LDL levels.)

Table 61. Shift Table for LDL - Trial APPLY-PNH, Randomized Treatment Period

			Post-baseline value				
Treatment		Baseline n (%)	<= 130 n (%)	>130-160 n (%)	>160-190 n (%)	> 190 n (%)	Missing n (%)
LNP023 200mg b.i.d.(N=62)	<= 130	60 (96.8)	41 (68.3)	10 (16.7)	5 (8.3)	4 (6.7)	0
	>130-160	0	0	0	0	0	0
	>160-190	1 (1.6)	0	0	0	1 (100.0)	0
	> 190	0	0	0	0	0	0
	Missing	1 (1.6)	1 (100.0)	0	0	0	0
	Total	62 (100.0)	42 (67.7)	10 (16.1)	5 (8.1)	5 (8.1)	0
Anti-C5 antibody(N=35)	<= 130	33 (94.3)	32 (97.0)	1 (3.0)	0	0	0
	>130-160	2 (5.7)	0	2 (100.0)	0	0	0
	>160-190	0	0	0	0	0	0
	> 190	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	35 (100.0)	32 (91.4)	3 (8.6)	0	0	0

Source: Applicant's Information Request Response and verified by CDS
Baseline percentage is based on N. Percentage for worst post-baseline value is based on Baseline n.
On-treatment period for LNP023 is from first dose date until 7 days after the date of last dose administered.
On-treatment period for Anti-C5 is from the first dose date until 1 day prior to next dose or First LNP023 dose, whichever earlier.
Abbreviations: b.i.d., twice a day; CDS, clinical data scientist; LDL, low density lipoprotein; LNP023, iptacopan; N, number of subjects; n, number of subjects with given characteristics; PNH, paroxysmal nocturnal hemoglobinuria

Lipid laboratory values from the APPLY-PNH RTP are presented in Table 62 below. More subjects in the iptacopan arm had elevated total cholesterol, LDL-cholesterol, and triglycerides compared to the anti-C5 arm. In addition, two subjects in the iptacopan arm with elevated lipids initiated a cholesterol lowering treatment.

Table 62. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial APPLY-PNH, Randomized Treatment Period

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	30/62 (48.4)	4/35 (11.4)	37.0 (20.7, 53.3) *
Level 2 (>210)	25/62 (40.3)	3/35 (8.6)	31.8 (16.4, 47.1) *
Level 3 (>225)	19/62 (30.6)	0/35 (0)	30.6 (19.2, 42.1) *
HDL, males, low (mg/dL)			
Level 1 (<40)	8/19 (42.1)	6/11 (54.5)	-12.4 (-49.3, 24.4)
Level 2 (<30)	1/19 (5.3)	2/11 (18.2)	-12.9 (-37.8, 12.0)
Level 3 (<20)	0/19 (0)	0/11 (0)	0 (0, 0)
HDL, females, low (mg/dL)			
Level 1 (<50)	11/43 (25.6)	12/24 (50.0)	-24.4 (-48.3, -0.5) *
Level 2 (<40)	5/43 (11.6)	5/24 (20.8)	-9.2 (-28.1, 9.7)
Level 3 (<20)	0/43 (0)	0/24 (0)	0 (0, 0)
LDL, high (mg/dL)			
Level 1 (>130)	20/61 (32.8)	3/35 (8.6)	24.2 (9.2, 39.2) *
Level 2 (>160)	10/61 (16.4)	0/35 (0)	16.4 (7.1, 25.7) *
Level 3 (>190)	5/61 (8.2)	0/35 (0)	8.2 (1.3, 15.1) *

Laboratory Parameter	Iptacopan N=62 n/N_w (%)	Anti-C5 N=35 n/N_w (%)	Iptacopan vs. Anti-C5 Risk Difference (%) (95% CI)
Triglycerides, high (mg/dL)			
Level 1 (>150)	20/61 (32.8)	7/35 (20.0)	12.8 (-4.9, 30.5)
Level 2 (>300)	3/61 (4.9)	0/35 (0)	4.9 (-0.5, 10.3)
Level 3 (>500)	0/61 (0)	0/35 (0)	0 (0, 0)

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria

APPOINT-PNH

The change in lipid laboratory values from baseline APPOINT-PNH are shown in the table below. There was an increase in total cholesterol, LDL-cholesterol, and triglycerides, although results should be interpreted with caution as this was an uncontrolled trial.

Table 63. Mean Change in Baseline Lipid Values, APPOINT-PNH, Core Treatment Period

	Iptacopan N=40 Mean (SD)		
Laboratory Value	Baseline	Day 168	Change From Baseline
Total cholesterol (mg/dL)	163 (33.8)	180 (28.1)	17 (30.96)
LDL (mg/dL)	87 (30.4)	105 (26.9)	18 (25.1)
Triglyceride (mg/dL)	97 (40.1)	113 (48.4)	15 (44.2)

Source: FDA clinical reviewer
Abbreviations: dL, deciliter; FDA, Food and Drug Administration; LDL, low-density lipoprotein; N, number of subjects; PNH, Paroxysmal Nocturnal Hemoglobinuria; SD, standard deviation

Of the 34 iptacopan-treated subjects who had a normal cholesterol level at baseline in APPOINT-PNH, 24% developed grade 1 hypercholesterolemia during the core treatment period. Of the 37 iptacopan-treated subjects who had a normal triglyceride level at baseline in APPOINT-PNH, 27% developed grade 1 elevated triglycerides in the core treatment period. Of the 31 iptacopan-treated subjects who had a normal LDL level at baseline, 16% developed elevated LDL levels. The shift table for LDL laboratory values is shown in the table below.

Table 64. Shift Table for LDL - Trial APPLY-PNH, Randomized Treatment Period

			Post-baseline value				
Treatment		Baseline n (%)	<= 130 n (%)	>130-160 n (%)	>160-190 n (%)	> 190 n (%)	Missing n (%)
LNP023 200mg b.i.d.(N=40)	<= 130	36 (90.0)	31 (86.1)	4 (11.1)	1 (2.8)	0	0
	>130-160	3 (7.5)	1 (33.3)	2 (66.7)	0	0	0
	>160-190	1 (2.5)	0	1 (100)	0	0	0
	> 190	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	40 (100)	32 (80.0)	7 (17.5)	1 (2.5)	0	0

Source: Applicant's Information Request Response and verified by CDS
Baseline percentage is based on N. Percentage for worst post-baseline value is based on Baseline n.
On-treatment period for LNP023 is from first dose date until 7 days after the date of last dose administered.
Abbreviations: b.i.d., twice a day; CDS, clinical data scientist; LNP023, iptacopan; N, number of subjects; n, number of subjects with given characteristics; PNH, paroxysmal nocturnal hemoglobinuria

Pooled Results

In the pooled PNH studies, five subjects were initiated on a statin to lower cholesterol. Two of the five subjects were initiated on other lipid-modifying agents (fish oil and omega-3). Of those five subjects, three had a history of high LDL cholesterol, obesity and hyperinsulinemia, and hypertriglyceridemia.

In the pooled renal studies, one subject with C3 glomerulopathy nephropathy started a cholesterol-lowering treatment (atorvastatin), and one subject with C3 glomerulopathy had an increase of his baseline statin dose.

In the safety update, eight additional subjects in the pooled PNH studies had an increase in total cholesterol from within the normal range at baseline to CTCAE grade 1 on treatment, and one additional subject had an increase from grade 1 to grade 2. No subjects had shift to grade 3 or 4.

Mechanism of Action

The mechanism of action by which iptacopan, a factor B inhibitor, increases lipid levels has not been fully elucidated. The literature states that complement pathways are involved in lipid metabolism. In discussion with the Agency's pharmacology/toxicology review team, the hypercholesterolemia observed clinically with iptacopan might be related to the pharmacological effect of iptacopan on components of the alternative complement pathway or there could be an undetected off-target activity on cholesterol metabolism. Ultimately, the mechanism by which iptacopan may lead to hypercholesterolemia in humans remains undetermined. See Section 7.1 for further details. The Applicant states that elevated cholesterol could be related to improvement of anemia and consequent increase in hemoglobin in subjects with PNH treated with iptacopan. The Applicant supported this statement with literature references including Ozdemir et al. (Ozdemir et al. 2007), that showed a negative correlation between anemia and total cholesterol (positive correlation with hemoglobin) as well as LDL-cholesterol, and Shalev et al. (Shalev et al. 2007) showed that serum cholesterol levels negatively correlate with the degree of erythropoietic activity. However, sufficient data were not provided by the Applicant from the iptacopan clinical development program to support this conclusion.

Conclusion

Abnormalities in total cholesterol, LDL cholesterol, and serum triglycerides occurred with exposure to iptacopan in clinical trials. Some subjects initiated cholesterol-lowering medications due to increased lipid levels. Lipid disorders will be included in the iptacopan label as a Warning and Precaution. .

7.7.3. Thrombocytopenia

Issue

A higher rate of thrombocytopenia occurred in subjects treated with iptacopan than in subjects treated with anti-C5 complement inhibitors in APPLY-PNH.

Background

During the RCP of trial APPLY-PNH, thrombocytopenia was reported as an adverse event in 4 (6.5%) subjects in the iptacopan arm compared to no subjects in the C5-inhibitor arm. Based on the laboratory data, approximately, 24% of subjects in the iptacopan arm experienced a platelet count <100,000 compared to 37% of subjects in the C5 inhibitor arm. Thrombocytopenia is not described as an adverse reaction of C5 inhibitors. Further analysis of the risk of thrombocytopenia was conducted.

Table 65. Mean Change in Baseline Platelet Values, APPLY PNH

	Iptacopan N=62 Mean (SD)			Anti-C5 N=35 Mean (SD)		
Laboratory Value	Baseline	Day 168	Change From Baseline	Baseline	Day 168	Change From Baseline
Platelets (10^9/L) Mean (SD)	162 (65.8)	142 (53)	-20 (46.1)	147 (35.6)	142 (73.7)	-5.6 (29.7)

Source: Applicant's Clinical Study Report, Table 14.3-2.1a - Summary statistics of hematology parameters by visit - randomized treatment period
Change from baseline = summary of changes from baseline for individual patients.
At each visit-window, only patients with a value at both Baseline and that visit-window are included.
On-treatment period for LNP023 is from first dose date until 7 days after the date of last dose administered. On-treatment period for Anti-C5 is from the first dose date until one day before the next planned dose.
Abbreviations: N, number of subjects; PNH, paroxysmal nocturnal hemoglobinuria; SD, standard deviation

Assessment

In APPLY-PNH RCP, in the iptacopan arm, 37 subjects had a normal platelet count (grade 0) at baseline and 15 of the 37 subjects (40.5%) shifted from a grade 0 to grade 1 thrombocytopenia. See Table 66 below for further details. In total, three subjects treated with iptacopan experienced decreased platelets that worsened from baseline (one subject with normal platelets worsened to grade 4, one subject with baseline grade 1 that worsened to grade 4; and one subject with baseline grade 3 that worsened to grade 4). One subject (Subject (b) (6) had a platelet decrease from 144 x 10^9/L (normal value) on Day 1 to 10 x 10^9/L (Grade 4) at Day 61 and back to 45 x10^9/L on Day 70. This subject was later diagnosed with myelodysplastic syndrome. The second subject (Subject (b) (6)) had Grade 3 thrombocytopenia on Day 1 (48 x10^9/L) which decreased to Grade 4 on Day 28 (16 x 10^9/L). The decrease in platelets occurred when the subject was diagnosed with COVID-19. The platelet count on Day 56 was 57 × 10^9/L, which was similar to the subject's values at baseline. The third subject (Subject (b) (6)) on Day 1 had a platelet count of 104 x 10^9/L, which decreased to 17 x10^9/L (Grade 4) on Day 28, increased to 48 x10^9/L (Grade 3) on Day 57 and 45 x10^9/L on Day 169 and back to 70 x 10^9/L (Grade 2) on Day 336. This subject had concurrent immune thrombocytopenia (ITP), treated with IVIG on Day 36 and Day 65.

Five subjects had thrombocytopenia (two subjects) or platelet count decrease (three subjects) in the extension period of trial APPLY-PNH after switching to iptacopan.

In the pooled PNH studies, there were 13 (7.6%) subjects with thrombocytopenia. All events occurred in subjects with PNH who had previously been treated with anti-C5 treatment (i.e., all were subjects in APPLY-PNH and study X2201).

The exposure-response relationship for platelet count demonstrated a decrease in platelets compared to C5 inhibitors, however, there was a flat dose response relationship for iptacopan, in which increasing doses of iptacopan did not lead to a lower platelet count (Please see Section 14.2). Thrombocytopenia is not a listed adverse reaction for C5 inhibitors, although shifts to a lower platelet count was observed in APPLY-PNH as shown in Table 66 below.

Table 66. CTCAE Category Shift Table for Platelets - Randomized Treatment Period Safety Population

Treatment	Baseline	n (%)	Post-baseline value: Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Missing n (%)
LNP023 200mg b.i.d.(N=62)	Grade 0	37 (59.7)	21 (56.8)	15 (40.5)	0	0	1 (2.7)	0
	Grade 1	20 (32.3)	0	16 (80.0)	3 (15.0)	0	1 (5.0)	0
	Grade 2	2 (3.2)	0	2 (100.0)	0	0	0	0
	Grade 3	3 (4.8)	0	0	0	2 (66.7)	1 (33.3)	0
	Grade 4	0	0	0	0	0	0	0
	Total	62 (100.0)	21 (33.9)	33 (53.2)	3 (4.8)	2 (3.2)	3 (4.8)	0
Anti-C5 antibody(N=35)	Grade 0	17 (48.6)	10 (58.8)	7 (41.2)	0	0	0	0
	Grade 1	12 (34.3)	1 (8.3)	7 (58.3)	3 (25.0)	1 (8.3)	0	0
	Grade 2	4 (11.4)	0	0	2 (50.0)	2 (50.0)	0	0
	Grade 3	2 (5.7)	0	0	0	2 (100.0)	0	0
	Grade 4	0	0	0	0	0	0	0
	Total	35 (100.0)	11 (31.4)	14 (40.0)	5 (14.3)	5 (14.3)	0	0

Source: Applicant's Clinical Study Report, Page 2105 of 3175 and verified by CDS
Baseline percentage is based on N. Percentage for worst post-baseline value is based on Baseline n.
On-treatment period for LNP023 is from first dose date until 7 days after the date of last dose administered. On-treatment period for Anti-C5 is from the first dose date until one day before the next planned dose.
CTCAE grading version 4.03 is used. Grade 0 means normal values.
Abbreviations: b.i.d., twice a day; CDS, clinical data scientist; CTCAE, common terminology criteria for adverse events; LNP023, iptacopan; N, number of subjects; n, number of subjects with given characteristics

Conclusion

An increased risk of thrombocytopenia was observed in the clinical trials. Thrombocytopenia occurred more frequently in the iptacopan arm than in the anti-C5 arm in APPLY-PNH; decreased platelets is not described as an adverse reaction in other complement inhibitors. While serious bleeding events did not occur with thrombocytopenia in the small clinical trials, an increased risk of bleeding is expected in patients who develop thrombocytopenia. Thrombocytopenia will be included as a clinically relevant adverse reaction in Section 6 of the iptacopan United States prescribing information.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Impact of Age, Sex, Body Weight and Race

The population PK model was developed with data from 234 subjects who received either 100 mg or 200 mg BID of iptacopan treatment. The population PK analysis was restricted to iptacopan doses 100 and 200 mg BID because of less than proportional PK at doses below 100 mg. The covariate effect was tested for the following factors: age (18 to 84 years of age); body weight (34.9 to 120 kg); baseline eGFR (27.4 to 143 mL/min/1.73 m^2); sex (female [n=124, 53%] and male [n=110, 47%]); ethnicity (Chinese [n=33, 14.1%], Japanese [n=12, 5.1%], non-China/Japan Asian [n=36, 15.4%], and others [n=153, 65.4%]); and disease (PNH [n=159, 68%], IgAN [n=48, 21%], C3G [n=27, 12%]). Body weight, baseline eGFR, and ethnicity as covariates on apparent clearance (CL/F) were retained in the final model, indicating increasing CL/F with increasing body weight and baseline eGFR and decreasing CL/F in Chinese and other Asian ethnicities (Chinese and Japanese excluded) compared to ethnicities in the rest of the world. Additional covariate analysis suggested Asian (n=81, 34.6%) appeared to have decreased CL/F comparing to White (n=145, 62.0%), Black or African American (n=6, 2.6%), and other races, the effect of which was within the range of estimated effects in the 3 ethnicity subcategories ("Chinese", "Japanese", "non-China/Japan Asian"). Visual inspection suggested substantial overlap for the model estimated CL/F across all races (White [n=145, 62.0%]; Asian [n=81, 34.6%]; Black or African American [n=6, 2.6%]; others [n=2, 0.8%]). The effects of the above-mentioned covariates were not considered clinically relevant because (1) the PK exposure associated with the proposed 200 mg BID was near the plateau of the PK/PD curve and the exposure-response relationship for efficacy, and (2) no exposure-response correlations were identified for safety outcomes. See Appendix 14.3 for additional details.

Renal Impairment

A dedicated renal impairment study was not conducted. Based on population PK analyses, the baseline estimated glomerular filtration rate (eGFR) is a significant covariate on iptacopan clearance. Estimated GFR was calculated by the Applicant using the Chronic Kidney Disease Epidemiology Collaboration equation (Levey et al. 2009). Mean eGFR (range) was 84.8 (27.5 to 142.8) mL/min/1.73 m^2. The PK modeling dataset consisted of subjects with mild (27%), moderate (24%), or severe renal impairment (3%). Apparent clearance increases with increasing baseline eGFR. Iptacopan AUC_{0-24} in a subject with eGFR of 34.3 mL/min/1.73 m^2 (5^{th} percentile of the pooled data) was 38% higher than that of the reference population (eGFR of 87.5 mL/min/1.73 m^2). Iptacopan AUC_{0-24} in subjects with eGFR of 59.7 mL/min/1.73 m^2 was 14% higher than that of the reference population (Source Table 7-8 population PK report). Because there are no exposure-dependent changes in safety parameters, the impact of mild and moderate renal impairment is considered to be clinically insignificant. However, there are limited data in patients with severe renal impairment (eGFR 15 to 30 mL/min/1.73 m^2) and there is uncertainty that the potential increase in iptacopan exposures in these patients may well go beyond the current clinical experience. Therefore, the clinical pharmacology team recommends avoiding use in patients with severe renal impairment (<30 mL mL/min/1.73 m^2). Iptacopan is

being evaluated for renal indications in subjects with IgAN and C3 glomerulopathy (C3G). PK data from these ongoing clinical trials may inform the dosing recommendations in patients with severe renal impairment. The need for dose adjustment in patients with severe renal impairment should be reassessed upon the completion of ongoing studies of iptacopan in subjects with IgAN and C3G.

Hepatic Impairment

Iptacopan undergoes extensive hepatic metabolism, based on the results of the human absorption, distribution, metabolism, and excretion study, CLNP023A2101. The target plasma protein factor B is produced by the liver. Iptacopan binds directly to and inhibits factor B. A dedicated hepatic impairment study, CLNP023A2105, was conducted in subjects with normal hepatic function and mild (Child-Pugh A), moderate (Child-Pugh B), and severe hepatic impairment (Child-Pugh C). Following the administration of a single dose of 200 mg iptacopan, mean total iptacopan maximum plasma concentration (C_{max}) and AUC_{inf} did not change to a clinically relevant degree in any hepatic impairment group compared to the normal reference group. However, the geometric mean ratio (GMR) of unbound C_{max} in subjects with mild, moderate, and severe hepatic impairment relative to the normal reference group was 1.38, 1.67, and 2.11, respectively. In addition, the GMR of unbound AUC_{inf} in subjects with mild, moderate, and severe hepatic impairment relative to the normal reference group was 1.48, 1.58, and 3.71, respectively. The increase in unbound exposures with mild and moderate hepatic impairment is within the observed clinical exposures and the exposure-safety relationships (for both total and unbound exposures), which suggests that there are no exposure-dependent changes in safety parameters. Therefore, dose adjustments in patients with mild and moderate hepatic impairment is not necessary. However, the increase in unbound exposure in severe hepatic impairment is beyond the current clinical experience, and there is uncertainty of the impact on safety at such high exposures at steady state. The clinical pharmacology team also found dose adjustment for severe hepatic impairment is not advisable due to (1) the poor predictability of the PK behavior at steady state attributable to the nonlinear PK and lower hepatic factor B production in subjects with severe hepatic impairment, and (2) the availability of only one strength of 200 mg. Therefore, the review team does not recommend the use of iptacopan in patients with PNH and severe hepatic impairment.

Pharmacogenomics

***CYP2C8* and *SLCO1B1* Genotype**

The Applicant investigated effects of variants in PK-related genes on iptacopan PK by combining data from the first-in-human and Japanese ethnic sensitivity studies. The Applicant reported associations of cytochrome P450 (*CYP) 2C8*3* and *SLCO1B1*1B* with reduced exposure and found that no Japanese participants were carriers of *CYP2C8*3*. The reviewer verified the Applicant's analyses. The observed lack of *CYP2C8*3* carriers in Japanese participants is consistent with allele frequencies. *CYP2C8*3* may contribute to the observed 20% lower mean AUC_{inf} after a single 400 mg dose of iptacopan in non-Japanese participants compared to that in Japanese participants. Overall, no dose adjustment is recommended because PK-pharmacogenomic (PGx) findings were exploratory with only minor PK differences noted, they were not linked to potential impact on safety or efficacy, and there were no CYP2C8 or

OATP1B1 drug-drug interactions with similar magnitude of exposure differences that have proposed dose adjustments. See Appendix 14.6 for additional details.

8.2. Extrinsic Factors

Effect as Perpetrator

In vitro studies showed that treatment with iptacopan caused no time-dependent inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. In vitro time-dependent inhibition was only demonstrated for CYP2C8. The induction potential of iptacopan by measuring CYP1A2, CYP2B6, CYP2C9, and CYP3A4 mRNA appears to be low.

The inhibition effects of iptacopan were assessed by physiologically-based pharmacokinetic (PBPK) modeling and simulation using repaglinide as a CYP2C8 substrate. The AUC_{inf} and C_{max} of repaglinide did not change to a clinically relevant degree when coadministered with iptacopan. In addition, iptacopan is not expected to inhibit CYP2C8 based on its Ki value and expected clinical concentration. Hence no dose adjustment is necessary when coadministered with CYP2C8 substrates.

In vitro studies showed that treatment with iptacopan did not inhibit BCRP, MRP2, BSEP, OAT1, and MATE2-K. Iptacopan inhibits P-gp, OATP1B1, OATP1B3, MATE1, OCT1, OCT2, and OAT3 in vitro. The Applicant conducted a clinical DDI study, CLNP023A2104, which investigated the interaction of iptacopan on digoxin (P-gp substrate) and rosuvastatin (BCRP, OATP1B1, and OATP1B3 substrate). The GMR for C_{max}, AUC_{last}, and $AUC_{0-\infty}$ following coadministration of a single oral dose of 0.25 mg digoxin and 100 mg BID of iptacopan relative to digoxin administered alone was 1.08, 1, and 1.02, respectively. The GMRs for C_{max}, AUC_{last}, and $AUC_{0-\infty}$ following coadministration of a single oral dose of 10 mg rosuvastatin and 100 mg BID of iptacopan relative to rosuvastatin administered alone was 1, 1.01, and 1.3, respectively. As the exposures of digoxin and rosuvastatin did not change significantly, drugs that are substrates of P-gp, BCRP, and OATP1B1/3 can be coadministered with iptacopan. Further, iptacopan is not expected to inhibit OCT1/2, OAT3, and MATE1 based on its Ki value and expected clinical concentration. Overall, the potential for iptacopan to inhibit drug transporters appears to be low.

Effect as Victim

Iptacopan is a CYP2C8 substrate. The Applicant conducted a clinical DDI study, CLNP023A2104, which assessed the interaction of clopidogrel (moderate CYP2C8 inhibitor (FDA 2023)) on iptacopan PK. In the presence of clopidogrel, iptacopan GMR for $C_{max,}$ AUC_{last}, $AUC_{0-\infty}$ was 1.05, 1.33, and 1.36, respectively. The increase in exposure of iptacopan observed with clopidogrel is within the observed clinical exposure, and there are no iptacopan exposure-dependent increases in safety parameters. Therefore, no dose adjustment for iptacopan is needed when used concomitantly with moderate CYP2C8 inhibitors.

However, the worst-case scenario for CYP2C8 inhibition may not have been captured by the interaction with clopidogrel, as clopidogrel is only a moderate inhibitor of CYP2C8. The interaction with a strong CYP2C8 inhibitor, e.g., gemfibrozil, was evaluated using PBPK modeling. However, the current model cannot be adequately validated to assess this interaction in-silico. Therefore, in the absence of data and the uncertainly that the potential increases in

iptacopan exposure may go well beyond the available clinical exposure, the clinical pharmacology team does not recommend the use of iptacopan in the presence of a strong CYP2C8 inhibitor (e.g., gemfibrozil).

The induction effect of rifampin (CYP2C8 inducer, OATP1B1 inhibitor) was assessed by PBPK modeling and simulation. As stated earlier, because the current PBPK model cannot be adequately validated, this interaction cannot be assessed in silico. However, to address a potential decrease in iptacopan exposure with a CYP2C8 inducer, the label will recommend monitoring for efficacy and discontinuing use of CYP2C8 inducers if loss of efficacy is evident.

Iptacopan is a substrate of P-gp, BCRP, MRP2, OATP1B1, and OATP1B3. Iptacopan is not a substrate of OAT1, OAT2, OAT3, and OCT2. The Applicant conducted a clinical DDI study, CLNP023A2104, which investigated the interaction of cyclosporine (OATP1B1, OATP1B3, BCRP, and P-gp inhibitor (FDA 2023)) on iptacopan PK. In the presence of cyclosporine, iptacopan GMR for C_{max}, AUC_{last}, $AUC_{0-\infty}$ was 1.41, 1.46, and 1.50, respectively. Because there are no iptacopan exposure-dependent changes in safety parameters, no dose adjustment is needed for patients treated with both iptacopan and a P-gp, BCRP, OATP1B1, or OATP1B3 inhibitor.

8.3. Plans for Pediatric Drug Development

Iptacopan was granted an ODD for the treatment of PNH on July 31, 2020 (ODD# DRU-2020-7519). Therefore, this application is exempt from the requirements of the Pediatric Research Equity Act.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Animal Data

The following nonclinical data are used to support the label. Additional detailed information is available in Section 13.

Table 67. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	In an embryo-fetal development study in rats, oral administration of iptacopan during organogenesis did not cause embryo-fetal toxicity when given up to the highest dose of 1,000 mg/kg/day, which corresponds to 4-times the MRHD based on AUC.
	In an embryo-fetal development study in rabbits, oral administration of iptacopan during organogenesis did not cause embryo-fetal toxicity when given up to the highest dose of 450 mg/kg/day, which corresponds to 6-times the MRHD based on AUC.
	In a pre- and postnatal development study in rats, oral administration of iptacopan during gestation, parturition, and lactation did not cause adverse effects in offspring when given up to the highest dose of 1,000 mg/kg/day, which corresponds to 4-times the MRHD based on AUC.

Labeling Section	Nonclinical Data
8.2 Lactation	There are no data on the presence of iptacopan or its metabolite in either human or animal milk, the effects on the breastfed child, or on milk production. Since many medicinal products are secreted into human milk, and because of the potential for serious adverse reactions in a breastfed child, breastfeeding should be discontinued during treatment and for 5 days after the final dose.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Iptacopan was not genotoxic or mutagenic in a battery of in vitro and in vivo assays. Carcinogenicity studies conducted with oral administration of iptacopan in RasH2 transgenic mice with doses up to 1,000 mg/kg/day for 6 months and in rats with doses up to 750 mg/kg/day for 2 years did not identify any carcinogenic potential. The highest exposure to iptacopan in rats corresponds to ~9-times the MRHD based on AUC. In a fertility study in male rats, iptacopan did not adversely impact fertility up to the highest dose tested of 750 mg/kg/day, which corresponds to 4-times the MRHD based on AUC. Reversible effects on the male reproductive system (testicular tubular degeneration and cellular debris in epididymis) were observed in repeat-dose toxicity studies with oral administration in dogs at doses ≥2-times the MRHD based on AUC, with no clear effects on sperm numbers, morphology, or motility. In a fertility and early embryonic developmental study in female rats, oral administration of iptacopan caused increased pre- and post-implantation losses when given at the highest dose of 1,000 mg/kg/day orally, which corresponds to ~11-times the MRHD based on AUC.

Source: PI Labeling and FDA Reviewer
Details of above information and dose multiples shown are based on body surface area compared between animals.
Abbreviations: AUC, area under the concentration-time curve; BSA, body surface area; FDA, Food and Drug Administration; MRHD, maximum recommended human dose; PI, prescribing information

9. Product Quality

The Office of Pharmaceutical Quality has determined that this NDA meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective. A shelf life of 24 months is granted when the drug product is stored at 20 C to 25 C. For additional information and lifecycle considerations, see the Integrated Quality Assessment #1 for NDA 218276.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The APPLY-PNH and APPOINT-PNH clinical trials were conducted under International Council on Harmonisation GCP guidelines. A signed written informed consent form was required to enroll in any of the trials. The trials were reviewed and monitored by an institutional review board, research ethics board, or an independent ethics committee depending on the country in which the trial site was located.

The results of the clinical site inspections and Applicant inspection support the conclusion that the trials were conducted adequately, and that the data generated support the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section 22 for a summary of inspection findings and Section 25 for financial disclosures.

11. Advisory Committee Summary

An advisory committee meeting was not convened to discuss this application. No issues were identified that would have benefitted from a public discussion with external experts.

III. Additional Analyses and Information

12. Summary of Regulatory History

On October 16, 2019, a type B pre-IND meeting was held under PIND 134655. The purpose of this meeting was to discuss whether the completed and planned nonclinical and clinical pharmacology studies were adequate to support the initiation of the planned phase 3 study; the design of the phase 3 study in paroxysmal nocturnal hemoglobinuria (PNH); and whether the proposed clinical development plan is adequate to support registration for the treatment of PNH.

On July 31, 2020, iptacopan was granted orphan drug designation for the treatment of PNH (ODD# DRU-2020-7519).

On August 28, 2020, an IND application was submitted under IND 134655. A study may proceed letter was issued on September 28, 2020.

On December 1, 2020, iptacopan was granted breakthrough therapy for the treatment of PNH.

On January 21, 2021, the Applicant requested a type B meeting to discuss the possibility of filing for accelerated approval of iptacopan. The Applicant withdrew this meeting request on March 19, 2020, after receiving the Agency's preliminary meeting comments on March 12, 2020, and based on the clear feedback received from the Agency.

On May 18, 2022, written responses were issued to the Applicant to provide feedback on their proposed data presentation and format for a planned NDA submission. The feedback to the Applicant stated that the proposed package was not ready for NDA submission and that the Applicant should address how they intend to establish substantial evidence of effectiveness.

On July 18, 2022, the Applicant requested another type B meeting to discuss the proposed data presentation and format for the planned NDA. The Applicant withdrew this meeting request on September 13, 2022, after receiving the Agency's preliminary meeting comments on September 8, 2022, stating that the preliminary comments were sufficient and that no further discussions were necessary.

On December 14, 2022, a type B, pre-NDA meeting was held to discuss the top-line data from the phase 3 study, CLNP023C12302 (APPLY-PNH).

One April 5, 2023, the Applicant submitted the NDA. The Applicant requested priority review with the plan to use a priority review voucher.

On June 20, 2023, the proprietary name, FABHALTA, was conditionally approved for iptacopan.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Primary Pharmacology

Iptacopan inhibits the alternative complement pathway by binding to the Bb domain of Factor B, which reduces formation of the Bb-containing C3 convertase. Reduction in C3 convertase activity is anticipated to reduce the degree of both intravascular and extravascular hemolysis in certain complement-driven disorders such as PNH (study RD-2015-00232). Results of study RD-2022-00256 provided evidence that iptacopan does not have any effects on C3 convertase (C4b2b) associated with the classical and lectin complement pathways.

Table 68.Summary of Pharmacology Studies

Study/ Study No.	Findings
Mechanism of action:	
<In Vitro Inhibition of Alternative Pathway and Complement Pathway Selectivity>	
Study RD-2015-00230	Iptacopan activity was assessed in a time-resolved fluorescence resonance energy transfer (TR-FRET) based competitive binding assay using the catalytic domain of human factor B (FB) and factor D (FD) protein. Iptacopan inhibits FB with IC_{50} of 9.6nM (4 ng/mL) and does not inhibit FD (IC_{50} >100µM).
Potency of Iptacopan Studies RD-2015-00230; RD-2015-00152; RD-2014-00605; RD-2017-00357; RD-2017-00003; RD-2014-00521; RD-2015-00228; RD-2015-00153; RD-2022-00256	To determine inhibitory action of iptacopan (IC_{50} and IC_{90}) in the alternative pathway and classical pathway, TR-FRET assay, Zymosan-induced MAC deposition assay in serum of mouse, rat, rabbit, dog, monkey, pig, and human, and CP Wieslab assay in human serum were evaluated. Zymosan-induced MAC deposition assays exhibited IC_{50} of ~100nM in serum of mouse, rabbit, pig, and human (in serum and whole blood), and ~500nM in serum of rat and dog. IC_{50s} in monkey serum were between 90 and 400nM in 2 different assays. Cross-reactivity of iptacopan with the human classical pathway (CP) C3 convertase was evaluated using the Wieslab assay with 1% serum, which showed iptacopan had no impact on activation of the CP up to 100µM (42200 ng/mL), suggesting that iptacopan does not have significant effects on classical pathway C3 convertase.

Study/ Study No.	Findings

Table 69. Summary of Iptacopan Inhibition Concentrations (IC_{50} and IC_{90}) of Alternative Pathway or Classical Pathway

Assay type	Species	Assay medium	IC_{50} nM ± SD	IC_{90} nM ± SD	n	RD report
TR-FRET	Human	Biochemical assay	10 ± 3	n.d.	6	RD-2015-00230
AP assay: Zymosan-induced MAC deposition (C3 deposition for mouse)	Mouse	6% serum	16 ± 12	n.d.	16	RD-2015-00152
	Mouse	50% serum	110 ± 10	n.d.	4	RD-2015-00152
	Mouse	50% serum	120 ± 110	350 ± 300	6	RD-2014-00605
	Rat	6% serum	190 ± 90	680 ± 330	12	RD-2017-00357
	Rat	50% serum	560 ± 230	1230 ± 1150	12	RD-2017-00357
	Rabbit	50% serum	110 ± 20	n.d.	4	RD-2017-00003
	Dog	50% serum	410 ± 270	1550 ± 1030	7	RD-2014-00521
	Cynomolgus monkey	50% serum	400 ± 80	n.d.	2	RD-2015-00152
	Cynomolgus monkey	50% serum	90 ± 20	460 ± 210	2	RD-2014-00605
	Pig	50% serum	120 ± 60	n.d.	2	RD-2014-00605
	Human	6% serum	32 ±19	n.d.	16	RD-2015-00152
	Human	50% serum	120 ± 40	450 ± 210	6	RD-2015-00228
	Human	50% serum	130 ± 61	n.d.	6	RD-2015-00152
	Human	50% whole blood	150 ± 94	n.d.	18	RD-2015-00153
CP Wieslab assay	Human	1% serum	>100'000	n.d.	3	RD-2022-00256

Source: Applicant's submission
Abbreviations: AP, alternative pathway; CP, classical pathway; IC_{50}, half-maximal inhibitory concentration; IC_{90}, 90% inhibitory concentration; MAC, membrane attack complex; n, number of subjects; n.d., not determined; SD, standard deviation; TR-FRET, time-resolved fluorescence resonance energy transfer

In vitro plasma protein binding Study RD-2015-00439

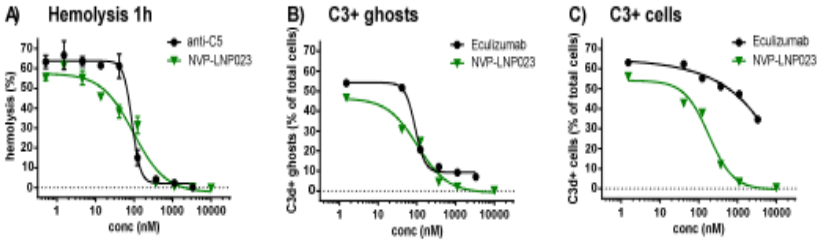
In vitro plasma protein binding of unlabeled iptacopan (~5µM) was evaluated in mouse, rat, rabbit, dog, monkey, and human plasma using rapid equilibrium dialysis.

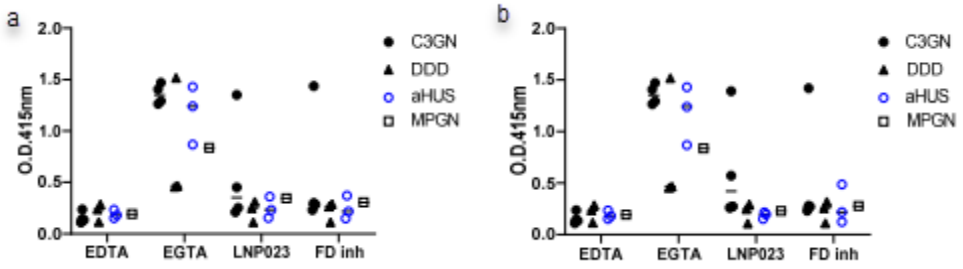
Binding of iptacopan to plasma proteins was in the order of rabbit > dog > rat > human > mouse > monkey.

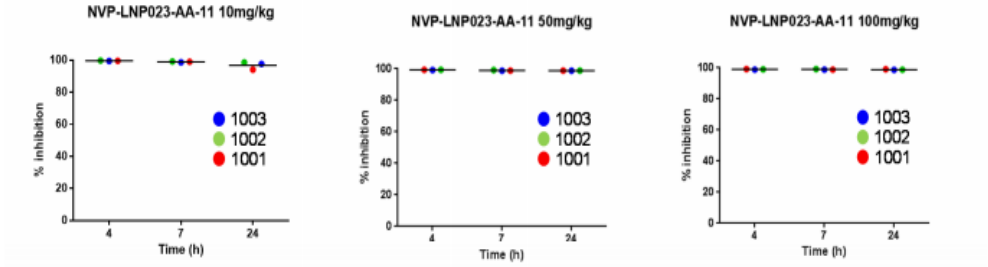
Table 70. Protein Binding (% PPB) and % Unbound Fraction (% fu) of Iptacopan in Mouse, Rat, Rabbit, Dog, Monkey, and Human Plasma

Species	% PPB (mean ± S.D., n=3)	% fu (mean ± S.D., n=3)	% Plasma Stability	% Recovery
Mouse	57.4 ± 1.8	42.6 ± 1.8	≥ 70	≥ 70
Rat	65.3 ± 1.8	34.7 ± 1.8	≥ 70	≥ 70
Rabbit	> 99	< 1	≥ 70	≥ 70
Dog	74.3 ± 0.9	25.7 ± 0.9	≥ 70	≥ 70
Monkey	54.7 ± 1.8	45.3 ± 1.8	≥ 70	≥ 70
Human	62.5 ± 0.7	37.5 ± 0.7	≥ 70	≥ 70

Source: Applicant's submission
Abbreviations: fu, free fraction of drug in plasma; n, number of subjects; PPB, plasma protein binding; S.D., standard deviation

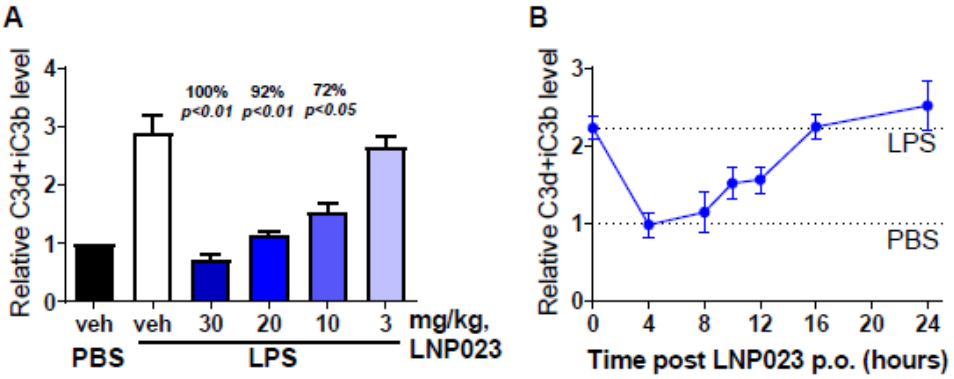
Study/ Study No.	Findings
	<Cellular Activity>
Study RD-2015-00232 Inhibition of complement factor B suppresses hemolysis and C3 deposition in a PNH surrogate assay	Efficacy of iptacopan was evaluated in a surrogate PNH assay with human erythrocytes. PNH-like erythrocytes were generated from healthy volunteers' erythrocytes by incubation with blocking antibodies against complement regulatory proteins CD55 and CD59 to make erythrocytes vulnerable to complemented-mediated lysis like erythrocytes in PNH. To block the classical and lectin pathways, $MgCl_2$ and EGTA were added to buffer. Hemolysis was quantified by absorbance in supernatants, and C3d and C5b-9 on erythrocytes were measured using flow cytometry. The IC_{50} and IC_{90} for C3d and C5b-9 deposition and hemolysis of PNH-like erythrocytes were evaluated in 50% or 95% acidified human serum. Iptacopan dose-dependently inhibited both hemolysis and C3 deposition on erythrocytes, while eculizumab inhibited hemolysis but surviving erythrocytes remained strongly coated with C3 fragments. **Table 71. Summary of Inhibition (IC_{50} and IC_{90}) of Iptacopan and Eculizumab on Hemolysis (Top: 50% Serum, Bottom: 95% Serum)** **Experiment** / **NVP-LNP023 IC_{50} (nM)** / **NVP-LNP023 IC_{90} (nM)** / **Date** / **max hemolysis** 2014-TK017 / 33 / 292 / 22.04.2014 / 5% 2014-TK019 / 115 / 310 / 07.05.2014 / 19% 2014-TK020 632 / 95 / 604 / 09.05.2014 / 8% 2014-TK021 / 86 / 255 / 14.05.2014 / 10% 2014-TK022 / 115 / 323 / 16.05.2014 / 11% 2014-TK023 / 175 / 302 / 20.05.2014 / 15% 2014-TK024 / 111 / 288 / 23.05.2014 / 5% Average / 104 / 339 Experiment / NVP-LNP023 IC_{50} (nM) / NVP-LNP023 IC_{90} (nM) / Eculizumab IC_{50} (nM) / Eculizumab IC_{90} (nM) / Date / max hemolysis 2015-JW-PNH14 / 96.7 / 792.8 / 88.7 / 154.3 / 24.04.2015 / 55% 2015-JW-PNH15 / 59.6 / 762.1 / 144.1 / 337.2 / 20.05.2015 / 50% 2015-JW-PNH16 / 221.3 / 634.3 / 178.7 / 351.7 / 01.06.2015 / 90% 2015-JW-PNH18 / 156.5 / 700.7 / 90.5 / 209.3 / 16.06.2015 / 50% 2015-JW-PNH19 / 35.3 / 820.5 / 158.4 / 268.5 / 01.07.2015 / 55% Average / 113.9 / 742.1 / 132.1 / 264.2 Source: Applicant's submission Abbreviations: IC_{50}, half-maximal inh bitory concentration; IC_{90}, 90% inh bitory concentration; NVP-LNP023, Novartis Pharmaceuticals iptacopan **Figure 3. Effects of Iptacopan and Eculizumab on Hemolysis in the PNH Erythrocytes and C3 Deposition**  Source: Applicant's submission Abbreviations: A, Hemolysis after 1 hour; B, % C3d ghosts after 1 hour; C, % C3d positive cells after 1 hour; NVP-LNP023, Novartis Pharmaceuticals iptacopan; PNH, paroxysmal nocturnal hemoglobinuria Results suggest that iptacopan suppress intravascular and extravascular hemolysis.

Study/ Study No.	Findings
Study RD-2020-00407 LNP023 inhibits AP dysregulation in serum from patients with atypical hemolytic uremic syndrome (aHUS)	Iptacopan was evaluated for inhibition of hemolysis in sheep red blood cell (SRBC) lysis assay. Inhibition of lysis of SRBCs was assessed in 20% serum from patients with different diseases [C3 glomerulopathy (C3G) n=7 {subclass C3GN n=4, dense deposit disease (DDD) n=3}, atypical hemolytic uremic syndrome (aHUS) n=3, and membranoproliferative glomerulonephritis (MPGN) n=1] at concentration of 150 and 600nM. Assay buffer contained Mg2+ and EGTA was used to selectively block the classical and lectin pathways, while leaving the AP intact. CMS4487 (Factor D inhibitor) was used as a comparator. Iptacopan and CMS487 inhibited hemolysis of SRBCs incubated with the serum of patients with C3GN, DDD, aHUS and MPGN at both concentrations. **Figure 4. Inhibition of Iptacopan on Hemolysis of SRBCs Incubated With Serum From Patients With C3G (C3GN and DDD), aHUS and MPGN (a. 150 nM inhibitors, b. 600 nM inhibitors)**  Source: Applicant's submission Abbreviations: aHUS, atypical hemolytic uremic syndrome; C3G, C3 glomerulopathy; DDD, dense deposit disease; EDTA, ethylenediaminetetraacetic acid; EGTA, ethylene glycol tetraacetic acid; factor D protein; FD inh, factor D inhibitor; LNP023, iptacopan; MPGN, membranoproliferative glomerulonephritis; SRBCs, sheep red blood cells
Study RD-2022-00012 LNP023 (iptacopan) binds to and inhibits FB mutants identified in patients with atypical hemolytic uremic syndrome (aHUS)	Binding affinity of iptacopan to wild-type FB and 8 FB mutants was evaluated by competitive inhibition of binding of an active site reporter ligand (Cy5-labelled NVP-CKJ036-DA-1) to the protease domain of human complement factor B (amino acids 470-764). C3 convertase assay was conducted measuring C3a using ELISA to evaluate the effect of iptacopan on C3 cleavage, and Zymosan assay was conducted for AP inhibition analysis. Iptacopan bound to wild-type FB and FB mutants (tested) with similar affinity and inhibited AP activation, which suggests the potential therapeutic use of iptacopan in aHUS characterized by FB point mutations.

Study/ Study No.	Findings
	<Ex Vivo Analysis of Iptacopan Inhibition of Alternative Pathway>
Study RD-2019-00023 Rat, 26-week, 0, 50, 150, 750 mg/kg/day, p.o. Study RD-2018-00505 Dog, 39-week, 0, 5, 30, or 150 mg/kg/day, p.o. Study RD-2020-00544 Dog (Juvenile) 52-week p.o., 0, 5, 30, or 150 mg/kg/day, p.o. Study RD-2015-00106 Monkey, single dose 0, 10, 50, 100 mg/kg, p.o.	Alternative pathway (AP) inhibition was evaluated using an ex vivo MAC-deposition assay in the serum of rats, dogs, and monkeys from toxicology studies. Serum samples were collected 24 hours after the last dose of iptacopan. AP activity was inhibited in dog serum in the 39-week toxicology study at doses of 5 mg/kg/day (partial inhibition) and 30 or 150 mg/kg/day (full inhibition). In a juvenile dog study of 52 weeks, AP was inhibited by 84% at 30 mg/kg/day and by 97% at 150 mg/kg/day. (Results from 26-week rat study was inconclusive) Full inhibition of AP activity was observed in the range of 94.1-98.6% in serum from iptacopan-treated-monkeys (oral doses at 10, 50 or 100 mg/kg) at 24 hours post-dose. **Figure 5. Ex Vivo Inhibition of AP Activity in Serum From Monkeys After Iptacopan Single Oral Doses**  Animal ID / 10 mg/kg po / 4hr 7hr 24hr / % inhibition relative to pretest 1001 99.6 99.0 94.1 1002 99.8 99.2 98.6 1003 99.5 98.7 97.7 Animal ID / 50 mg/kg po / 4hr 7hr 24hr / % inhibition relative to pretest 1001 99.4 98.9 98.9 1002 99.4 99.2 98.9 1003 99.2 98.8 98.8 Animal ID / 100 mg/kg po / 4hr 7hr 24hr / % inhibition relative to pretest 1001 99.2 98.9 99.1 1002 99.0 99.2 98.8 1003 98.9 98.9 98.7 Source: Applicant's submission Abbreviations: NVP-LNP023, iptacopan
	<In Vivo Pharmacology_ Mechanistic Model>
Study RD-2015-00210 Effect of orally administered complement Factor B inhibitor, NVP-LNP023, on LPS-induced complement activation in Mice 0, 3, 10, 20 or 30 mg/kg p.o.	C57BL/6 mice were injected with 50 µg lipopolysaccharide (LPS, from *Salmonella typhimurium*) intraperitoneally to induce complement activation and iptacopan was administered orally 3.5 hours post LPS treatment at 3, 10, 20, or 30 mg/kg. C3 activation fragments C3d and iC3b were quantified from blood 7.5 h post LPS injection or 4 h post iptacopan administration using Western Blots. LPS treatment for 7.5 h resulted in 2-to-3-fold increase of C3 breakdown products (C3d and iC3b) in plasma. Iptacopan effectively inhibited the generation of C3 breakdown products in a dose-and time-dependent manner. Plasma compound exposure correlated with % inhibition of C3 cleavage. [IC_{50}=560nM (240 ng/mL), IC_{90}= 1120nM (470 ng/mL)]

Study/ Study No.	Findings

Figure 6. Iptacopan Inhibition of C3 Cleavage

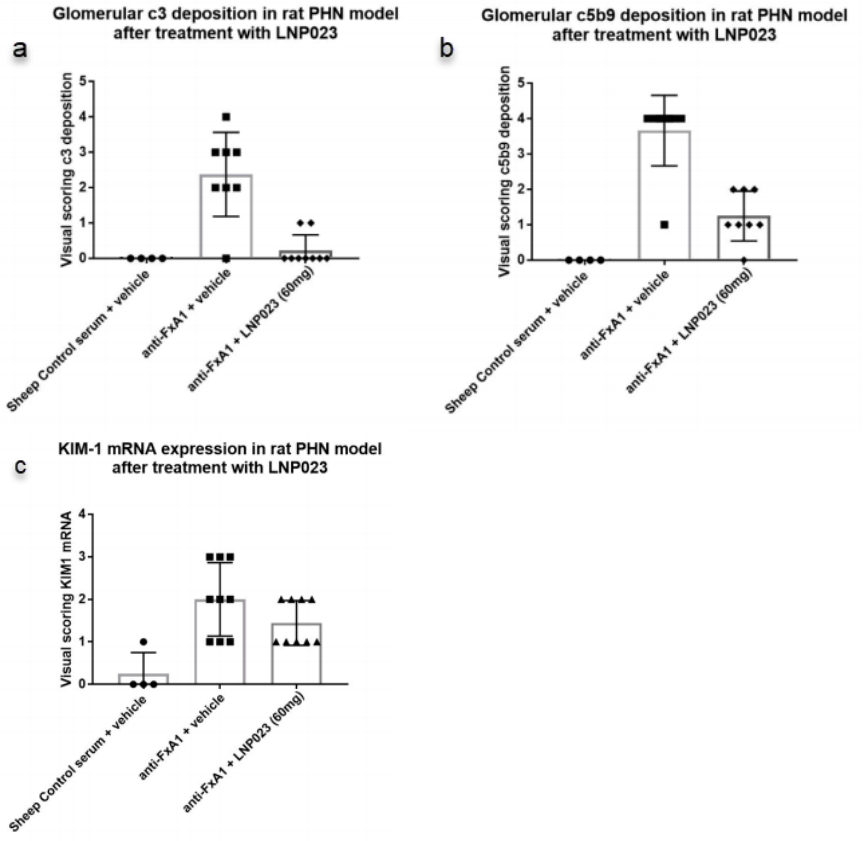


Source: Applicant's submission
Abbreviations: LNP023, iptacopan; LPS, lipopolysaccharide; PBS, phosphate-buffered saline; p.o., by mouth; Veh, vehicle

<In Vivo Pharmacology_ Disease Model>	
Study DIS-R1820106 LNP023 therapeutic efficacy study in rat Passive Heymann nephritis (PHN) model	Heymann nephritis is a model in rats for membranous nephropathy and glomerulonephritis, characterized by the development of immune complexes in the subepithelial space on the outer surface of the glomerular basement membrane (GBM) following administration of anti-Fx1A serum targeting megalin and receptor associated protein (RAP). The model was used to assess the activity of iptacopan on essential complement activation for disease development. Disease was induced with IV injection of sheep anti-rat Fx1A (tubular epithelial fraction from rat renal cortex) serum into male Sprague Dawley rats. Iptacopan was dosed orally at 60 mg/kg (BID) either prophylactically starting at day 0 or therapeutically starting at day 6, after disease onset. Iptacopan reduced 1) disease progression of nephritis (albuminuria, kidney weights, incidence and severity of membranous glomerulopathy with tubular degeneration/regeneration, complement deposition (C5, C5b9) and 2) severity of tubular injury (measured by KIM-1) in rats when compared to control anti-Fx1A injected animals.

Study/ Study No.	Findings

Figure 7. Iptacopan Inhibition of Complement Deposition (A and B) and KIM-1 mRNA



Source: Applicant's submission
Abbreviations: FxA1, tubular epithelial fraction from rat renal cortex; KIM-1, Kidney injury molecule-1; LNP023, iptacopan; mRNA, messenger RNA; PHN, Heymann nephritis model

T cell-dependent B cell responses	
B cell response to DNP-KLH mice Study RD-2018-00517 Study DIS-R1820029 Study DIS-R1820030	Dinitrophenyl (DNP) conjugated with Keyhole limpet hemocyanin (KLH) is a hapten-carrier complex that elicits T cell-dependent B cell responses when administered to mice in a colloidal aluminum hydroxide as adjuvant. Iptacopan was given orally at 30 or 100 mg/kg (BID) from the day of DNP-KLH injection. There were no effects of iptacopan on DNP-specific IgM or IgG antibody titers during primary (8 days post immunization) or secondary response (19 days post primary immunization with boost immunization on day 8). Full inhibition of AP was observed based on C3 and FB cleavage in plasma at 100 mg/kg (BID) iptacopan, but there was no significant impact on germinal center (GC) response as confirmed by Ki67 staining of the spleen. T and B cell, proportions of GC B cells, follicular T cells (TFH), CD138+ plasmablasts, follicular and marginal zone B cells were not altered. Taken together, the results show that iptacopan did not impair the generation of antibody responses to DNP-KLH

Study/ Study No.	Findings
B cell response to sheep red blood cells in rats Study RD-2018-00519 Study 1570192 39-week dog study	The primary antibody response to sheep red blood cells (SRBC) injected IV is one of the most predictive assays for human T cell-dependent antibody (TDAR) responses. The effect of iptacopan was evaluated on the primary T cell-dependent B cell response to SRBCs in rats after oral doses at 6, 20, 60 or 120 mg/kg (BID). T-Dependent Antibody Response (TDAR) assay conducted with blood from dogs in 39-week toxicology study presented minimal effects on the humoral responses with reduced IgM and/or IgG titers following primary response to KLH challenge in both genders. Iptacopan did not impact the T cell-dependent antibody responses

Source: Reviewer's analysis
Abbreviations: aHUS, atypical hemolytic uremic syndrome; AP, alternative pathway; BID, twice a day; CP, classical pathway; C3G, C3 glomerulopathy; C3a, complement component 3a; C3d, complement component 3d; C5b-9, membrane attack complex; DDD, dense deposit disease; DNP, Dinitrophenyl; EGTA, ethylene glycol tetraacetic acid; ELISA, enzyme-linked immunoassay; FB, human factor B protein; FD, human factor D protein; Fx1A, tubular epithelial fraction from rat renal cortex; GC, germinal center; h, hour; IgG, immunoglobulin G; IgM, immunoglobulin M; iC3b, inactivated complement component 3b; GBM, glomerular basement membrane; IV, intravenous; IC_{50}, half-maximal inhibitory concentration; IC_{90}, 90% inh bitory concentration; KIM-1, kidney injury molecule 1; KLH, keyhole limpet hemocyanin; LPS, lipopolysaccharides; MAC, membrane attack complex; $MgCl_2$, magnesium chloride; MPGN, membranoproliferative glomerulonephritis; NVP-LNP023, Novartis Pharmaceuticals iptacopan; PNH, Heymann nephritis model; p.o., by mouth; RAP, receptor associated protein; SRBs, sheep red blood cells; TDAR, T cell dependent antibody; TFH, follicular T cells; TR-FRET, time -resolved fluorescence resonance energy transfer

13.1.2. Secondary Pharmacology

Table 72. In Vitro Secondary Pharmacology Studies

Study No. / Study	Findings
Study DIS R1720165 Testing for inhibition of cathepsins by LNP023	Iptacopan was evaluated up to 100µM concentration in a panel of 12 human cathepsin proteases. No inhibition of iptacopan was observed on the tested proteases.
Study RD-2015-00689 NVP-LNP023: Secondary Pharmacology Profile	Iptacopan was assessed for its in vitro off-target activity on 122 targets (74 GPCRs, 8 transporters, 16 ion channels, 7 nuclear receptors and 16 enzymes) There was no significant activity towards these targets.
Study RD-2020-00450 NVP-LNP023-AA-12_(b) (4) Report_100021796_in vitro pharmacology profiling EP1 EP3 FP TP	Iptacopan was evaluated up to 100µM concentration in cellular and nuclear receptor functional assays (prostaglandin receptors EP1, EP3, FP and TP) Iptacopan did not exhibit activity on tested receptors.
Study RD-2019-00018 NVP-LNP023: Kinase Profiling Report	Thirty-one in vitro kinase assays were performed to assess the effects of iptacopan. No cytotoxicity was observed in reporter cells at doses up to 200µM iptacopan as determined by ATP measurement in cell lysate and lactate dehydrogenase activity in supernatants. Iptacopan showed inhibition in an ATP-competitive mTOR assay (IC_{50}=9.9µM).

Source: Reviewer's analysis
Abbreviations: ATP, adenosine triphosphate; GPCRs, G protein-coupled receptors; IC_{50}, half-maximal inhibitory concentration; mTOR, mammalian target of rapamycin; NVP-LNP023, Novartis Pharmaceuticals iptacopan

13.1.3. Safety Pharmacology

Table 73. Safety Pharmacology Studies: Nervous System and Respiratory Function

Study/ Study No.	Findings
Study No. 1470566: Study Title: LNP023: Single-dose oral safety pharmacology study in rats (Nervous system and Respiratory function) GLP: Yes Species/ Strain: Rat, Han Wistar Number/Sex/Group: 6 males/group LNP023: Monohydrochloride Moda Fine.002 Dose: 0, 100 (112), 1000 (770) mg/kg Vehicle Control: 0.5% (w/w) methylcellulose and 0.5% w/w Tween 80 (Polysorbate 80) Route of Administration and Dosing Frequency: Oral gavage, single dose	<u>Nervous System Assessment</u> Modified Irwin Test No iptacopan-related behavioral or body temperature changes occurred in male rats compared to control. <u>Respiratory Function Assessment</u> Iptacopan-related statistically significant decrease in Rate, and minute (MV) and tidal volume (TD) occurred at different time intervals at both doses tested compared to control; however, no statistical significance was observed at those time points when compared to baseline. Iptacopan-related decreases in Rate, MV and TV were not considered biologically significant based on the lower magnitude of change compared to baseline values and within similar ranges of variation as control.

Source: Reviewer's analysis
Abbreviation: GLP, good laboratory practice; LNP023, iptacopan; MV, minute volume; TD, tidal volume

Table 74. Safety Pharmacology Studies: Cardiovascular Function

Study No/ Study Title	Findings
In Vitro	
Study 1414526 (Patch clamp): Human Ether-ago-go-related Gene (hERG) channel current in Human Embryonic Kidney (HEK) 293 cells (surrogate for I_{Kr}, the rapidly activating delayed rectifier cardiac potassium current) GLP: No Concentration: 3 or 10µM	<u>hERG current inhibition (Mean ± SEM%)</u> 3: 2.9 ± 0.4 10: 4.1 ± 0.6 Positive Control Cisapride (90nM): 58.8 ± 3.8 IC_{50} > 10 µM; solubility limited testing at higher concentrations
Study 1414561 (Patch clamp): hERG channel current in HEK293 cells (surrogate for I_{Kr}, the rapidly activating delayed rectifier cardiac potassium current) GLP: No Concentration: 30, 100, or 300µM	<u>hERG current inhibition (Mean ± SEM%)</u> 30: 4.0 ± 1.3 100: 15.5 ± 0.7 300: 30.7 ± 1.5 Positive Control Cisapride (90nM): 62.4 ± 0.3 IC_{50} > 300 µM

Study No/ Study Title

Findings

Study 1470561 (Patch clamp): hERG channel current in HEK293 cells (surrogate for I_{Kr}, the rapidly activating delayed rectifier cardiac potassium current)

GLP: Yes

Concentration: 100, 300, 600, or 1000µM

hERG current inhibition (Mean ± SEM%)

Control	2.8 ± 0.7
100:	8.9 ± 0.5
300:	32.1 ± 1.2
600:	68.8 ± 3.0
1000:	86.3 ± 1.2

Positive Control Terfenadine (60nM): 83.0 ± 2.3

IC_{50} = 414.9 µM

Study 1415004 (Patch clamp): hKir2.1, hKvLQT1/hminK, hKv4.3 and hCav1.2 cloned channel current in mammalian cells

GLP: No

Concentration: 3 or 10µM

Table 75. Summary of Effects of Iptacopan on Four Channels

Channel	Concentration (µM)	% Inhibition	SD	SEM	n
hKir2.1	3	2.6%	0.6%	0.3%	3
	10	8.8%	3.3%	1.9%	3
hKvLQT1/hminK	3	1.1%	0.6%	0.3%	3
	10	1.1%	0.5%	0.3%	3
hKv4.3	3	3.3%	0.6%	0.4%	3
	10	4.8%	0.6%	0.3%	3
hCav1.2	3	4.7%	2.4%	1.4%	3
	10	5.0%	0.9%	0.5%	3

Source: Applicant's submission
Abbreviations: n, number of subjects; SD, standard deviation; SEM, standard error of mean

Table 76. Summary of Effects of Positive Controls

Channel	Positive Control	Concentration (µM)	% Inhibition	SD	n
hKir2.1	Barium Chloride	100	93.6%	3.3%	2
hKvLQT1/hminK	Chromanol 293B	30	71.4%	3.5%	2
hKv4.3	Flecainide	100	68.0%	15.9%	3
hCav1.2	Nifedipine	0.1	90.6%	0.2%	2

Source: Applicant's submission
Abbreviations: n, number of subjects; SD, standard deviation

IC_{50} >10µM

<table>
<tr><th>Study No/ Study Title</th><th>Findings</th></tr>
<tr><td>Study 1415008 (Patch clamp): hKir2.1, hKvLQT1/hminK, hKv4.3 and hCav1.2 cloned channel current in mammalian cells

GLP: No

Concentration: 100, 300µM or 100, 180, 300µM for hKv4.3</td><td>Table 77. Summary of Effects of Iptacopan on Four Channels
<table>
<tr><th>Channel</th><th>Concentration (µM)</th><th>% Inhibition</th><th>SEM</th><th>n</th></tr>
<tr><td>hKir2.1</td><td>100</td><td>0.6%</td><td>0.2%</td><td>3</td></tr>
<tr><td></td><td>300</td><td>0.4%</td><td>0.2%</td><td>3</td></tr>
<tr><td>hKvLQT1/hminK</td><td>100</td><td>0.6%</td><td>0.1%</td><td>3</td></tr>
<tr><td></td><td>300</td><td>0.9%</td><td>0.7%</td><td>3</td></tr>
<tr><td>hKv4.3</td><td>100</td><td>7.0%</td><td>2.3%</td><td>4</td></tr>
<tr><td></td><td>180</td><td>18.2%</td><td>1.8%</td><td>3</td></tr>
<tr><td></td><td>300</td><td>22.0%</td><td>1.6%</td><td>3</td></tr>
<tr><td>hCav1.2</td><td>100</td><td>3.6%</td><td>2.2%</td><td>3</td></tr>
<tr><td></td><td>300</td><td>5.1%</td><td>2.5%</td><td>3</td></tr>
</table>
Source: Applicant’s submission
Abbreviations: n, number of subjects; SEM, standard error of mean

Table 78. Summary of Effects of Positive Controls
<table>
<tr><th>Channel</th><th>Positive Control</th><th>Concentration (µM)</th><th>% Inhibition</th><th>SD</th><th>n</th></tr>
<tr><td>hKir2.1</td><td>Barium Chloride</td><td>100</td><td>96.7%</td><td>0.7%</td><td>2</td></tr>
<tr><td>hKvLQT1/hminK</td><td>Chromanol 293B</td><td>30</td><td>78.5%</td><td>3.1%</td><td>2</td></tr>
<tr><td>hKv4.3</td><td>Flecainide</td><td>100</td><td>74.8%</td><td>3.7%</td><td>2</td></tr>
<tr><td>hCav1.2</td><td>Nifedipine</td><td>0.1</td><td>90.7%</td><td>0.1%</td><td>2</td></tr>
</table>
Source: Applicant’s submission
Abbreviations: n, number of subjects; SD, standard deviation

IC_{50} > 300µM</td></tr>
<tr><td>Study 1415101 (Trafficking assay): hERG channel expression in HEK293 cells

GLP: No

Concentration: 0.1, 0.3, 1, 3, 10, 30, or 100µM</td><td>Iptacopan was not considered a hERG trafficking inhibitor based on the lack of effects on relative surface expression for hERG-WT compared to vehicle-treated cells.

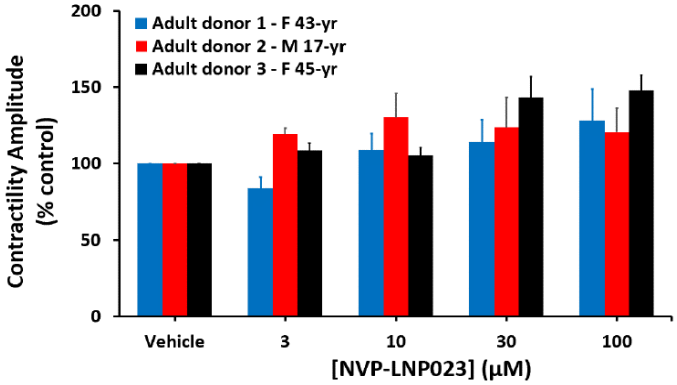
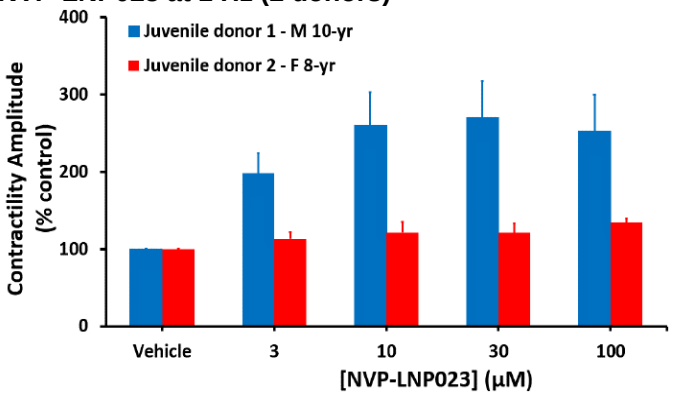
Iptacopan was not considered a hERG channel blocker based on the lack of effects on relative surface expression for hERG-SM compared to vehicle-treated cells.</td></tr>
<tr><td>Study 1415103 (Trafficking assay): hERG channel expression in HEK293 cells

GLP: No

Concentration: 0.1, 0.3, 1, 3, 10, 30, 100, or 300µM</td><td>Iptacopan was not considered a hERG trafficking inhibitor based on the lack of effects on relative surface expression for hERG-WT compared to vehicle-treated cells.</td></tr>
<tr><td>Study 1520203 (Vasoreactivity assay): Rat and dog aortic and mesenteric artery rings

GLP: No

Concentration: 1, 3, 10, or 30 µM</td><td>Iptacopan did not appear to have direct vasodilatory activity on rat arteries (aorta and mesentery) or on dog arteries (aorta and mesentery).</td></tr>
</table>

Study No/ Study Title	Findings
Study 2120033-A (Contractility assay, Calcium imaging assay): Human primary ventricular cardiomyocytes (CMs) from adult donors (≥17- and ≤60-year-old) and young donors (≤10-year-old) GLP: No Iptacopan Concentrations: 3, 10, 30, or 100µM LEVOSIMENDAN: 0.1, 1, 10, 30µM RANOLAZINE: 10, 30, 100, 200µM MILRINONE: 3, 10, 30, 100µM Positive control (Isoproterenol): 0.0003, 0.003, 0.010, or 0.030µM Positive control (Verapamil): 0.01, 0.1, 1, or 10µM Note: Juvenile data are highly exploratory, due to lack of historical data and very small N from this study.	**Figure 8. Percent Changes in Contractility Amplitude for NVP-LNP023 at 1 Hz (3 Adult Donors)**  Source: Applicant's submission Abbreviations: F, female; Hz, hertz; M, male; NVP-LNP023, Novartis Pharmaceuticals iptacopan; yr, year Iptacopan does not affect the contraction and relaxation kinetics of cardiomyocytes from adult donors. Iptacopan showed a low pro-arrhythmic risk at the highest concentration of 100µM based on producing lower than the predefined threshold of 40% pro-arrhythmia for contractility, After Contractions (AC) and Short-Term Variability (STV) in cardiomyocytes from adult donors. **Figure 9. Percent Changes in Contractility Amplitude for NVP-LNP023 at 1 Hz (2 donors)**  Source: Applicant's submission Abbreviations: F, female; Hz, hertz; M, male; NVP-LNP023, Novartis Pharmaceuticals iptacopan; yr, year There was a high variability in response to iptacopan on contractility amplitude between the 2 donors; these effects were of larger amplitude in donor M 10-yr as compared to donor F 8-yr.

Study No/ Study Title	Findings
Study 2120033-B (Contractility assay, Calcium imaging assay): Human primary ventricular cardiomyocytes (CMs) from 2 adult donors (≥17- and ≤60-year-old) and 1 young donor (10-year-old) GLP: No Iptacopan Concentrations: 10, 30, or 100 µM (adult); 3 or 10 µM (juvenile) LEVOSIMENDAN: 1 µM MILRINONE: 100 µM Note: Juvenile data are highly exploratory, because the lack of historical data and very small N from this study.	Iptacopan did not show any pro-arrhythmic risk in cardiomyocytes from 2 adults based on the lack of effects on either the Calcium Transient Amplitude or Kinetics in both acute (5-min and 10-min incubation) and chronic (24-incubation) experiments. Iptacopan did not show any pro-arrhythmic risk in cardiomyocytes from a 10-year-old donor based on the lack of effects on either the Calcium Transient Amplitude or Kinetics in both acute (5-min and 10-min incubation) and chronic (24-incubation) experiments.
In Vivo	
Study 1570154 Cardiovascular function assessment in male rats following oral (gavage) administration (Telemetry) GLP: No Rat/Wistar Han 8/male/group Dose: 0, 1000 mg/kg/day Oral, Gavage, Once Dose volume: 5 mL/kg	No iptacopan-related effects on blood pressure, heart rate, and body temperature
Study 1470817 Oral cardiovascular telemetry study in male dogs GLP: No Dog/Beagle 3/male/group Dose: 0, 600 mg/kg/day Oral, Gavage, Once Dose volume: 5 mL/kg	<u>Clinical Signs</u> Emesis occurred in 2 of 3 dogs. No mortality occurred. <u>Body Weight / Food Consumption</u> No iptacopan-related effects on body weight. Reduced food consumption after dosing was considered related to emesis. <u>Telemetry</u> Iptacopan-related decrease in blood pressure up to 26 mmHg (23%) and a concurrent increase in heart rate up to 40 beats/min (43%) compared to baseline-adjusted values in the control group. Values for blood pressure and heart rate returned to baseline within 16-18 hours postdosing. Decreased PR or QT intervals were noted and considered to be secondary to the increase in heart rate, and slight decreases in QTc interval occurred as a result of under-correction of QT because of the increased heart rate. Therefore, no iptacopan-related effects on QTc interval were identified.

Study No/ Study Title

Study 1570153
Cardiovascular function assessment in male dogs following oral (gavage) administration
(Telemetry)

GLP: No

Dog/Beagle
4/male/group

Dose: 0, 50, 100, 200, or 600 mg/kg
Oral, Gavage, Once
Dose volume: 5 mL/kg

Findings

Clinical Signs

Iptacopan-related emesis and diarrhea occurred in 3/4 and 2/4 dogs, respectively at 600 mg/kg. No mortality occurred.

Telemetry

Figure 10. Percent Change in Cardiovascular Function

Dose (mg/kg)	Blood Pressure	Heart Rate	Total Peripheral Resistance[a]
50	None	None	↓19
100	↓15	↑38	↓38
200	↓21	↑50	↓39
600	↓33	↑71	↓51

Source: Reviewer's analysis, a: measured in one animal

- Decreases in blood pressure occurred at approximately 2 to 4 hours post dose and values returned to vehicle control levels at approximately 12 hours except for the decrease at the highest dose which remained lower at the end of the recording period (24 h).
- Maximal increases in heart rate occurred at approximately 2-3 hours post dose and values returned to vehicle control levels at approximately 4, 8, and 18 hours.
- Total Peripheral Resistance values returned to vehicle control levels at approximately 6 to 8 hours except for the decrease at the highest dose which remained lower at the end of the recording period (24 h).

Study 1470565
LNP023: Single-Dose Oral Gavage Cardiovascular Telemetry Study in Male Dogs Dog/Beagle

GLP: Yes

Dog/Beagle
4/Male/group

LNP023: batch no. 1010006947
Dose: 0, 15, 50, or 300 mg/kg
Vehicle Control: 0.5% (w/w) methylcellulose and 0.5% w/w Tween 80 (Polysorbate 80)

Route of Administration and Dosing Frequency:
Oral, Gavage, Once
Dose volume: 5 mL/kg

Electrocardiogram (ECG) Qualitative Review

No iptacopan-related disturbances in rhythm and waveform morphology were observed on a visual inspection of the ECG wave forms when compared with predose forms.

Cardiovascular Function Assessment

Iptacopan-related and statistically significant decreases in blood pressure, with secondary increases in heart rate and decreases in RR and PR intervals occurred at the highest dose tested 300 mg/kg.

Table 79. Cardiovascular Function Assessment

Parameter	Dogs (#)	Change	Time (h)	
			Onset	Maximum
Blood Pressure	3 / 4	(mmHg)		
Systolic		↓33	0.25 – 20	2 – 5.25
Diastolic		↓18		
Mean Arterial		↓21	2 – 13	2.25 – 4.5
Heart Rate	3 / 4	(beats/min) ↑48	0.25 - 17	1.25 - 5
PR interval	3 / 4	(msecond) ↓14	0.25 - 7	0.25 – 7.25

Source: Reviewer's Analysis
Abbreviations: h, hour; min, minute; msecond, millisecond; #, number

Study No/ Study Title	Findings
Study 2170052 A 14-day oral (gavage) repeat dose cardiovascular safety pharmacology study with a 1-week recovery period in juvenile and young adult beagle dogs GLP: No	Mortality of a single 150 mg/kg/day female on Day 12 caused by low platelet count and skin petechia that corresponded with mild hemorrhage in multiple tissues. Additional decrease in red blood cell mass, increased megakaryocyte cellularity in bone marrow and alveolar septa of the lung. Follicular cell hypertrophy of the thyroid gland and multifocal necrosis of the heart left ventricle, as well as eosinophilic material in the lumen of blood vessels (possibly thrombi-like).
Dog/Beagle 4/Female/group	LNP023 plasma concentrations increased with dose levels, no accumulation over time observed.
Dose: 0, 30, or 150 mg/kg/day Juvenile: oral gavage from pups on PND 59/60 to 73/74 Young adults: oral gavage starting at 8 months old Recovery for 1 week after 14-days of dosing	LNP023 quantifiable concentrations in 150 mg/kg/day CSF samples in a single juvenile, 3 adult dogs and one adult dog at the end of recovery.

Source: Reviewer's analysis
Abbreviations: AC after contractions; CMs, cardiomyocytes; CSF, cerebrospinal fluid; ECG, electrocardiogram; F, female; GLP, good laboratory practice; h, hour; HEK, Human Embryonic Kidney; hERG, human ether-ago-go-related Gene; IC_{50}, half-maximal inh bitory concentration; I_{Kr}, rapidly delayed rectifier K+ currents; M, male; Min, minute; n, number of subjects; LNP023, iptacopan; PND, postnatal day; PR, PR interval; QTc, corrected QT interval; SEM, standard error of mean; STV, short term viability; yr, year

13.1.4. ADME/PK

Table 80. Summary of ADME/PK Studies

Absorption

Single oral dose in animals and human

Absorption was estimated at 82% in rats and 71% in human after a single oral dose of radiolabeled [^{14}C]iptacopan based on the plasma AUC. In humans, the absorption was 71% based on the sum of radioactivity recovered in urine and feces, See Table 82.

Table 81. Mean Pharmacokinetic Parameters of Iptacopan in Plasma of Animals and Humans After Single Intravenous and Oral Dose of Radiolabeled [^{14}C]iptacopan

Species (Reference)	Route	Dose (mg/kg)	T_{max} (h)	C_{max} (µM)	AUC_{last} (µM·h)	AUC Interval (h)	$T_{1/2}$ (h)	Absorption (%)
Rat (R1500361)	iv	2	0.083[a]	5.19	7.77	24	5.21	-
Rat (R1500361)	po	10	0.5	2.59	31.3	24	8.18	81.8[e]
Human (CLNP023A2101)	po	1.22[b]	1.51[c]	6.33[d]	64.1[d]	48	14.7	70.6[f]

Source: Applicant's submission modified
[a] First time point measured
[b] 100 mg dose, mean body weight: 81.65 kg
[c] Median
[d] Calculated from ng-eq/mL using the equation µM = (ng-eq/mL) / 422.5
[e] Value of fraction absorbed is related to the dose normalized AUC_{inf} of total radiolabeled components determined after intravenous administration ((AUC_{inf}/D p.o./AUC_{inf}/D iv)*100)
[f] Estimated from the sum of mean recovery of radioactivity in urine (24.8%) and mean radiolabeled metabolites excreted in feces (45.8%)
Abbreviations: AUC, area under the concentration-time curve; AUC_{inf}, area under the concentration time curve estimated to infinity; AUC_{last}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; D, day; h, hour; iv, intravenous; po, by mouth; T_{max}, time to maximum concentration; $T_{1/2}$, half-life

Iptacopan has high solubility and moderate permeability with a rapid absorption across species with oral administration with T_{max} ranging between 0.5-2 hrs and $T_{1/2}$ ranging from 6-10 hrs. The oral bioavailability was 46%, 40-68%, and 60% in mouse, rat, and dog, respectively. The absorption of iptacopan may potentially be modulated by intestinal efflux by P-glycoprotein (P-gp) for which iptacopan is a substrate. However, the transport of iptacopan was not saturated when tested in vitro, even at high concentrations of iptacopan expected in the gut.

Continued

Table 80, continued

Table 82. Mean Pharmacokinetic Parameters of Iptacopan in Plasma of Animals and Humans After Single Oral Dose of Iptacopan

Species (Study No.)	Dose (mg/kg)	T_{max} (h)[b]	C_{max} (µM)	AUC_{last} (µM·h)	AUC Interval (h)	$T_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	F (%)
Mouse (RD-2016-00013)	10	0.6	2.25[a]	7.604[a]	7	-	-	-	46
Rat (RD-2016-00014)	30	2	12.3[a]	53.0[a]	7	-	-	-	40
Rat (DMPK R1500361)	10	0.25	1.35	16.9	24	9.70	-	-	49.7
Rat (DMPK R2100550)	10	0.5	3.34[c]	21.4[c]	48	4.46	-	-	68.3
Dog (RD-2016-00020)	10	0.8	19.5[a] [f]	114[a, f]	24	5.6	-	-	60
Human (CLNP023A2101)	1 22[d]	1.51 [b]	5.05[c]	54.3[c]	48	12.3	4.35	76.9	-
Human (CLNP023X2101)	2.51[e]	1.13 [b]	7.64 [c]	86.4[c, g]	-	18.0	0.151	3.46	-

Source: Applicant's submission modified
[a] Calculated from nM using the equation µM = nM/1000
[b] Median
[c] Calculated from ng/mL with µM = ng/mL / 422.5 g/mol
[d] 100 mg dose, mean body weight: 81.65 kg
[e] 200 mg dose, mean body weight: 79.8 kg
[f] Blood parameters were determined. Plasma parameters were obtained by multiplying by the blood parameters using a fixed value of Cb/Cp = 0.904 (tested at 1000 ng/mL)
[g] AUCinf
Abbreviations: AUC, area under the concentration-time curve; AUC_{last}, area under the concentration-time curve to the last measurable concentration; Cb/Cp, blood-to-plasma concentration ratio; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; D, day; F, bioavailability; h, hour; T_{max}, time to maximum concentration; $T_{1/2}$, half-life; Vz/F, apparent volume of distribution during terminal phase

Distribution

Blood/Plasma Distribution & Plasma Protein Binding

Iptacopan distribution into blood cells was evaluated in rat, dog, and human, See Table 83. (Study DMPK R1500362)

- The blood-to-plasma (Cb/Cp) concentration ratios increased in a concentration dependent manner.
- The human plasma protein binding of iptacopan was also concentration dependent with the range of 75% (10000 ng/mL) to >98% at 100 ng/mL.
- A qualitative similar concentration dependency of the plasma protein binding was found for rat and dog.
- As the non-linearity in plasma protein binding of iptacopan observed in all species is likely related to a saturable target (factor B) binding, the exposure multiples (safety margins) were initially calculated based on total drug concentrations.
- The non-linear binding of iptacopan to plasma protein may be related to on-target binding to Factor B (target) which is known to be highly abundant (315 ±102 mg/L; mean ±SD) in human plasma (Silva et al. 2012).

Continued

Table 80, continued

Table 83. Blood-Plasma Distribution and Plasma Protein Binding of Iptacopan

		Blood/Plasma Distribution				Plasma Protein Binding	
Species	Iptacopan Concentration (ng/mL)	Hematocrit	Fraction In Plasma (%)	Blood/ Plasma Ratio (Cb/Cp)	Blood/ Blood Cell Ratio (Cbc/Cp)	Bound Fraction (%)	Unbound Fraction (%)
Rat	10	0.46	54.3	0.99	0.99	96.0	4.03
	100	0.41	49.0	1.20	1.50	94.2	5.76
	1000	0.41	38.2	1.55	2.33	86.5	13.5
	10000	0.41	16.4	3.59	7.31	62.7	37.3
Dog	10	0.49	71.1	0.72	0.42	90.5	9.47
	100	0.48	64.0	0.81	0.61	89.8	10.2
	1000	0.48	57.5	0.90	0.80	82.2	17.8
	10000	0.48	37.6	1.38	1.80	65.0	35.0
Human	10	0.44	93.3	0.60	0.09	95.6*	4.35*
	100	0.48	80.1	0.65	0.27	98.8	1.23
	1000	0.48	52.1	1.00	1.00	93.0	7.00
	10000	0.48	24.3	2.14	3.37	74.6	25.4

Source: Applicant's submission
* Two samples were below the limit of detection (total N=2)
Abbreviations: Cb/Cp, blood-to-plasma concentration ratio; N, number of subjects

Tissue Distribution

Following an oral dose of 10 mg/kg in rats [albino and pigmented (Study DMPK R1500361), male and female (DMPK R1701426)], total radiolabeled components of iptacopan (^{14}C-iptacopan) were distributed throughout the body and majority of tissues.

- T_{max} was reached between 0.25 and 2 hrs.
- $T_{1/2}$ was comparable to blood (4 hrs) in most tissues except in kidney (72 hrs) and liver (168 hrs) of albino rats, and in liver (up to 72 hrs) pigmented skin (72 hrs), uveal tract and eyes (up to 336 hrs) in pigmented rats.
- Iptacopan was no longer detected at 24 hrs post dose in most organs except in blood, intestine, kidney, liver, lung, lymph nodes, pancreas, and penis.
- Iptacopan showed a very low exposure to the brain up to 2 hrs with brain to blood ratio of <0.08. Note: Iptacopan appeared to cross the blood-brain barrier and was detected in the brain and spinal cord toxicology study in dogs associated with clinical signs leading to moribundity (Study pcs-r1470220)
- C_{max} levels were observed in the uveal tract, liver, small intestine, liver, and kidney.
- In pigmented animals, iptacopan was detected in melanin containing eye tissues (choroid and ciliary body) up to 168 hrs which suggests affinity to ocular melanin.
- The volume of distribution (Vss) was 3.01 L/kg in rat.

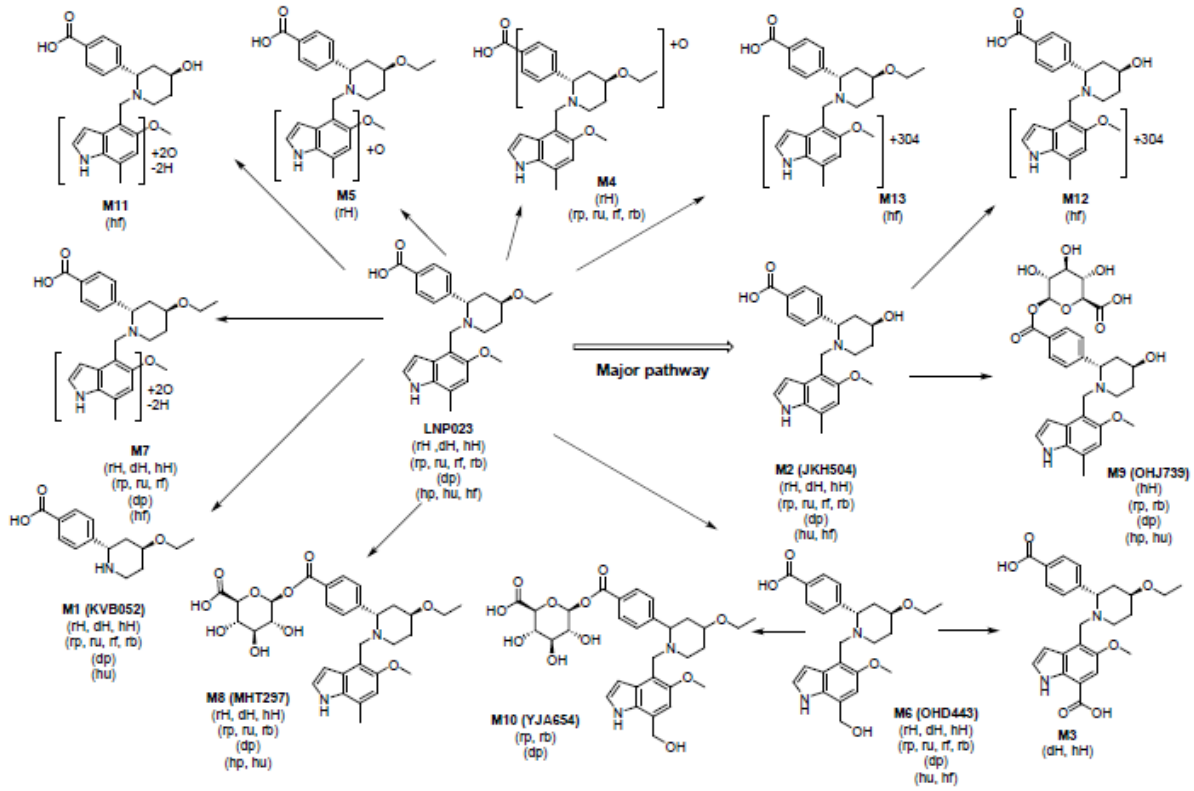
Continued

Table 80, continued

Metabolism

Hepatic metabolism appears to be the predominant (about 80%) mechanism of elimination for iptacopan in animals and human. Metabolism of iptacopan was investigated across species in vitro and in vivo.

Figure 11. Possible Metabolic Pathway of Iptacopan



Source: Applicant's submission
Abbreviations: dH, dog hepatocytes; dp, dog plasma; hf, human feces; hH, human hepatocytes; hp, human plasma; hu, human urine; LNP023, iptacopan; rb, rat bile; rf, rat feces; rH, rat hepatocytes; rp, rat plasma; ru, rat urine

Continued

Table 80, continued

Metabolites M1, M2 (JKH504), M6 (OHD443), M7, M8 (MHT297), and M9 (OHJ739) were detected in the human plasma AUC_{0-8h} pool. Metabolite analysis from chronic toxicology studies in rats and dogs include iptacopan, M1, M2, M6, M7, M8, M9, and M10 (Study DMPK R1570192, DMPK R1570193). In human, M8 and M9 were the most abundant systemic metabolites (8.05% and 5.17%, respectively). Multiple oral doses of iptacopan 200 mg twice daily to patients with IgAN resulted in M8 and M9 at 17.8% and 6.5% of the AUC_{0-12h} at steady state (Study CLNP023X2203). Further evaluation of exposure to M8 was conducted in toxicology study in dogs and animal:human exposure ratios are presented in Table 84.

Table 84. Metabolites Exposure Ratio in Dog Versus Human

	Ratio Dog (150 mg/kg/Day)/Human	
Metabolites	**Male**	**Female**
Iptacopan	12.0	12.9
M1	6.86	6.29
M2	0.907	0.735
M6	13.9	14.4
M7	10.9	6.22
M8	2.72	1.40
M9	0.0159	0.0101

Source: Applicant's submission modified
* Metabolites in human plasma from clinical study CLNP023X2101

The metabolites with ≤1 exposure multiples [M2 (NVP-JKH504), M8 (NVP-MHT297) and M9 (NVP-OHJ739)] were evaluated for the inhibition of complement factor B. The result showed the inhibition of binding of an active site reporter ligand (NVP-CKJ036-DA-1) to human complement factor B occurred in a concentration dependent manner with binding affinities between 0.27-1.52µM, 27- and 150-fold compared to that of parent compound iptacopan (0.0096µM) (Study DMPK R1809129).

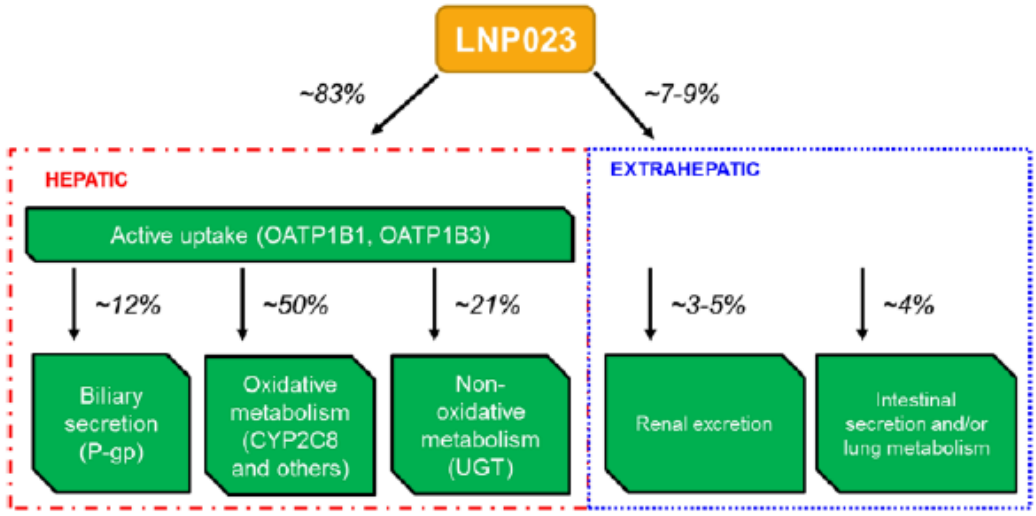
Continued

Table 80, continued

Excretion

The predominant mechanism of elimination in the rat is liver metabolism with about 50% excreted as oxidative metabolites and about 21% as acyl-glucuronides. Data from the rat ADME and bile excretion study further suggest some contribution of direct renal excretion of iptacopan of about 3-5% and a more significant direct biliary excretion of iptacopan of about 12% of the total dose. Hepatobiliary disposition of iptacopan was investigated in cultured human hepatocytes and the role of P-gp mediated efflux in the direct biliary excretion confirmed. Direct excretion of iptacopan of about 4% across the intestinal wall may also contribute to the overall disposition of iptacopan. The anticipated fractional elimination pathway contributions in human can be estimated from available animal studies, see Figure 12 (Study DMPK R1500361).

Figure 12. Different Elimination Pathways to the Clearance of Iptacopan



Source: Applicant's submission
Abbreviations: CYP, cytochrome P4502C8; LNP023, iptacopan; OATP1B1, organic anion transporting polypeptide B1 OATP1B3, organic anion transporting polypeptide B3; UGT, UDP-glucuronosyltransferases; P-gp, P-glycoprotein

Source: Reviewer's Analysis
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}8h}$, area under the concentration-time curve from time 0-8 h; $AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0-12 h; ADME, absorption, distribution, metabolism and excretion; C_{max}, maximum plasma concentration; Cb/Cp, blood-to- plasma concentration ratio; DMPK, drug metabolism and pharmacokinetics; Hrs, hours; IgAN, immunoglobin A nephropathy; NVP-LNP023, iptacopan; P-gp, P-glycoprotein; SD, standard deviation; T_{max}, time to maximum concentration; $T_{1/2}$, half-life; Vss, volume of distr bution

Table 85. Toxicokinetic Data

Study/ Study No.	Major Findings
General Toxicology Studies	
Analysis of toxicokinetic data from toxicology studies in monkeys, rats, and dogs are included in Section 13.1.5.1. The toxicokinetic comparison between rats and dogs for the same duration of toxicology study is as below. Rats (Wistar Han): 0, 50, 150, or 500 mg/kg/ day, p.o. once daily for 13 weeks Dogs (Beagle): 0, 5, 30, or 150 mg/kg/ day, p.o. once daily for 13 weeks • In general, a rapid absorption was observed in rats and dogs with C_{max} reaching at 0.5 -1 h. • For both rat and dog, an approximately dose-linear exposure (AUC) was observed up to the highest dose administered. The measured dose normalized AUCs (at week 13) were about 5450 (ng·h/mL)/(mg/kg) for dogs and about 12 times lower in the rat amounting to about 440 (ng·h/mL)/(mg/kg). Respective normalized C_{max} values of about 720 (ng/mL)/(mg/kg) for rats and about 85 (ng/mL)/(mg/kg) for dogs were obtained • T_{max} was between 0.5 and 3 hours in rats and dogs at Day 1 and 0.5 to 1h at Week 13 • No apparent exposure differences (>30%) between males and females was detected in rat and dogs at all dosage levels and only a trend to slightly lower exposures observed in rat females • No apparent exposure increases or decreases from Week 1 to Week 13 were observed in dogs at all doses and in rats at the low and mid dose. In the male rats only at the low dose of 50 mg/kg/day the accumulation factor based on $AUC_{(0-24h)}$ amounted to 1.26 and based on C_{max} amounted to 1.46.	

Source: Reviewer's analysis
Abbreviations: AUC; area under the concentration-time curve; AUC(0-24h), area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; h, hour; p.o., by mouth; T_{max}, time to maximum concentration

13.1.5. Toxicology

13.1.5.1. General Toxicology

Study 1370389: An Oral (Gavage) Rising Dose Toxicity Study With Non-Invasive Telemetry in Male Monkeys

Table 86. Study Information, Study 1370389

Study Features and Methods	Details
GLP Compliance:	No
Dose and frequency of dosing:	10, 50, 100, 300, or 600 mg/kg, single rising dose
Route of administration:	Oral (gavage)
Formulation/vehicle:	0.5% (w/v) methylcellulose, type 15 cPs aqueous solution containing 0.5% (v/v) Polysorbate 80, NF (aka MC/Tween)
Species/strain:	Monkey/Cynomolgus
Number/sex/group:	3/male/group
Age:	2-4 years (2.6-3.0 kg weight)
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice

Table 87. Observations and Results, Study 1370389

Parameters	Major Findings
Mortality, Clinical signs, Body weight	No iptacopan-related effects were observed.
ECG	QTc interval prolongation was observed at 300 and 600 mg/kg with dose dependency (also described in Section 13.1.3).
Hematology	Iptacopan-related increases in neutrophil counts (up to +99%), decreases in lymphocyte and eosinophil counts (up to -51% and -89%) were observed at all doses
Clinical chemistry	Iptacopan-related increase in levels of total bilirubin (+124%), and alanine aminotransferase (ALT) & aspartate aminotransferase (AST) with minimal magnitude (+64% & +25%) compared to baseline were observed at 600 mg/kg
Toxicokinetics	Systemic exposure (C_{max} and AUC_{0-24}) to iptacopan increased dose-proportionately in general. T_{max} ranged from 0.667 to 6 hours. Elimination of iptacopan was slower at higher dose (5-fold difference between 100 to 600 mg/kg) which could result in accumulation of iptacopan after repeated dosing.

Source: Reviewer's analysis
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{0-24}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; ECG, electrocardiogram; Qtc, corrected QT interval; T_{max}, time to maximum concentration

Study 1370303/ 2-Week Oral (Gavage) Pilot Toxicity Study in Male Rats

Key Study Findings

- The no-observed-adverse-effect-level (NOAEL) was determined at 1000 mg/kg/day (maximum plasma concentration [C_{max}]=83800 ng/mL and area under the concentration-time curve over the last 24-hour dosing interval [AUC_{0-24h}]=653000).
- Minimal increases in neutrophil counts at all dose levels (without dose relation) and increased mean thyroid weights (% body weight, +49%) without histopathological finding. These findings were not considered adverse, which determined the NOAEL at 1000 mg/kg/day.

Table 88. Study Information, Study 1370303

Study Features and Methods	Details
GLP compliance:	No
Dose and frequency of dosing:	0, 100 (LD), 300 (MD), or 1000 (HD) mg/kg/day, once daily
Route of administration:	Oral (gavage)
Formulation/vehicle:	0.5% w/v methylcellulose + 0.5% v/v Tween 80 (polysorbate 80)
Species/strain:	Rat/Wistar Han
Number/sex/group:	5/male/group
Age:	10 weeks
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; HD, high dose; LD, low dose; MD, mid dose

Table 89. Observations and Results, Study 1370303

Parameters	Major Findings
Mortality, clinical signs, body weights, clinical chemistry, gross pathology	No iptacopan-related effects were observed.
Hematology	Minimal increases in neutrophil counts (+44-66%) were observed when compared to controls.
Organ weights	Thyroid weights (% body weight) was increased at HD by +49% compared to controls without correlating macroscopic/microscopic findings.
Histopathology Adequate battery: Yes	No iptacopan-related effects were observed.
Toxicokinetic	Systemic exposure (C_{max} and AUC_{0-24h}) to iptacopan increased with dose increment with dose-proportionality in general. T_{max} ranged from 0.5 to 3 hours and accumulation of iptacopan was not evident.

Source: Reviewer's analysis
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; HD, high dose; T_{max}, time to maximum concentration

Study 1470568/ 4-Week Oral (Gavage) Toxicity Study in Rats With a 4-Week Recovery Period and Micronucleus Assessment

Key Study Findings

- The NOAEL was determined at 300 mg/kg/day (C_{max}= 33650 ng/h, AUC_{0-24h}= 178000 ng·h/mL) based on the adverse findings in harderian gland at high dose (HD)
- No iptacopan-related adverse effects on mortality, clinical signs, body weights, ophthalmoscopy, electrocardiogram, hematology, urinalysis, gross pathology, and organ weights

Table 90. Study Information, Study 1470568

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 100 (LD), 300 (MD), or 1000 (HD) mg/kg/day, once daily
Route of administration:	Oral (gavage)
Formulation/vehicle:	0.5% w/w methylcellulose, type 15 cPs, aqueous solution containing 0.5% (v/v) polysorbate 80, NF
Species/strain:	Rat/Wistar Han
Number/sex/group:	16/sex/group (control, HD; 6/sex/group for recovery phase), 10/sex/group (LD, MD)
Age:	10 weeks
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	There were no deviations from the study protocol altering the interpretation of results or the integrity of the study.

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; HD, high dose; LD, low dose; MD, mid dose; NF, national formulary

Table 91. Observations and Results, Study 1470568

Parameters	Major Findings
Mortality, Clinical signs, Body weights, Ophthalmoscopy, Hematology, Gross pathology, Organ weights	No iptacopan-related effects were observed.
Food consumption	Statistically significant, transient decrease of food consumption was noted in both sexes at HD (-11.1% in males and -9.2% in females) on Day 8 compared to controls.
Clinical chemistry	• Dose-dependent increases in serum total and direct bilirubin level were observed at ≥LD. • Total protein and albumin were decreased in HD females which resolved at the end of recovery phase. • Urea was increased at ≥MD in males and females up to +27%, which resolved after the recovery phase. • Minimal increase of alkaline phosphatase was observed at HD. **Table 92. Clinical Chemistry Parameter Percent Change After Iptacopan Treatment for 4 Weeks** Analyte / 100 mg/kg/day (Male, Female) / 300 mg/kg/day (Male, Female) / 1000 mg/kg/day (Male, Female) Alkaline phosphatase: - / - / - / - / +18% / +52% Total bilirubin: +63.8% / +23.3% / +82.6% / +45.7% / +212.5% / +118.7% Direct bilirubin: +247.3% / +152.9% / +387.8% / +333.5% / +945.9% / +971% Indirect bilirubin: - / - / - / - / +36.6% / - Total protein: - / - / -4% / - / -7.7% / -10.3% Albumin: - / -8.1% / -5.4% / -7.1% / -5.7% / -14.6% Urea: - / - / +15.2% / +17.4% / +26.9% / +24.5% Chloride: - / - / - / - / +4% / - Bicarbonate: - / - / - / - / -15.2% / - Calcium: - / - / - / - / -7.1% / -7.7% Triglycerides: +97.2% / - / +96.1% / - / +81% / - Source: Applicant's submission - = similar to controls
Urinalysis	Proteinuria (moderate to severe, ≥100 mg/dL) occurred at MD (1/10) and HD (15/15) in males and at HD (12/16) in females, which resolved on recovery Day 11.
Histopathology Adequate battery: Yes	• Thyroid gland: Follicular cell hypertrophy (minimal to mild) was observed in HD females (2/10) with corresponding thyroid weight increases. These changes resolved after the recovery period. • Harderian gland: Degeneration/regeneration with iptacopan-related increases in the incidence and severity at HD did not fully resolve after the recovery period, which was considered an iptacopan-related adverse finding.
Hormone Analysis	• No iptacopan-related effects were noted in all groups except one HD female. • TSH level was increased by 4.5-fold in one HD female (#4507) compared to controls without change in total serum T3 and T4 levels.

Parameters	Major Findings
Toxicokinetics	• Systemic exposure (C_{max} and AUC_{0-24h}) to iptacopan increased with dose increment with dose-proportionality in general. T_{max} ranged from 0.5 to 7 hours. Accumulation of iptacopan or sex differences in exposures were not evident.

Table 93. Toxicokinetic Parameters in Rats After Iptacopan Treatment for 4 Weeks

Dose (mg/kg/Day)	Study Day	Gender	AUC_{0-24h}	C_{max}	T_{max}
100	1	Male	52000	11100	1.0
		Female	57100	22100	0.5
		MF	54550	16600	0.75
	28	Male	61000	13200	1.0
		Female	55600	19000	0.5
		MF	58300	16100	0.75
300	1	Male	189000	31500	0.5
		Female	166000	35500	0.5
		MF	177500	33500	0.5
	28	Male	170000	31300	0.5
		Female	186000	36000	1.0
		MF	178000	33650	0.75
1000	1	Male	614000	42900	1.0
		Female	599000	85100	1.0
		MF	606500	64000	1.0
	28	Male	952000	67100	7.0
		Female	802000	90100	1.0
		MF	877000	78600	4.0

Source: Applicant's submission
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; MF, average of male and female; T_{max}, time to maximum concentration

Micronucleus assay	• No iptacopan-related effects were observed.

Source: Reviewer's analysis
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; HD, high dose; LD, low dose; MD, mid dose; T_{max}, time to maximum concentration TSH, thyroid stimulating hormone

Study 1570195/ LNP023: 13 Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by an 8 Week Recovery Period

Key Study Findings

- The NOAEL was determined to be 150 mg/kg/day in males and 500 mg/kg/day in females (C_{max}= 15700 and 29800 ng/mL; AUC_{0-24h}= 69500 and 181000 ng·h/mL, respectively), based on microscopic findings in thyroid and testes in males.
- Target organs of toxicity for iptacopan in rats included thyroid, prostate, and testis.

Table 94. Study Information, Study 1570195

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 50 (LD), 150 (MD), or 500 (HD) mg/kg/day, once daily
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose (type 15 cPs) + 0.5% w/w Tween® 80 (polysorbate 80)
Species/strain:	Rat/Wistar Han
Number/sex/group:	15/sex/group (control, HD; 5/sex/group for recovery phase), 10/sex/group (LD, MD)
Age:	8-10 weeks
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	There were no deviations from the study protocol altering the interpretation of results or the integrity of the study.

Source: Reviewer's analysis
Abbreviations: GLP good laboratory practice; HD, high dose; LD, low dose; MD, mid dose

Table 95. Observations and Results, Study 1570195

Parameters	Major Findings
Mortality	• There were 2 deaths (one control #106F and one MD #128F) with cause of death determined as procedure-related gavage error. • No death/moribundity related to iptacopan treatment occurred during the duration of the study.
Clinical signs	Iptacopan-related salivation (infrequent) was observed at 2 hours post-dose at HD.
Body weights, Ophthalmoscopy, Hematology, Urinalysis	No iptacopan-related effects were observed.
Clinical chemistry	• Minimal decreases in albumin (-7%), total protein (-4%), and triglyceride concentrations (-22%) compared to controls were noted in HD females, and these findings resolved at the end of recovery. • Minimal decreases in calcium concentrations in MD and HD females were considered secondary to the decreases in albumin concentrations. • In females, increases of cholesterol (+31%) at HD and glucose (+18-23%) at MD and HD compared to controls were observed in females, and the change didn't resolve at the end of recovery phase. In males, decreases of cholesterol at MD and HD (-14-16%) and triglyceride (−26%) were noted which resolved at the end of recovery period
Gross pathology	There were minor increased incidences of pale mottled liver in HD males.
Organ weights	• Iptacopan-related thyroid weight (% body weight) increase by 13% was observed in HD males compared to controls with corresponding dose-related higher incidence and severity of thyroid follicular hypertrophy. This finding resolved at the end of recovery phase. • Prostate weights (% body weight) were increased at all doses (+11-24%) at the end of dosing phase which persisted after the recovery phase (+36% at HD). This change was without any corresponding macroscopic or microscopic findings.

Parameters	Major Findings
Histopathology Adequate battery: Yes	• Thyroid follicular hypertrophy (minimal to slight) was noted at HD with dose-related increase in incidence and severity. • Minor testis tubular degeneration was observed in one HD male (#44), which resolved by the end of recovery phase.
Seminology	• Total sperm count and, sperm motility/velocity were analyzed only in HD and the parameters were within the historical control data (provided by the Applicant; 2012-2015). Without sperm analysis of control animal data, the conclusion on iptacopan-related effect on seminology cannot be made.
Hormone analysis	• Iptacopan-related effects on thyroid hormones consisted of reversible increases in total triiodothyronine (T3) and thyroxine (T4) levels at ≥LD, compared to controls in males. Females dosed at ≥LD also presented reversible minimal increases in T3 and T4 levels.

Table 96. Percent Difference in Hormone Levels

Sex	Dose	T3	T4	TSH
Male	LD	+20	+25	-9
	MD	+22	+33	-6
	HD	+45 (+16)	+25 (+1)	+14 (+128)
Female	LD	+1	-1	-52
	MD	+11	+17	-22
	HD	+10 (-3)	+26 (-14)	-23 (+65)

Source: Reviewer's analysis
+/- = increase/decrease, ( ) = values from recovery animals
Abbreviations: HD, high dose; LD, low dose; MD, mid dose; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine

- Reversible increase of T3 and T4 levels corresponds to the histopathological findings of reversible thyroid follicular cell hypertrophy in HD animals.
- Circulating testosterone/androstenedione was decreased starting in dosing Week 7 followed by an increase in dihydrotestosterone in dosing Week 13 in all doses. This finding resolved at the end of recovery period.

Parameters	Major Findings
Toxicokinetics	• Systemic exposure (C_{max} and AUC_{0-24}) to iptacopan increased with dose increment with dose-proportionality in general. T_{max} ranged from 0.5 to 3 hours. Accumulation of iptacopan or sex difference in exposure were not evident.

Table 97. Toxicokinetic Parameters in Rats After Iptacopan Treatment for 13 Weeks

Dose (mg/kg/Day)	Study Day	Gender	AUC_{0-24h}	C_{max}	T_{max}
50	1	Male	20600	3490	1.0
		Female	24400	4860	0.5
		MF	22500	4175	0.75
	87	Male	26000	5110	0.5
		Female	22300	4750	0.5
		MF	24150	4930	0.5
150	1	Male	68700	12800	1.0
		Female	57000	12000	0.5
		MF	62850	12400	0.75
	87	Male	69500	15700	0.5
		Female	49700	12100	1.0
		MF	59600	13900	0.5
500	1	Male	222000	27500	0.5
		Female	298000	41600	1.0
		MF	260000	34550	0.75
	87	Male	249000	32400	3.0
		Female	181000	29800	1.0
		MF	215000	31100	2.0

Source: Applicant's submission
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; MF, average of male and female; T_{max}, time to maximum concentration

Source: Reviewer's analysis
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; F, female; HD, high dose; LD, low dose; MD, mid dose; T_{max}, time to maximum concentration T3, triiodothyronine; T4, thyroxine

Study 1570193/ LNP023: 26 Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 27 Week Recovery Period

Key Study Findings

- There were 8 deaths during the study period, and 4 of the deaths were determined as procedure-related (gavage error) incidences at necropsy. But the cause of the other 3 deaths (two males [#R0201 and R0206] at mid dose [MD] and one female [#R0705] at HD) was not determined at necropsy.
- The mortality with unknown cause in HD is likely iptacopan-related, as this was also seen in the 2-year carcinogenicity study in rats at the same dose. Deaths at MD are not likely to be iptacopan related based on the no trend of mortality observed with significance at the same dose in the 2-year rat carcinogenicity study with the NOAEL defined at 150 mg/kg/day in males and females (Cmax=29000 ng/mL, AUC0-24h=100000 ng·h/mL).

- Increases in thyroid/parathyroid organ weight ratios occurred in HD male rats as well as minimal to moderate thyroid follicular cell hypertrophy that increased in incidence and severity with increasing dose at terminal sacrifice. Both the increase in thyroid weight and incidence of thyroid follicular cell hypertrophy were reversible during the recovery period. Finally, increases in T3, T4, and thyroid stimulating hormone levels observed at the end of the dosing period were not seen at the end of the recovery period, indicating reversibility.
- In the prostate, no adverse histopathological findings were observed after hematoxylin and eosin staining, but an increase in the severity of Ki67 positive staining of epithelial cells was observed with increasing dose at terminal sacrifice. This finding was not observed after the recovery period, indicating reversibility.
- Increases in testes weights and testes weight ratios were noted at all doses but were not observed after the recovery period, indicating reversibility.
- Findings in thyroid/parathyroid organ weight ratios that corresponded with thyroid follicular cell hypertrophy and increases in T3, T4, and thyroid stimulating hormone levels, as well as microscopic findings in prostate and testes weight ratios also occurred in the 13-week study in rats (Study 1570195).
- The NOAEL was determined at the mid-dose of 750 mg/kg/day based on the lack of adverse findings.
- Potential target organs of toxicity include thyroid, prostate, and testis.

Table 98. Study Information, Study 1570193

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 50 (LD), 150 (MD), or 750 (HD) mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose (Type 15 cPs) + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Rat/Wistar Han
Number/sex/group:	20/sex/group. Additional 10/sex/group for recovery phase in control and HD
Age:	9-10 weeks
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	There were no deviations from the study protocol altering the interpretation of results or the integrity of the study.

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; HD, high dose; LD, low dose; MD, mid dose

Table 99. Observations and Results, Study 1570193

Parameters	Major Findings
Mortality	Eight rats were found dead or euthanized in moribund condition at unscheduled intervals (7 during the dosing phase and one control rat during the recovery phase). Four deaths were determined as procedure-related (gavage error) incidence at necropsy and one death in the control presented lymphoid lymphoma. The cause of another three deaths [two males (# R0201 and R0206) at MD, and one female (# R0705) at HD] were not determined at necropsy. All three early decedents presented slight follicular cell hypertrophy and the two males presented slight to moderate Ki67 positive in prostate epithelial cells. The deaths at MD in males are not likely iptacopan-related based on the same dose in the 2-year carcinogenicity study that lacked any convincing evidence of an iptacopan-related trend for deaths.
Clinical signs	Minimal thin appearance, minimal to moderate salivation prior to and following dosing (MD and HD), noisy respiration, raised hair and vocalization were noted with increased incidences at HD during the dosing phase, and were no longer observed during the recovery period.
Body weights / Food consumption	Minimal reduced body weight gain noted in iptacopan-treated males with LD, MD, and HD (-4, -13, -7%, respectively), while minimal increases in body weight gain were noted in females at LD, MD, and HD (+6, +8, and +20%, respectively) during the dosing phase. Comparable body weight gain in control and HD rats was observed during recovery. No iptacopan-related effects on food consumption occurred during the study.
Ophthalmoscopy, Hematology	No iptacopan-related findings occurred.
ECG	Not evaluated.
Clinical chemistry	Iptacopan-related changes were minimal in magnitude, limited to HD males and included increases in alkaline phosphatase activity and total bilirubin observed at the end of dosing phase, which resolved during the recovery phase.
Urinalysis	Iptacopan-related changes were minimal in magnitude and consisted of decreased urinary creatinine concentrations in MD-HD males (-18 to -28%) and HD females (-42%) that suggested an effect on renal/tubular creatinine secretion and/or reabsorption. Increase in urine protein/creatinine ratios in HD rats (+38-42%) were considered related to the effect on urinary creatinine concentration based on the absence of microscopic correlates. Ratios remained minimally elevated in HD males during the recovery phase but resolved in females. An increased incidence and magnitude of positive urine protein reactions (Days 90/91) at all doses in both sexes were of uncertain significance based on lack of dose-relation and corresponding microscopic findings in the kidney.
Gross pathology	Large thyroid was observed in two HD males that corresponded with follicular cell hypertrophy at terminal euthanasia. Higher number of red colored mandibular lymph node was observed in HD rats (4/10) compared to controls (2/9) recovery euthanasia.

Parameters	Major Findings
Organ weights	Thyroid/parathyroid and testes weight ratios (% body weight) were increased compared to controls at the end of dosing phase, which resolved at the end of recovery period. Thyroid/parathyroid increased ratios: +5, +7, +13 and +11, +2, +14 for male and female rats at LD, MD and HD, respectively. Testes increased ratios: +4, +13, +10% for male at LD, MD and HD, respectively.
Histopathology Adequate battery: Yes	• Thyroid follicular hypertrophy (minimal to moderate) increased in severity with dose increment at the end of dosing, resolved by the end of recovery phase. This finding corresponded to higher thyroid/parathyroid weight and large thyroids macroscopic findings. • Prostate did not present any microscopic findings except minimal to slight increase in the severity of Ki67-positive epithelial cells staining in HD males, which showed trend of recovery at the end of the recovery period. • Females developed neoplasms including mammary adenocarcinoma (one LD), stromal polyp in the uterus (one HD), benign C-cell adenoma of the thyroid (one HD). These findings are spontaneous in this rat strain and age.
Seminology	No iptacopan-related effects were observed at the end of the study.
Alternative Pathway Complement Activation (non-GLP)	Lack of AP activation in the vehicle-treated control group prevented assessments of iptacopan-related AP activity in rats.
Hormone Analysis (non-GLP)	Hormones of the pituitary-testis axis (FSH, LH, testosterone, androstenedione, and dihydrotestosterone) and hormones of the pituitary-thyroid axis (TSH, T3, T4, and rT3) were evaluated. • T3 levels in HD rats were increased during the dosing period and corresponded with T4 increased levels on specific weeks. These findings were no longer noted during the recovery phase.
Metabolism (non-GLP)	All metabolites identified (M1, M2, M6, M7, M8, M8a,c,d, M9 and M10) have been previously characterized in other studies. Metabolism pathways included glucuronidation, N-dealkylation, O-dealkylation, oxidation and dehydrogenation. However, the metabolite levels were not quantifiable in rats in this study.

Parameters	Major Findings
Toxicokinetics	

Table 100. Toxicokinetics Parameters After Iptacopan Treatment in Rats on Week 22

Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (µg/mL)	DN C_{max} [(µg/mL)/(mg/kg/day)]	T_{max} (h)	$AUC_{(0-24)}$ (µg·h/mL)	DN $AUC_{(0-24)}$ [(µg·h/mL)/(mg/kg/day)]
2	50	M	7.21	0.144	0.542*	45.7	0.914
		F	5.87	0.117	0.575*	30.9	0.617
		MF	6.54	0.131	0.558*	38.3	0.766
3	150	M	35.5	0.237	0.542*	101	0.672
		F	26.5	0.176	1	99.3	0.662
		MF	29.0	0.193	0.542*	100	0.667
4	750	M	63.9	0.0851	3	295	0.394
		F	65.2	0.0869	3	369	0.493
		MF	64.5	0.0860	3	332	0.443

Source: Applicant's submission
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; DN, dose-normalized; F, female; h, hour; M, male; MF, average of male and female; T_{max}, time to maximum concentration

Source: Reviewer's analysis
Abbreviations: AP, alternative pathway; ECG, electrocardiogram; FSH, follicle-stimulating hormone; GLP, good laboratory practice; HD, high dose; LD, low dose; LH, luteinizing hormone; M, metabolite; MD, mid dose; rT3, reverse triiodothyronine; TSH, thyroid stimulating hormone; T2, Triiodothyronine; T3, triiodothyronine; T4, Thyroxine

Study 1470220/ LNP023: 2 Week Oral (Gavage) Repeat Dose Toxicity Study With a Rising Dose Phase, Including Non-Invasive Telemetry in Male Dogs:

Key Study Findings

- The NOAEL was determined at 300 mg/kg/day, based on mortalities, adverse microscopic findings and iptacopan exposure to cerebrospinal fluid and brain tissue at HD.

Table 101. Study Information, Study 1470220

Study Features and Methods	Details
GLP compliance:	No
Dose and frequency of dosing:	• Single rising doses 50, 100, 300, 600, or 1000 mg/kg/day • Repeat-doses 0, 100 (LD), 300 (MD), or 1000 (HD) mg/kg/day, once daily for 2 weeks
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Dog/Beagle
Number/sex/group:	3/male/group
Age:	47-63 weeks
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	There was no deviation from the study protocol altering the interpretation of results or the integrity of the study.

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; HD, high dose; LD, low dose; MD, mid dose

Table 102. Observations and Results, Study 1470220

Parameters	Major Findings
Mortality	Iptacopan-related deaths occurred at HD (2/3)
Clinical signs	• Single rising doses were generally well tolerated except the clinical signs of dose-related incidences of vomiting and salivation. • Repeat-dose study presented iptacopan-related effects mainly at the HD on clinical signs of toxicity including salivation, vomiting, subdued/sluggish behavior, head shaking and staggering, convulsion, partially closed eyelids, and death in one of the two animals (# 14M). These clinical signs are likely from the high exposure of iptacopan in CSF and brain (6-fold higher compared to LD).
Body weights	Lower body weight gain was noted with iptacopan-related change in food consumption at MD and HD.
ECG	Increased heart rate and slight increase in QRS, increased QT-interval and QTc interval were noted compared to pre-dose baseline at the MD and HD.
Hematology	• Fibrinogen increase was noted at the end of 2 week repeat-dosing with HD. • Decreases in reticulocytes and mean corpuscular volume (MCV) in MD and HD and decreases in eosinophil and/or lymphocyte counts in HD males were noted
Clinical chemistry, urinalysis, gross pathology, organ weights	No iptacopan-related findings were observed.
Histopathology Adequate battery: Yes	Iptacopan-related findings at the HD were inflammation and/or erosion/ulcer in the esophagus, stomach and duodenum, cardiomyocyte degeneration in the heart, tubular degeneration in the kidney, follicular cell hypertrophy in the thyroid (also observed at MD), hepatocyte vacuolation in the liver, lymphoid atrophy in the thymus, decreased cellularity in the mandibular lymph node and degranulation in the pancreas.
Iptacopan in CSF and brain tissue	• Iptacopan was measurable in all CSF and brain tissue samples collected on Day 15 with exposure generally proportional across all dose groups. • One HD dog (M14) which was in a moribund state, and the mean brain tissue exposure was 6-fold higher compared to MD and LD. High exposure to iptacopan is likely associated with the poor condition leading to mortality.

Parameters	Major Findings
Gene expression analysis of heart Study DIS-r1470220	• Iptacopan-related dose dependent modulation of gene signatures [Cardiac biomarkers for prognosis/survival of heart failure (SPP1, NPNT, and VIPR2)] were observed at ≥LD. • Cardiomyocyte adrenergic and calcium signaling, and heart pacing gene signatures were downregulated at LD (transient) while upregulation of these genes were observed at MD. • At ≥LD, blood pressure regulation and relaxin pathway gene signatures were upregulated, while cardiomyocyte contraction gene signature was downregulated. This finding is likely a cardiovascular compensatory action to hemodynamic effect. • At LD and MD, dose-dependent upregulation of genes associated with adaptive changes including heart fibrosis/repair, ischemia/hypoxia and angiogenesis gene signatures were observed. This upregulation is likely associated with the promotion of heart regeneration and post-ischemia healing. • Genes associated with cardiomyocyte energy metabolism (cardiomyocyte fatty acid oxidation) were modulated and thyroid hormone signaling pathway gene signature downregulation was also observed. • Heart hypertrophy/remodeling GPCR:cAMP/cGMP/MAPK/AMPK pathway and RAS/PI3K/AKT pathway gene were mostly upregulated at MD (vs. downregulated at LD), which suggests a heart adaptation /protection hemodynamic effect caused by iptacopan were present at LD but not at MD.

Toxicokinetics
Systemic exposure (C_{max} and AUC_{0-24}) to iptacopan increased with dose increment in dose-proportional manner in general. T_{max} ranged from 1 to 3 hours.

Table 103. Toxicokinetic Parameters After Iptacopan Treatment in Dogs for 2 Weeks

Dose (mg/kg)	StudyDay	n	AUC_{0-24h} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)
			Mean	Mean	Mean
100	1	3	558000	68700	3.00
	14	3	561000	84700	1.00
300	1	3	2020000	146000	3.00
	14	3	2280000	200000	3.00
1000	1	2	2370000	189000	3.00
	14	1	5600000	349000	3.00

Source: Applicant's submission
Abbreviations: n, number of subjects; AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; h, hour; T_{max}, time to maximum concentration

Source: Reviewer's analysis
Abbreviations: AKT, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; C_{max}, maximum plasma concentration; CSF, cerebrospinal fluid; ECG, electrocardiogram; F, female; GPCE, G protein coupled receptor; HD, high dose; LD, low dose; M, male; MAPK, mitogen-activated protein kinase; MCV, mean corpuscular volume; MD, mid dose; NPNT, nephronectin; PI3K, phosphoinositide 3-kinase; QRS, QRS complex; QT, QT interval; QTc, corrected QT interval; RAS, rat sarcoma; SPP1, secreted phosphoprotein 1; T_{max}, time to maximum concentration; VIPR2, vasoactive intestinal peptide receptor 2; vs, versus

Study 1470568/ 4-Week Oral (Gavage) Toxicity Study in Dogs With Non-Invasive Telemetry and a 4-Week Recovery Period:

Key Study Findings

- The NOAEL was determined at 50 mg/kg/day (C_{max}=38700 ng/mL, AUC_{0-24h}= 238500 ng·h/mL) based on irreversible microscopic findings including testicular germ cell exfoliation, cell debris in epididymis, and cardiomyocyte degeneration at HD.
- Target organs of toxicity included male reproductive system and heart.

Table 104. Study Information, Study 1470568

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 15 (LD), 50 (MD), or 300 (HD) mg/kg/day
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Dog/Beagle
Number/sex/group:	5/sex/group (control, HD; 2/sex/group for recovery phase), 3/sex/group (LD, MD)
Age:	9.5-10 months
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	There was no deviation from the study protocol altering the interpretation of results or the integrity of the study.

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; HD, high dose; LD, low dose; MD, mid dose

Table 105. Observations and Results, Study 1470568

Parameters	Major Findings
Mortality, clinical signs, ophthalmoscopy, hematology, urinalysis, gross pathology	No iptacopan-related effects were observed.
Body weights	At HD, one male and 2 females presented body weight losses -0.4 to 0.6 kg on Day 8. Dietary supplement was provided until improvement was seen and the body weight loss was improved after 1 week.
ECG	• Iptacopan-related increased heart rates were observed at Weeks 1 and 4 at HD in females, and on Day 2 at all doses (+27%, +41%, and +71% at LD, MD, and HD, respectively) and during week 4 at HD (+125%) in males. • The effects on heart rate peaked at 1-3 hours post-dose and returned to control level ~ 5hours post-dose. • Decreased PR interval secondary to increased heart rate was observed.
Clinical chemistry	Total bilirubin level was increased with dose-dependency, which corresponded with histopathological findings of bile duct hyperplasia and pigment (suspected of bile) in Kupffer cells. This finding was resolved by the end of recovery phase.

Parameters	Major Findings
Organ weights	• Thyroid weights were increased with dose dependency in iptacopan-treated animals compared to controls. Corresponding histopathological finding of thyroid follicular hypertrophy was noted. • Testis and epididymis weights were decreased at HD.
Histopathology Adequate battery: Yes	Heart • Cardiomyocyte degeneration/necrosis (minimal to mild) was present in males (2/3) and in females (1/3) at HD, which was characterized by myocyte degeneration/necrosis associated with inflammatory cells predominantly in the papillary muscle of the left ventricle. There was no corresponding cardiac damage based on no change in cardiac biomarkers of cardiac Troponin I (cTnI) and N-terminal pro a-type natriuretic peptide (NTproANP). This finding is likely to be related to ischemia associated with the increased heart rate and decreased PR interval. • The recovery was partial due to one HD female showed minimal fibrosis in the papillary muscle in the heart. Liver • Bile duct hyperplasia (minimal) was observed in one HD female, which has corresponding finding of reversible increased level of total bilirubin. Thyroid • Follicular cell hypertrophy (minimal to moderate) was observed at all doses. This finding was resolved by the end of recovery phase. Testis and epididymis • Testicular germ cell exfoliation and oligospermia and cell debris in epididymis were noted with corresponding organ weight decrease at HD.
Hormone analysis	Thyroid hormones: Decreases in serum T4 correlated with hypertrophy without TSH level change was noted.

Parameters	Major Findings
Gene expression Study DIS-R1470567 Study DIS-R1470567c	• In the thyroid: Iptacopan dose-dependently upregulated a thyroid follicular cell gene signature; genes involved in thyroid hormone biosynthesis, and iron-binding gene signature and down regulated cathepsin K, which is important for T4 liberation (Friedrichs et al. 2003). These gene expression changes are aligned with microscopic finding of thyroid follicular cell hypertrophy. Although, hypertrophy did not result in T3 and T4 serum level which translates to impaired hormone synthesis and/or release. • In the liver: CYP1A2 and some metabolism associated genes are upregulated by iptacopan at HD, which could be secondary effect from body weight and diet change. Liver metabolism and thyroid hormone transport defects are not likely the primary cause of thyroid follicular hypertrophy. • In the heart: No iptacopan-related effects on cardiac biomarkers (cTnI and NTproANP). Iptacopan-related effects on transcriptional changes in the heart were seen at HD, which include upregulation of heart failure cardiac biomarker (SPP1, NPNT, NPYR and VIPR2), heart pacing and cardiomyocyte contraction, adrenergic and calcium signaling gene signature. Blood pressure regulation and relaxin pathway gene signatures, genes associated with adaptive changes (GPCR, RAS, Wnt pathway etc.) were downregulated at HD. The changes seen are likely responses to the CV hemodynamic effects at HD leading to tachycardia and cardiomyocyte degeneration.
Thyroid peroxidase (TPO) activity Study DIS-R1470567b	Thyroid peroxidase (TPO) activity was analyzed to investigate the correlation of thyroid follicular cell hypertrophy and decreased T4 levels observed in dogs at ≥LD. The results presented no inhibition of TPO by iptacopan in dog thyroid microsomes in vitro up to 100µM.

Parameters	Major Findings
Toxicokinetics Systemic exposure (C_{max} and AUC_{0-24h}) to iptacopan increased with dose increment in dose-proportional manner in general. T_{max} ranged from 0.5 to 3 hours. T_{max} was 3-7 hours for the rising dose phase and 1-3 hours for the repeat dose phase. Accumulation of iptacopan were not observed.	

Table 106. Toxicokinetic Parameters After Iptacopan Treatment in Dogs on Dosing Day 25

Dose(mg/kg/day)	Day	Gender	AUC_{0-24h} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (hour)
15	1	Male	83200	11900	1.00
		Female	75600	13100	0.833
		MF	79400	12500	0.917
	25	Male	91800	14100	0.833
		Female	88000	13400	1.00
		MF	89900	13750	0.917
50	1	Male	230000	33600	1.00
		Female	230000	36400	1.00
		MF	230000	35000	1.00
	25	Male	253000	41200	0.833
		Female	224000	36200	1.00
		MF	238500	38700	0.917
300	1	Male	1790000	137000	2.60
		Female	1470000	132000	2.60
		MF	1630000	134500	2.60
	25	Male	2220000	215000	3.00
		Female	1810000	188000	2.20
		MF	2015000	201500	2.60

Source: Applicant's submission
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; MF, average of male and female; T_{max}, time to maximum concentration

Source: Reviewer's analysis
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; cTnI, cardiac troponin; CV, cardiovascular; CYP, cytochrome P450; ECG, electrocardiogram; F, female; GPCR, G protein-coupled receptors; HD, high dose; LD, low dose; M, male; MCV, mean corpuscular volume; MD, mid dose; NPNT, nephronectin; NPYR, neuropeptide Y receptor; NTproANP, N-terminal pro a type natriuretic peptide; QRS, QRS complex; QT, QT interval; QTc, corrected QT interval; RAAS, renin-angiotensin system; RAS, rat sarcoma; SPP, secreted phosphoprotein; T_{max}, time to maximum concentration; TPO, Thyroid peroxidase; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, Thyroxine; VIPR, vasoactive intestinal peptide receptor; Wnt pathway, wingless related integration site

Study 1570194/ LNP023: 13 Week Oral (Gavage) Administration Toxicity Study in the Dog Followed by an 8-Week Recovery Period

Key Study Findings

- The NOAEL was determined at 5 mg/kg/day in males and at 30 mg/kg/day in females (C_{max}=4390 and 22600 ng/mL, and AUC_{0-24h} = 35500 and 149000 ng·h/mL, respectively) based on adverse findings in testis and epididymides and inflammatory changes in liver.
- Adverse findings were observed in testes (tubular degeneration) and epididymis (cell debris in the lumen) at MD and HD, which resolved partially at the end of recovery period in males. Lymphoid depletion observed at HD did not fully resolve at the end of recovery period. Inflammatory changes (mixed cell infiltration with single cell necrosis in liver and neutropenia with increased monocyte, globulin and fibrinogen) were observed at MD and HD.
- Target organs of toxicity included male reproductive system, lymphoid tissues and liver.

Table 107. Study Information, Study 1570194

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 5 (LD), 30 (MD), or 150 (HD) mg/kg/day, once daily
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose Type 15 cPs + 0.5% w/w and Tween 80 (Polysorbate 80)
Species/strain:	Dog/Beagle
Number/sex/group:	5/sex/group (control, HD; 2/sex/group for recovery phase), 3/sex/group (LD, MD)
Age:	55-59 weeks
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	There were no deviations from the study protocol altering the interpretation of results or the integrity of the study.

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; HD, high dose; LD, low dose; MD, mid dose

Table 108. Observations and Results, Study 1570194

Parameters	Major Findings
Mortality	No mortality occurred.
Clinical signs	Salivation was noted at MD (1/3) and HD (1/5) in males and soft brown feces was observed in one HD female (1/5).
Body weights	Body weight gain decrease occurred in ~34% and 58% of males and females at the HD, respectively. The change resolved at the end of recovery period.
ECG	Mean heart rate was increased (~30% in males, 20% in females) at approximately 3 hours post-dose on Day 2 in HD animals. The changes in heart rate were accompanied by the expected secondary changes in RR and QT intervals.
Hematology	Findings consistent with infection/inflammation were noted including decreased neutrophils, white blood cells, indicators of red blood cell mass, platelet count and albumin concentrations in one HD male and minimal neutropenia with decreased neutrophil counts and increased monocyte and fibrinogen concentrations in one HD female.
Clinical chemistry	• Increased monocyte counts and/or decreased neutrophils, likely contributed to the clinical condition and other changes in hematology and coagulation parameters were found at HD. • Minimally to slightly increased total bilirubin concentration (2-fold increase compared to pretreatment) was observed in one HD male (# 15) with a trend of recovery at the end of the recovery. This change in a single animal was considered of uncertain relationship to iptacopan
Ophthalmoscopy, Urinalysis Gross pathology	No iptacopan-related findings were observed.
Organ weights	• Thyroid weight ratio (% body) increased at MD and HD (+22% and +46%) in males and at ≥LD (+~26%) in females with corresponding microscopic findings of follicular cell hypertrophy. • Organ weight ratio (% body) of prostate, testis and epididymis were increased by +52%, +40%, and +39%, respectively at HD.

Parameters	Major Findings
Histopathology Adequate battery: Yes	Liver • Inflammatory changes with the presence of single cell necrosis was observed in a few HD animals associated with an increase in severity above background of diffuse mixed cell infiltrate especially in the periportal areas, in one HD male (Animal 14) and one HD female (Animal 114). • Minimal to mild hepatocyte pigment, and an increase in severity above background of Kupffer cell pigment were recorded in one male and one female at HD (Animals 14 and 112). The presence of lipofuscin and iron were detected. Staining for bilirubin was negative in all. Bile duct hyperplasia was recorded in two males and one female at HD (Animals 12, 13 and 112). • Bile duct hyperplasia with an increase in the number of small bile ducts in the periportal areas were observed at HD. • At the end of the recovery period, Iptacopan-related findings in the liver had resolved. Thyroid • Follicular cell hypertrophy occurred at ≥LD, and the changes resolved at the end of recovery period. Male reproductive organs • Decrease in motility and velocity were observed at HD (Animals 12 and 15) compared to pretreatment, yet control animals (Animal 3 and 4) also presented similar findings. • Iptacopan-related tubular degeneration in the testis and cell debris in the epididymis were observed at MD and HD, and these findings were partially reversed at the end of recovery period. Lymphoid tissues • Increase in incidence of lymphoid depletion was observed in the mesenteric lymph node of MD and HD animals and in the mandibular lymph node of HD males. • Lymphoid depletion was noted in the spleen of one HD female (Animal 112) with reduction in the size and number of germinal centers and paracortex in the lymph nodes and white matter of the spleen. • Iptacopan-related findings showed partial recovery at the end of recovery period. Bone marrow • Iptacopan-related minimal increase of myeloid:erythroid (M:E) ratio with corresponding increase of % maturing myeloid cells and decrease of % maturing erythroid cells.
Hormone analysis	• Transient increase of TSH was noted in HD male (Animal 16) on Day 47 whereas decreased T4 was noted in other HD male (Animal 13) on Day 89. These were considered unrelated to iptacopan based on lack of corresponding findings. • No iptacopan-related changes in the levels of triiodothyronine (T3), thyroxine (T4) and thyroid stimulation hormone

Parameters	Major Findings
Mechanism analysis	• Thyroid pathway associated genes and gene signatures for thyroid follicular cells, iron binding, endo-lysosome or mitochondria identified in the 4-week dog study (with higher exposures) were not modulated by iptacopan up to HD in this 13-week study. • No other major transcriptional change in the thyroid gland was observed after iptacopan treatment up to HD. • Gene expression profiling showed that LPN023 did not have a major effect on the global transcriptional profile of the testis in this study, however additional assessments mapping of active regions of the epigenome in testis tissue identified enrichment for testis-determining transcription factors SRY and SOX 5 (See Study No.1570194). The evidence suggests the effects on male reproductive organs in dogs may be due to epigenetic changes in genes regulating spermatogenesis, although exposures are not anticipated to be achieved clinically that may result in these effects. • Limited changes in androgen hormones were observed in this study likely due to compensatory mechanisms.

Toxicokinetics
Systemic exposure (C_{max} and AUC_{0-24h}) to iptacopan increased with dose increment in dose-proportional manner. T_{max} ranged from 0.5 to 3 hours. Sex difference in exposure or accumulation of iptacopan were not noted.

Table 109. Toxicokinetic Parameters After Iptacopan Treatment for 13 Weeks in Dogs

Dose (mg/kg/Day)	Study Day	Gender	AUC_{0-24h}	C_{max}	T_{max}
5	1	Male	28200	4050	0.5
		Female	23200	3580	0.5
		MF	25700	3815	0.5
	89	Male	35500	4390	0.5
		Female	32700	4000	0.5
		MF	34100	4195	0.5
30	1	Male	113000	18100	1
		Female	105000	21000	1
		MF	109000	19550	1
	89	Male	148000	25600	0.5
		Female	149000	22600	1
		MF	148500	24100	0.75
150	1	Male	576000	62900	3
		Female	607000	74300	3
		MF	591500	68600	3
	89	Male	733000	75000	1
		Female	611000	79800	1
		MF	672000	77400	1

Source: Applicant's submission
Dose unit = mg/kg/day; TK units: ng*h/mL for AUC_{0-24h}, ng/mL for C_{max}, hours for T_{max}.
* Median instead of mean reported for $T_{max.}$
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; MF, average of male and female; TK, toxicokinetic; T_{max}, time to maximum concentration

Source: Reviewer's Analysis
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; ECG, electrocardiogram; HD, high dose; LD, low dose; LPN023, iptacopan; MD, mid dose; M.E., myeloid erythroid; QT, QT interval; RR, respiratory rate; SOX, SRY-box transcription factor; SRY, sex-determining region Y gene; T_{max}, time to maximum concentration; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, Thyroxine

Study 1570192/ LNP023: 39-Week Oral (Gavage) Administration Toxicity Study in the Dog Followed by a 27-Week Recovery Period

Key Study Findings

- One male early decedent occurred at HD based on moribundity (pale ears and gums, subdued/sluggish behavior, and cold to touch), which was likely from the hypo-regenerative anemia associated with bone marrow fibrosis and signs of inflammation (decrease of leukocyte parameters and albumin and increase of fibrinogen and liver enzymes).
- Thyroid weight increase with follicular hypertrophy were observed at HD, and reversible findings of testis weight decrease with testicular tubular degeneration and prostate weight increase occurred at MD and HD males.
- The NOAEL was determined at 5 mg/kg/day in males and at 30 mg/kg/day in females (C_{max}=4580 and 21000 ng/mL; AUC_{0-24h}= 39300 and 155000 ng·h/mL, respectively) based on iptacopan-related adverse findings at higher doses.
- Target organs of toxicity included thyroid, male reproductive system, lymphoid tissues, liver and bone marrow.

Table 110. Study Information, Study 1570192

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 5 (LD), 30 (MD), or 150 (HD) mg/kg/day, once daily
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose (Type 15 cPs) + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Dog/Beagle
Number/sex/group:	6/sex/group (control, MD, HD; 2/sex/group for recovery phase), 4/sex/group (LD)
Age:	50-58 weeks
Unique design:	All animals were administered Keyhole Limpet Hemocyanin (KLH) subcutaneously (inter-scapular region) on two occasions (Days 190 or 188 and 218 or 216 of the dosing phases for males and females, respectively) at approximately 2 hours post-dose and on Day 33 (females) and Day 35 (males) of the recovery phase for T cell dependent antibody response (TDAR) assay.
Deviation from study protocol affecting interpretation of results:	There were no deviations from the study protocol altering the interpretation of results or the integrity of the study.

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; HD, high dose; KLH, keyhole limpet hemocyanin; LD, low dose; MD, mid dose; TDAR, T cell dependent ant body response

Table 111. Observations and Results, Study 1570192

Parameters	Major Findings
Mortality	No iptacopan-related deaths occurred. One LD male (#D0104) was sacrificed moribund on dosing Day 236, and the cause of death was likely procedure-related dose aspiration based on the histopathological finding of slight inflammation associated with foreign material in the laryngeal ventricle at necropsy. One HD male (#D0306) was prematurely terminated on recovery Day 103 due to moribundity (pale ears and gums, subdued/sluggish behavior, and cold to touch) which was likely from the hypo-regenerative anemia associated with bone marrow fibrosis. Signs of inflammatory response is noted based on the decrease of leukocyte parameters and albumin and increase of fibrinogen and liver enzymes. Body Weight Reduced body weight gain (11%) was noted from dosing Week 34 and decreased body weight gain and food consumption was shown from recovery Day 29. Hematology • Increased fibrinogen concentration and decreased leukocyte parameters (neutrophil, lymphocyte, monocyte, and white blood cell) were observed which resolved at the end of recovery period. • Nucleated red blood cells (nRBC) presence and decreased indicators of red cell mass (RBC, packed cell volume, and hemoglobin concentration) and absolute reticulocyte counts were noted. • Reticulocyte counts were very low (8.4 x 10^9 cells/L). Clinical Chemistry • Decrease of albumin and increase of liver enzymes (ALT, AST, and ALP) were noted. Bone Marrow Smear • Erythropoiesis was evident based on marked decrease in indicators of red cell mass with corresponding findings of decreased absolute reticulocyte count, pale color of the marrow, marked fibrosis and slight increased trabecula bone in the femoral and sternal bone marrow. • Evidence of dis-hematopoiesis with frequent abnormal mitotic figures, binucleation, asynchronous maturation predominantly in the erythroid lineage, and to a lesser extent in the myeloid lineage with occasional hemophagocytosis were present in the bone marrow. • These changes in the myeloid cell line in the marrow were without the changes in the white blood cell count or corresponding leukocyte populations. • Corresponding findings of increased hematopoiesis in the spleen and liver was likely secondary to ineffective erythropoiesis in the bone marrow.

Continued

Table 111, continued

Parameters	Major Findings
Mortality (continued)	Histopathology • Findings potentially secondary to anemia were observed in liver (centrilobular hepatocyte degeneration, focal necrosis, extramedullary hematopoiesis – megakaryocytic) and spleen (hemopoiesis-early undifferentiated cells). • Pigment observed in hepatocytes (moderate) and Kupffer cells (slight) in liver and in tubular cells in the kidney were determined to be predominantly iron and lipofuscin, respectively. • Lymphoid atrophy was evident in thymus (marked) and spleen (slight) which is suspected to be caused by stress. Hepcidin plasma concentration was decreased in dosing Week 39 (-33%) and on recovery Day 103 (-19%) compared to pre-dose value in a HD male (#D0306)
Clinical signs	Vomiting at MD and HD and salivation in all groups (including control) were observed.
Body weights	One HD (#D0306) had reduced body weight gain (further information described in "Mortality"). Diet supplementation was provided to iptacopan-treated animals to aid appetence, which may have affected the body weight gain change.
ECG	• Iptacopan-related increased heart rate was observed at HD in males and females on dosing Day 2 with statistical significance and during Week 38 without the statistical significance, yet with notable increases with lesser magnitude compared to Day 2. • Decreases in the QT interval (as a reflective response to heart rate increase) were noted with statistical significance on dosing Day 2 in males and females and during Week 38 in males.
Hematology	One HD male (# D0306) presented iptacopan-related changes in hematological parameters (further information described in "Mortality"). Leukocytes • HD male showed delayed response in decreased number of leukocytes (-14%) at the end of recovery period. • HD females showed decreased number of leukocytes (-13%) at the end of dosing period which did not resolve by the end of recovery period. Fibrinogen • MD and HD males showed drug-related increase of fibrinogen in the plasma, while HD females showed slight decrease at the end of dosing period.
Clinical chemistry, urinalysis, gross pathology, and ophthalmoscopy	No iptacopan-related effects were observed.
Organ weights (% body weight)	• Testis weight ratio (% body) was decreased by -23% at HD compared to controls with corresponding finding of testicular tubular degeneration. • Prostate weight ratio (% body) was increased at MD (+39%) and HD (+20%) compared to controls without corresponding histopathological findings. • Thyroid/parathyroid weight ratio (% body) was increased by 37% in HD males which corresponds to the histopathological findings of thyroid follicular cell hypertrophy (which occurred at all doses).

Continued

Table 111, continued

Parameters	Major Findings
Histopathology Adequate battery: Yes	• Thyroid follicular cell hypertrophy was observed with increased incidence and severity in all iptacopan treated groups with dose dependency. • Testicular tubular degeneration (germinal epithelium with disruption of the epithelial architecture, increased numbers of necrotic or multinucleate cells) was observed in males at MD and HD with a corresponding finding of testis weight decrease at HD which was considered adverse. • Epididymis exhibited minimal to slight cell debris in the lumen of the tubules with increase in incidence and severity at MD or HD. • Kupffer cell pigment was noted in liver which was identified as iron containing hemosiderin. • Findings in liver and spleen, potentially secondary to anemic condition of HD male (#D0306) were observed (further information described in "Mortality"). <u>Immunohistochemistry</u> • Analysis for C3 in spleen and bone marrow (sternum and femur) of HD animals was inconclusive due to high background. • The result of staining for IgG did not present any iptacopan-related immune-mediated effects. • Lymph node and spleen didn't show any changes in intensity of staining for Ki67, CD4, CD8, and CD20 compared to controls, which indicates no iptacopan-related immune-mediated anemia
Bone marrow smears	No iptacopan-related findings were observed in bone marrow parameters in HD animals. • One HD male (#0306) showed evidence of erythropoiesis (further information described in "Mortality").
Seminology	No conclusion was made due to high variability across all dosing groups including controls in comparison with pre-dose.
Hormone analysis	<u>Hormones of the pituitary-thyroid axis</u>: TSH, T3, T4, and Reverse T3 • Transient increase of T3 in plasma at MD and HD during dosing Week 13 and 26 (not in Week 39) was noted in males. • TSH increase (equivocal) in plasma in 2 HD males was noted during dosing Weeks 26 (#D0301) or Week 39 (#D0306) • No iptacopan-related changes of T4 and reverse T3 levels were observed in plasma during the dosing phase up to 39 weeks. <u>Hormones of pituitary-gonad axis</u>: FSH, LH, Testosterone, Dihydrotestosterone, and Androstenedione • No iptacopan-related changes were observed in the levels of FSH, LH, testosterone, dihydrotestosterone, and androstenedione in plasma until the end of dosing phase up to 39 weeks.
Hepcidin analysis (non-GLP)	There were no significant changes in hepcidin plasma concentration in all animals except the HD male (#D0306) which showed decrease in dosing Week 39 (-33%) and on recovery Day 103 (-19%) compared to pre-dose value.
Pharmacodynamic analysis (non-GLP)	Evaluation of alternate complement pathway (AP) activity using an ex vivo MAC-deposition assay showed full inhibition of AP activity at MD and HD, and partial inhibition at LD.

Continued

Table 111, continued

Parameters	Major Findings
Immunophenotyping	Circulating T lymphocytes (CD3+, CD3+/CD4+, and CD3+/CD8+) and B lymphocytes (CD21+) from dosing Days 174 (females)/176 (males) exhibited no noteworthy changes attributed to iptacopan treatment. HD females presented a slight transient reduction in B lymphocyte cell counts on dosing Day 199 (control group -50% vs. HD group -72%) which resolved by dosing Day 272.
T cell dependent antibody response (TDAR) assay (non-GLP)	Iptacopan did not impact B-cell response to Keyhole Limpet Hemocyanin (KLH) at pharmacologically active concentrations. The humoral responses (IgM and/or IgG) were robust, but slightly decreased following primary response anti-KLH at all doses compared to controls. Secondary recall response anti-KLH was decreased in females at MD and HD.
C-reactive protein (CRP) analysis	There were no remarkable changes in the level of CRP of the prematurely terminated HD male (#D0306).
Metabolite analysis (non-GLP)	The metabolites identified in the HD animals plasma were M1, M2, M6, M7, M8, M8a,c,d, M9 and M10 which were characterized previously in other DMPK studies, and the involved metabolism pathways included glucuronidation, N-dealkylation, O-dealkylation, oxidation and dehydrogenation.
Molecular profiling: transcription factor analysis for testicular toxicity	Iptacopan-related transcription factor motif enrichment of the transcription factors (SRY, SOX5, ALX3, BSX, HOXA9, NEUROG1, NFATC2, RARB, MEIS1, and TGIF2) in the at the end of dosing phase. The levels of upstream regulators (e.g., KDM3A) and down-stream targets of SRY showed similar trend which could suggest a potential role of these testis-determining transcription factors in testis toxicity in dog.

Continued

Table 111, continued

Parameters	Major Findings
Toxicokinetics	
	Systemic exposure (C_{max} and AUC_{0-24h}) to iptacopan increased with dose increment with dose proportional matter and there were no accumulation or sex difference in exposure.

Table 112. Toxicokinetic Parameters in Dogs After Iptacopan Treatment for 39 Weeks

Dose (mg/kg/Day)	Study Day	Gender	AUC_{0-24h}	C_{max}
5	1	Male	29100	3960
		Female	29500	4020
		MF	29300	3990
	273	Male	39300	4580
		Female	37900	4710
		MF	38500	4650
30	1	Male	139000	20300
		Female	132000	19300
		MF	136000	19800
	273	Male	183000	25000
		Female	155000	21000
		MF	169000	23000
150	1	Male	794000	71400
		Female	417000	55100
		MF	605000	63200
	273	Male	840000	88200
		Female	628000	65900
		MF	734000	77000

Source: Applicant's submission
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; MF, average of male and female

Source: Applicant's submission
Abbreviations: AP, alternative pathway; ALP, alkaline phosphatase; ALT, alanine transaminase; ALX, ALX homeobox; AST, aspartate aminotransferase; AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; BSX, brain-specific homeobox; CD, cluster of differentiation; C_{max}, maximum plasma concentration; CRP, C-reactive protein; C3, compliment component 3; DMPK, drug metabolism and pharmacokinetics; ECG, electrocardiogram; FSH, follicular stimulating hormone; GLP, good laboratory practice; HD, high dose; HOX, homeobox protein; IgG, immunoglobulin G; IgM, immunoglobulin M; KDM, lysine demethylase; KLH, keyhole limpet hemocyanin; LD, low dose; LH, luteinizing hormone; M, metabolite; MAC, membrane attack complex; MD, mid dose; MEIS, meis homeobox; NEUROG1, neurogenin 1; NFATC, nuclear factor of activated T cells; nRBC, nucleated red blood cells; QT, QT interval; RARB, retinoic acid receptor beta; RBC, red blood cells; SOX, SRY-Box transcription factor; SRY, sex-determining region Y gene; TDAR, T cell dependent antibody response; TGIF2, TGFB induced factor homeobox 2; T_{max}, time to maximum concentration; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, Thyroxine; vs, versus

Mechanistic Studies

Table 113. Summary of Mechanistic Studies

Study No. / Study	Findings
Study RD-2019-00025 NVP-LNP023-AA-13 (NA-04-WV99) effects in rat Thyroid receptor binding assay	Direct binding of iptacopan to rat TIIa and TIIP thyroid hormone receptors was evaluated by using a filter binding assay procedure for thyroid hormone receptors. The radioligand binding assay incubated [^{125}I]triiodothyronine with receptor proteins extracted from washed liver nuclei to measure thyroid hormone receptor activity. Iptacopan did not show specific binding activity to the thyroid hormone receptor at concentrations up to 100µM.
Study 1820225 In vitro assessment of androgen and thyroid hormone receptor reporter activities	In vitro androgen and thyroid hormone receptor assays were used to evaluate iptacopan's ability to modulate androgen and/or thyroid hormone receptor activities on target promoters. Commercially available androgen receptor (AR) and thyroid hormone receptor (THα and THβ) luciferase reporter assay evaluated 200µM LNP023 at 3 different agonist concentrations. • No cytotoxicity was observed when reporter cells were exposed to iptacopan at doses up to 200 µM as determined by ATP measurement in cell lysate and lactate dehydrogenase activity in supernatants. • A non-dose-dependent but statistically significant increase in androgen receptor (AR) reporter activities was observed. These findings were not considered to be biologically relevant. • At concentrations ≥ 80µM, LNP023 caused a statistically significant decrease in L-Triiodothyronine (T3) agonist activity on the thyroid hormone receptor reporters THα and THβ in a dose-dependent manner.
Study DIS-R1720270 Testicular toxicity evaluation of LNP023 on the ex vivo rat model, (b) (4) (Non-GLP) Study DIS-R1720277 Testicular Toxicity evaluation of LNP023 on the ex vivo dog model, (b) (4) (Non-GLP)	To evaluate the testicular toxicity of iptacopan, ex vivo (b) (4) models for rat and dog were analyzed. The culture contains somatic cells (mainly Sertoli cells) and germ cells at different stage of spermatogenesis: spermatogonia, young spermatocytes I/middle to late pachytene spermatocytes I, secondary spermatocytes, and round spermatids. The culture was maintained for 21 days and iptacopan was added at concentrations of 2 µM, 20 µM, and 200 µM. Results support a direct effect of iptacopan on the testis as evaluated in primary cultures of rat or dog seminiferous tubules. • Iptacopan did not exhibit cytotoxic effects at concentrations tested in rat and dog models. • Blood-testis barrier: Slight decrease in TEER at 200 µM was noted without dose dependency in rat model. Tight and gap junctions modulating genes were modulated in dog model. • Increase of somatic cells on Day 7/D8 as well as modulated Sertoli cells specific genes (including androgen receptor upregulation) were observed at all concentrations in rat and dog models. • No negative effect on the total number of germ cells, rather increase was noted at some time points and concentrations tested.

Study No. / Study	Findings
	• In Rat model: Transient decrease in the number of spermatogonia and round spermatids was noted at 200 µM at D7/D8, with decreases in the expression of genes specific for those cell types. In contrast, the numbers of round spermatids and spermatogonia were overall increased on D14/D15 and D21/D22 with strong induction of genes specific for round spermatids (TP1, TP2, PRM3) and spermatogonia (VASA, RET), partly following a bell-shaped concentration-response relationship with most pronounced effects at the mid-dose (20 µM) tested. • In Dog model: Increased number of spermatogonia and secondary spermatocytes on D7/D8 with increased expression of genes specific for spermatogonia, pachytene spermatocytes, and round spermatids. On D20/D21, spermatogonia number was unchanged but increase of pachytene spermatocytes and decrease of secondary spermatocytes and round spermatids were noted at all concentrations tested. • Iptacopan effect on testis of rat vs dog: Some kinetic differences on germ cell populations were noted. • In dog culture, transient enhancement of spermatogenic process after one week and negative effects after 3 weeks of iptacopan treatment was noted. • In rat, transient negative effect on the spermatogenetic process after 1 week, which resolved by the end of week 3). • Maturity (or sexual maturity) differences between species could be the factor attributing to these differences.

Source: Reviewer's analysis
Abbreviations: AR, androgen receptor; ATP, adenosine triphosphate; D, day; GLP, good laboratory practice; LNP023, iptacopan; NVP-LNP023, Novartis Pharmaceuticals iptacopan; PRM, protamine; RET, reticulocytes; TEER, transendothelial resistance; TH, thyroid hormone receptor; TP, transition protein; T3, triiodothyronine; vs, versus

Phototoxicity

Table 114. Summary of Phototoxicity Studies

Study No /Study Type GLP Status	Test System	Study Design/ Concentrations	Remarks
Study 1315506/ In vitro Phototoxicity Test GLP: No	Mouse Balb/c3T3 fibroblast cell line	Assessment of EC_{50} with/without simulated sunlight (normalized to 5 J/cm2 of UVA) up to solubility limit (160pM)	Weak photo-irritation potential was detected (PIF 7.0), EC_{50}=142µM The relative risk at the clinical dose is minimal based on the exposure multiple of 14-fold based on popPK C_{max} of 4163 ng/mL(10µM)

Study No /Study Type GLP Status	Test System	Study Design/ Concentrations	Remarks
Study 1470564/ murine photo-locol Lymph Node Assay GLP: Yes	Mouse (BALB/c)	6F/group, p.o. gavage 0,100. 300, or 1000 mg/kg/day ± irradiation, 3 days Irradiation with simulated sunlight (normalized to 10 J/cm2 of UVA) after each treatment	Low phototoxic potential. Minimal though statistically significant effects on ear weights at 100 and 300 mg/kg and sporadic/transient erythema in different groups of iptacopan-treated mice exposed to simulated sunlight.

Source: Reviewer's analysis
Abbreviations: C_{max}, maximum plasma concentration; EC_{50}, half maximal effective concentration; F; female; GLP, good laboratory practice; PIF, photo irritation factor; p.o., by mouth; UVA, ultraviolet A

Local Tolerance

Table 115. Summary of Local Tolerance Studies

Study No/ Study Type GLP Status	Test System	Study Design/ Concentrations	Remarks
Study 20253153/ In vitro Skin Irritation Test GLP: Yes	Standardized human three-dimensional epidermal system (Episkin)	Topical application for 15 minutes	No evidence of irritation occurred with iptacopan treatment.
Study 20253153/ contact sensitizing potential with the murine local lymph node assay GLP: Yes	Mouse (BALB/c)	6F/group, topical, once daily, 3 days Murine topical (dermal) local lymph node assay (LLNA TIER I)	No sensitizing or irritating potential was observed related to iptacopan treatment.

Source: Reviewer's analysis
Abbreviations: F; female; GLP, good laboratory practice; LLNA TIER I, local lymph node assay TIER I

13.1.5.2. Genetic Toxicology

Table 116. Summary of Genetic Toxicology Studies

Study No./ Study Title	Key Study Findings
Study 1313007/ In Vitro Miniscreen Ames Test GLP compliance: No Study is valid: Yes	Iptacopan was evaluated for mutagenicity up to 500 µg/mL in *Salmonella typhimurium* in vitro. Iptacopan did not present any evidence of a mutagenic potential.
Study 1470563/ In Vitro Bacterial Reverse Mutation Assay GLP compliance: Yes Study is valid: Yes	For mutagenicity evaluation, iptacopan was treated at concentrations up to 5000 µg/mL in *Salmonella typhimurium* (Strain TA98, TA100, TA1535, TA97a, and TA102) in ± S9 metabolic activation. There was no evidence of mutagenicity observed.

Study No./ Study Title	Key Study Findings
Study 1314004/ Micronucleus Test In Vitro using TK6 Cells GLP compliance: No Study is valid: Yes	Iptacopan was tested up to 500 µg/mL in mutagenic micronucleus assay using Epstein-Barr virus transfected and immortalized TK6 cells ± S9 metabolic activation. Iptacopan did not induce numbers of cells containing micronuclei.
Study 1470562/ In Vitro Human Lymphocyte Micronucleus Assay GLP compliance: Yes Study is valid: Yes	Iptacopan was tested at 300, 400 or 459 µg/mL for 3+21 hours (± *S9)* or 24+24 hours (– S9) in an in vitro micronucleus assay in human peripheral blood lymphocytes. The frequencies of micronucleated binucleated (MNBN) cells were within the normal ranges and iptacopan did not increase micronuclei in human lymphocyte micronucleus assay.

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; IND, investigational new drug; MNBN, micronucleated binucleated; S9, mammalian liver post-mitochondrial fraction

Table 117. Summary of Genetic Toxicology of Impurities Studies

Study No./ Study Title	Key Study Findings
Study 1912581 Study 2012508 In Vitro Bacterial Reverse Mutation Assay GLP compliance: No Study is valid:	(b) (4) showed evidence of a mutagenic potential in the salmonella strain TA98 in ± S9 metabolic activation
Study2070174 In vitro micronucleus assay GLP compliance: Yes Study is valid: Yes	(b) (4) was found to induce increases in micronuclei when tested in cultured human peripheral blood lymphocytes for 24+24 hours in the absence of S9 metabolic activation.
Study 2070173 GLP compliance: Yes Study is valid: Yes	(b) (4) was assessed in a Pig-a gene mutation assay using red blood cells (RBC) and reticulocytes (RET) with additional micronucleus assessment in peripheral blood reticulocytes. Male Wistar Han rats were orally gavaged once daily at doses of 31.25, 62.50 and 125 mg/kg/day for 4 weeks. (b) (4) did not induce increases of Pig-a gene mutations or micronuclei in the mature erythrocytes or immature reticulocytes. Therefore, no genotoxic potential was detected.

Study No./ Study Title	Key Study Findings
Studies 1912571, 2012513, 2012516, 1212590, 2012501, 1612513, 1612506, 1012603, 2012503, 1912577, 1912578, 1912579, 1912580, 1912589 In Vitro Bacterial Reverse Mutation Assay GLP compliance: No Study is valid: Yes	For mutagenicity evaluation, impurities were treated at concentrations up to 5000 µg/mL in *Salmonella typhimurium* (Strain TA1535, TA98, TA100, TA97a, and TA102) in ± S9 metabolic activation. There was no evidence of mutagenicity observed.

Source: Reviewer's analysis
Abbreviations: GLP, good laboratory practice; Pig-a, phosphatidylinositol glycan biosynthesis class A protein; RBC, red blood cells; RET, reticulocytes; S9, mammalian liver post-mitochondrial fraction

13.1.5.3. Carcinogenicity

Study No/ Study Title: Study 1770876/ LNP023: A 26-Week Oral (Gavage) Administration Carcinogenicity Study in the Transgenic rasH2 Transgenic Mouse

Good laboratory practice (GLP) compliance: Yes

Key Study Findings

- There were no iptacopan-related statistically significant increase in incidence of any neoplasm in rasH2 mice.
- There was no statistically significant dose response in mortality in male and female rasH2 mice.
- The positive control, N-methyl-N-nitrosourea, (MNU), significantly increased incidences of malignant lymphoblastic lymphoma (multiple sites) and squamous cell papilloma (skin/subcutis including ear) in the skin in male and female rasH2 mice relative to control. There was a statistically significant higher mortality rate (21/25 males, 24/25 females) for the positive control, for which the cause of death was related to tumor findings.

Executive CAC Conclusions

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that there was no evidence of drug-related neoplasms in male and female mice for the 26-week study.

Table 118. Methods, Carcinogenicity Study in rasH2 Mice With Iptacopan Treatment for 26 Weeks

Parameter	Method Details
Dose and frequency of dosing:	Controls= 0 (water), 0 (vehicle) Positive control= N-methyl-N-nitrosourea (MNU) 75 mg/kg/day Iptacopan=100, 300, or 1000 mg/kg/day Once daily (Iptacopan), Once on Day 1 (MNU)
Route of administration:	Oral gavage (iptacopan), intraperitoneal injection (MNU)

Parameter	Method Details
Formulation/vehicle:	Vehicle for Iptacopan: 0.5% w/w methylcellulose Type 15 cPs, + 0.5% w/w and Tween® 80 (Polysorbate 80) Vehicle for Positive control (MNU): acidified physiological saline (150mM sodium chloride and 15mM sodium citrate in reverse osmosis water adjusted to pH 4.5 (±0.1) with 1 N hydrochloric acid)
Species/strain:	Mouse/ CB6F1-TgN (RasH2)
Number/sex/group:	25/Sex/Group
Satellite groups:	TK group: 3 or 10/Sex/TK Group control or iptacopan groups, respectively
Study design:	Toxicokinetic group was included in the study design
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Reviewer's analysis
Abbreviations: MNU, N-methyl-N-nitrosourea; TK, toxicokinetic

Study No/ Study Title: Study 1770877/ LNP023: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Rat

GLP compliance: Yes

Key Study Findings

- There were no dose-dependent or statistically significant iptacopan-related neoplastic findings noted in both males and females.
- The survival rate was lower in HD animals compared to vehicle control with statistical significance.
- Toxicokinetics: The exposure to iptacopan (based on C_{max} and AUC_{0-24}) increased with dose increment in approximate dose-proportional manner. There was no evidence of accumulation of iptacopan or sex difference in exposure. Time to maximum concentration ranged from 0.5 to 3 hours.

Executive CAC Conclusions

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that there was no evidence of drug-related neoplasms in male and female rats for the 104-week study.

Table 119. Toxicokinetics Parameters in Rats After Iptacopan Treatment for 26 Weeks

Dose Level (mg/kg/day)	Interval	Sex	Cmax (µg/mL)	Cmax/D [(µg/mL) / (mg/kg/day)]	Tmax (h)	AUC0-24 (h*µg/mL)	AUC0-24/D [(h*µg/mL) / (mg/kg/day)]
150 (Group 3)	Day 1	M	11.7	0.0781	0.500	61.8	0.412
		F	12.1	0.0807	1.00	57.6	0.384
		MF	11.5	0.0769	1.00	59.7	0.398
	Day 176	M	16.8	0.112	0.500	88.8	0.592
		F	14.7	0.0980	0.500	58.1	0.388
		MF	15.8	0.105	0.500	73.5	0.490
300 (Group 4)	Day 1	M	24.9	0.0830	1.00	162	0.542
		F	19.8	0.0660	0.500	118	0.394
		MF	21.5	0.0715	0.500	140	0.468
	Day 176	M	21.7	0.0722	0.500	170	0.568
		F	19.1	0.0635	1.00	136	0.454
		MF	19.0	0.0634	1.00	153	0.511
750 (Group 5)	Day 1	M	52.9	0.0705	3.00	497	0.662
		F	40.5	0.0539	0.500	501	0.667
		MF	41.4	0.0552	0.500	499	0.665
	Day 176	M	94.6	0.126	3.00	733	0.978
		F	61.6	0.0821	3.00	498	0.664
		MF	78.1	0.104	3.00	620	0.827

Source: Applicant's submission
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; D, day; F, female; h, hour; M, male; MF, average of male and female; T_{max}, time to maximum concentration

Table 120. Methods, Carcinogenicity Study in Rats With Iptacopan Treatment for 2 Years

Parameter	Method Details
Dose and frequency of dosing:	Controls= 0 (water), 0 (vehicle) Iptacopan=150 (low dose; LD), 300 (mid dose; MD), or 750 (high dose; HD) mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% w/w methylcellulose Type 15 cPs, + 0.5% w/w and Tween® 80 (Polysorbate 80)
Species/strain:	Rat/Wistar Han
Number/sex/group:	50/sex/group
Satellite groups:	TK group: 10/sex/control
Study design:	Toxicokinetic group was included in the study design dosing up to 26 weeks
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Reviewer's analysis
Abbreviations: HD, high dose; LD, low dose; MD, mid dose; TK, toxicokinetic

13.1.5.4. Reproductive Toxicology

Study 1870193/ LNP023: Oral (Gavage) Fertility Study in the Male Rat

GLP compliance: Yes

Key Study Findings

- The NOAEL was determined at HD 750 mg/kg/day (C_{max}=63900 ng/mL and AUC_{0-24h}=295000 ng·h/mL from the 26-week rat toxicology study at Week 22) based on lack of iptacopan-related findings.

Table 121. Methods, Fertility and Early Embryonic Development (FEED) Study in Male Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 50 (LD),150 (MD), or 750 (HD) mg/kg/day, once daily Males: 13 weeks prior to pairing, during pairing and up to the day prior to necropsy (up to 116 days) Females: No treatment. Mated females and their litters were terminated on Gestation Day (GD) 13
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose (Type 15 cPs) + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Rat/Wistar Han
Number/sex/group:	25/male/group
Satellite groups:	No satellite groups
Study design:	Standard FEED study design based on ICH S5(R3)
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Reviewer's analysis
Abbreviations: FEED, fertility and early embryonic development; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose

Table 122. Observations and Results of Fertility and Early Embryonic Development (FEED) Study in Male Rats

Parameters	Major Findings
Mortality	There were 4 deaths at LD (one male), MD (one male) and HD (2 males), The cause of death was considered incidental and not iptacopan-related
Clinical signs	Slight salivation and mouth rubbing at MD and HD.
Body weights and Food consumption	No iptacopan-related effects on body weights, body weight gains and food consumption.
Reproductive performance (mating or fertility index)	No iptacopan-related effects on mating or fertility index.
Sperm evaluations (count, motility, density, and morphology)	Morphological abnormalities of sperm were noted with statistical significance at MD and HD by 1.3% and 2.3% compared to controls (0.9%). But the result was within the historical control range and no corresponding findings were observed in microscopic evaluation of testes and epididymides.
Embryofetal survival, fetal weight and gravid uterine weight	No iptacopan-related effects observed on embryonic development.
Necropsy findings	No iptacopan-related noteworthy findings were observed
Toxicokinetics	No TK data available

Source: Reviewer's analysis
Abbreviations: FEED, fertility and early embryonic development; HD, high dose; LD, low dose; MD, mid dose; TK, toxicokinetic

Study 1770670/ LNP023: Oral (Gavage) Fertility and Early Embryonic Development Study in the Female Rat

GLP compliance: Yes

Key Study Findings

- The NOAEL was determined at 300 mg/kg/day based on the high incidence of pre- and post-implantation loss, increased number of resorptions and reduced number of live embryos for each female at the HD (C_{max}=33650 ng/mL and $AUC_{0\text{-}24h}$=178000 ng·h/mL, taken from the females of 4-week toxicology study 1470568 in rats).

Table 123. Methods of Fertility and Early Embryonic Development (FEED) Study in Female Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 100 (LD), 300 (MD), or 1000 (HD) mg/kg/day, once daily Males: No treatment Females: 2 weeks prior to pairing, during pairing and up to GD 6, and were terminated on GD 13
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose (Type 15 cPs) + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Rat/Wistar Han
Number/sex/group:	24/female/group
Satellite groups:	No satellite groups
Study design:	Standard FEED study design based on ICH S5(R3)
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Reviewer's analysis
Abbreviations: FEED, fertility and early embryonic development; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose

Table 124. Observations and Results of Fertility and Early Embryonic Development (FEED) Study in Female Rats

Parameters	Major Findings
Mortality	None
Clinical signs	No-iptacopan related findings observed.
Body weights	Pre-paring body weight gain (BWG) was dose-dependently increased and the BWG during GD 0-13 was dose-dependently decreased; However, the total body weight was similar to control on GD 13. The lower BWG during GD was not considered adverse.
Estrous cycling, Mating, pregnancy number	No iptacopan-related findings were observed. Females at LD presented statistically significantly lower outcomes for fecundity and fertility indices based on the high incidence of non-pregnant females. These findings were considered incidental based on the lack of dose-response.

Table 125. Body Weight Gain Percent Change in Female Rats

Body Weight Gain (BWG, %)	Iptacopan (mg/kg/day)			
	0	100	300	1000
Pre-paring	16.3g	+19.6	+35	+65.6
GD 0-13	51.3g	-4.3	-13.6	-20.9

Source: Reviewer's analysis
Abbreviations: BWG, body weight gain; GD, gestation day

Parameters	Major Findings
Necropsy findings Cesarean section data	No iptacopan-related macroscopic observations were recorded. Iptacopan-related higher % pre-implantation loss (2-fold), increased % post-implantation loss % (10-fold), increased number of early resorptions and reduced mean number of live embryos (-27%) were observed at HD compared to controls. Implantation losses for four HD rats ranged between 69.2 and 90% compared to the highest control value for pre-implantation loss of 54.5%. Increased % post-implantation loss occurred in MD (7.1%) compared to control, but it did not result in a reduction in the mean number of live embryos for each female. This finding was considered incidental because the historical control range for post-implantation loss in fertility studies is 3.5 to 9.8%.
Toxicokinetics	No TK data available

Source: Reviewer's analysis
Abbreviations: BWG, body weight gain; FEED, fertility and early embryonic development; GD, gestation day; HD, high dose; TK, toxicokinetic

Study 1670321/ LNP023: Oral (Gavage) Study of Embryo-Fetal Development in the Rat

GLP compliance: Yes

Key Study Findings

- Based on the absence of iptacopan-related maternal and fetal effects, the NOAEL for maternal (F0) and fetal (F1) generation was defined at the HD 1000 mg/kg/day (maternal exposure C_{max}=36,000 ng/mL and $AUC_{0\text{-}24h}$=278,000 ng·h /mL).

Table 126. Methods of Embryo-Fetal Development (EFD) Study in Female Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 100 (LD), 300 (MD), or 1000 (HD) mg/kg/day, once daily Dosed with iptacopan during GD 6-17, and were terminated at GD 21
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose (Type 15 cPs) + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Rat/Wistar Han
Number/sex/group:	24/female/group
Satellite groups:	No satellite groups
Study design:	Standard EFD study design based on ICH S5(R3)
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Reviewer's analysis
Abbreviations: EFD, embryo fetal development; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose

Table 127. Observations and Results

Parameters	Major Findings
Mortality	One HD female was prematurely terminated on GD 13 following observations of labored, noisy, and rapid breathing and piloerection.
Clinical signs	Piloerection was observed in MD and HD on GD 6 or 17.
Body weights	Transient decrease of food consumption was observed at HD for 4 days at the start of dosing, which did not alter the body weights or BWG.

Parameters	Major Findings
Necropsy findings Cesarean section data	Mean number of corpora lutea, implantation sites were not affected by iptacopan. The mean % pre-implantation loss was increased at MD and HD (+48%) and mean % post-implantation loss at HD (-19%) was decreased at HD compared to controls. The mean number of live fetuses showed minimal decrease in HD (-7%) compared to controls.
Necropsy findings Offspring	Dose-related fetal skeletal variations of reduced ossification of the parietal and interparietal bones of the skull, and delay in ossification were observed. Two fetuses in one HD litter had a malformation of a cyst on the left side of the parietal region of the head, without affecting development of skull, brain, or any other head-based structure. This finding occurred in a single litter, and it was considered unlikely related to iptacopan administration.
Toxicokinetics	Systemic exposure to iptacopan (C_{max} and AUC) increased with dose increment and the increase was in a less than dose proportional manner.

Table 128. Findings in Embryo after Maternal Exposure to Iptacopan

Iptacopan	(mg/kg/day)			
	0	100	300	1000
Number	**Litters/Fetuses affected**			
Skeletal variations				
Skull-incomplete ossification of the interparietal (fetuses/litters)	1/1	2/2	5/13	7*12
Skull-incomplete ossification of the parietal (fetuses/litters)	1/1	4/5	6*/11	7*12
Fetal malformations				
Skull: Interfrontal suture wide	0/0	1/1		
Brain cerebral hemisphere misshapen/ internal hydrocephaly	0/0	1/1		
Ribs 5 and 6 right fused proximal with vertebra fused	0/0		1/1	
Head: Cyst, unilateral frontal parietal	0/0			1/2

Source: Reviewer's analysis
* Fisher 1-tail Ascending Test significant at the 0.05 level

Table 129. Toxicokinetic Parameters in Embryo-Fetal Developmental Study in Female Rats with Administration of Iptacopan

mg/kg/day	AUC_{0-24h}	C_{max}	T_{max}
100	41500	10400	0.5
300	123000	22700	1
1000	278000	36000	1

Source: Reviewer's analysis Applicant's submission
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Source: Reviewer's analysis
Abbreviations: AUC, area under the concentration-time curve; BWG, body weight gain; C_{max}, maximum plasma concentration; GD, gestation day; HD, high dose; MD, mid dose

Study 1670323/ LNP023: Oral (Gavage) Study of Embryo-Fetal Development in the Rabbit

GLP compliance: Yes

Key Study Findings

- The No-observed-adverse-effect level for maternal toxicity is determined at 250 mg/kg/day based on reduced body weight gain and food consumption (C_{max}=15000 ng/mL and AUC_{0-24h}=153000 ng·h/mL), and the NOAEL for embryofetal development toxicity at 450 mg/kg/day based on the absence of any adverse fetal changes or abnormalities (C_{max}=30600 ng/mL and AUC_{0-24h}=400000 ng·h/mL).

Table 130. Methods of Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing:	0, 100 (LD), 250 (MD), or 450 (HD) mg/kg/day, once daily Dosed with iptacopan during GD7-20, and were terminated at GD29
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose (Type 15 cPs) + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Rabbit/New Zealand White
Number/sex/group:	20/female/iptacopan groups (19/female/control)
Satellite groups:	No satellite groups
Study design:	Standard EFD study design based on ICH S5(R3)
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results

Source: Reviewer's analysis
Abbreviations: EFD, embryo fetal development; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose

Table 131. Observations and Results

Parameters	Major Findings
Mortality	None
Clinical signs	Thin appearance was noted at HD (4/20)
Body weights and Food consumption	Reduced BWG and food consumption were noted at HD between GD 7 and 21 compared to controls, which resolved after the iptacopan dosing stopped.
Necropsy findings Cesarean section data	• No iptacopan-related effects on number of pregnant females or on pregnancy parameters (mean number of corpora lutea and implantation sites) were noted. • Mean % pre-implantation loss was increased by 39% at HD and mean % post-implantation loss was increased by 32%

Table 132. Iptacopan-related Maternal Toxicity

	Iptacopan Dose (mg/kg/Day)			
Parameter	**0**	**100**	**250**	**450**
GD 7-21 BWG (%)	0.15 kg	+26.7	-6.7	-73.3*
Food consumption (%)	126.5g#	-0.5	-12.3	-34.2

Source: Reviewer's analysis
*=Dunnett Exact Homogeneous Test Significant: 0.01 level
#=animal/day
Abbreviations: BWG, body weight gain

Parameters	Major Findings
Necropsy findings Offspring	• Minimal decrease in mean fetal body weight (-6%) was noted at HD. • No iptacopan-related fetal abnormalities (malformation or variations) were observed.
Toxicokinetics	Systemic exposure to iptacopan (C_{max} and AUC) increased with dose increment in an approximately dose-proportional manner.

Table 133. Toxicokinetic Parameters in Embryo-Fetal Developmental Study in Female Rabbits with Administration of Iptacopan

Iptacopan Dose mg/kg/Day	AUC_{0-24h}	C_{max}	T_{max}
100	51800	5900	3
250	153000	15000	3
450	400000	30600	7

Source: Reviewer's analysis
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0-24 h; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Source: Reviewer's analysis
Abbreviations: AUC, area under the concentration-time curve; BWG, body weight gain; C_{max}, maximum plasma concentration; GD, gestation day; HD, high dose

Study 1770878/ LNP023: Oral (Gavage) Study of Pre- and Postnatal Development in the Rat

GLP compliance: Yes

Key Study Findings

- The NOAEL for both maternal toxicity (F0) and pre- and postnatal developmental (PPND) toxicity in F1 generation rats developing into adulthood is defined at 1000 mg/kg/day based on lack of biological important iptacopan-related effects (exposure is from EFD study with once daily (QD) dosing on GD 6 to 17, C_{max} 360000 ng/mL and AUC_{0-24h} 278,000 ng·h/mL).

Table 134.Methods of Pre- and Postnatal Development in the Rat

Parameter	Method Details
Dose and frequency of dosing:	0, 100 (LD), 300 (MD), or 1000 (HD) mg/kg/day, once daily Parental (F0) generation: Dosed with iptacopan during GD 6 through lactation day (LD) 21 F1 and F2 generation: not dosed
Route of administration:	Oral (gavage)
Formulation/vehicle:	Suspension in aqueous 0.5% w/w methylcellulose (Type 15 cPs) + 0.5% w/w Tween 80 (Polysorbate 80)
Species/strain:	Rat/Wistar Han
Number/sex/group:	F0: 22/female/group, F1: 20/female/group
Satellite groups:	No satellite groups
Study design:	Standard EFD study design based on ICH S5(R3)
Deviation from study protocol affecting interpretation of results:	None of the deviations impacted the overall integrity of the study or interpretation of study results.

Source: Reviewer's analysis
Abbreviations: EFD, embryo fetal development; F, filial generation; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose

Table 135. Observations and Results

Parameters	Major Findings
F0	
Mortality	Total of 4 deaths occurred in F0 generation. • One control was prematurely terminated on GD15 due to labored respiration and red coloration of the skin around the chin. At necropsy, gelatinous thymus, dark lungs, and fluid in the thoracic cavity were observed, which was likely from the dosing accident. • One LD was found dead on GD11. At necropsy, red ovaries and thymus were observed but the cause of death was not determined. • At HD, one rat was found dead on GD 13 and another was prematurely terminated due to moribundity (piloerection, audible, slow, labored respiration, red coloration of the skin around the nose, and red discharge from the mouth). Both rats presented evidence of dosing accident with red fluid in the thoracic cavity, dark area in the esophagus, dark lungs, and gelatinous thymus.
Clinical signs	After the oral dosing, dose-related mouth rubbing and jaw chomping were noted immediately after dosing at MD and HD for a few hours, which resolved after about 6 hours except in one HD animal. It is a suspected effect from the unpalatable taste of the drug.
Body weights	Transient reduction of food consumption up to GD12 was observed at HD, which did not affect BWG. During GD 6-20, there were no iptacopan-related body weight changes, and 19% increase of BWG was noted at MD and HD during LD1-21.
Reproductive performance	There were no iptacopan related effect on pregnancy.
Parturition, Litter size/number, gestation length and gestation indices	No iptacopan-related findings were noted. ** Stillborn: There were stillborn pups at HD (2 pups/1 litter), MD (1 pup/1 litter), LD (2 5 pups/2 litters), there were no stillborn pups in controls. Regardless, the data is within the historical control data range (0-6 still born pups).
Necropsy findings Cesarean section data	No iptacopan-related findings were observed.
Necropsy findings Offspring (F1)	No-iptacopan related macroscopic changes were noted in PND 4 or PND 22 F1 pups
F1 (pre-weaning)	
Mortality	No iptacopan-related death observed. One F1 pup from HD F0 was found dead on LD18 without any clinical signs prior to its death. At necropsy, dark brain and red cranial cavity was noted.
Clinical signs	No iptacopan-related findings were noted.

Table 136. Reproductive Performance in Rats After Iptacopan Treatment in PPND Study

	Iptacopan (mg/kg/day)			
Parameters	**0**	**100**	**300**	**1000**
Pregnant	19	22	21	20
Pregnant with total litter loss on GD26	1	0	1	1
Females with live pups on LD22	17	21	20	17

Source: Reviewer's analysis
Abbreviations: GD, gestation day; LD, low dose

Parameters	Major Findings
Physical and functional development data	F1 pups from the HD F0 showed lower number passing surface righting assessments compared with controls on PND 1 (70.8% compared with 78% of controls), with no statistical significance. On PND 17, all dose groups passed the surface righting assessments.
F1 (post-weaning)	
Mortality	No deaths occurred
Body weights	Minimal level of lower body weights (8-10%) were observed with statistical significance in F1 males of HD F0 during maturation day 22-36, and the body weight difference in HD compared to controls gradually diminished.
Physical and functional development data	MD F1 males had 95% pass rate compared to 100% pass rate in all other groups of males and females. Considering no dose-relationship, it is considered incidental, rather than iptacopan-related.
Locomotor activity	Decrease in motor activity parameters were observed in both sexes compared to controls during the maturation phase. However, the change noted was within the historical control data. • Dose-related reduction of activity (basic and fine movements) was noted after 20 minutes of testing in F1 pups of HD F0 and was not evident until after 40 minutes of testing in F1 pups of LD and MD F0, compared with controls. • Habituation was significantly reduced in F1 pups of HD F0 • The dose-dependent finding suggests the potential effect of iptacopan on locomotor activity development when exposed through maternal dosing. • These reductions did not adversely impact the F1 generation and were considered non-adverse.
Acoustic startle response, Learning and memory	No iptacopan-related effects were noted.
Reproductive performance (Sexual maturity, Fertility, Pregnancy, Mating performance	No iptacopan-related effects were noted.
Necropsy findings Cesarean section data (corpora lutea, implantation, pre-implantation loss, early resorptions, and live embryos)	No iptacopan-related findings were observed.
Toxicokinetics	Not measured.

Source: Reviewer's analysis
Abbreviations: BWG, body weight gain; F, filial generation; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose PND, postnatal day

13.1.5.5. Juvenile Toxicology

Study 1870009/ LNP023: A 52 Week Oral (Gavage) Toxicity Study With a 27-Week Recovery Period in the Juvenile

GLP compliance: Yes

Key Study Findings

- The NOAEL was defined at 5 mg/kg/day in males and 30 mg/kg/day in females based on the adverse findings in the aorta at ≥ MD in males and in aorta (mineralization) and heart (fibrosis with degeneration) at HD in females.

Table 137. Methods of Juvenile Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0 (control), 5 (LD), 30 (MD), or 150 (HD) mg/kg/day, once daily F0 generation dams were not dosed.
Route of administration:	Oral gavage
Formulation/vehicle:	Suspension/0.5% (w/w) methylcellulose (15 cPs) and 0.5% (w/w) Tween® 80 (Polysorbate 80, NF) in ultra-pure water
Species/strain:	Dog/ Beagle
Number/sex/group:	10/sex/control and HD group, 5/sex/ LD, MD group
Satellite groups:	None
Study design:	Untreated F0 generation delivered naturally and F1 generation rats were culled to 6 pups/litter (3/sex, if possible) on PND4. Dosing was initiated on PND28 and terminated on PND392. Recovery period was 27 weeks and animals were terminated on PND581.

Table 138. Study Design of Juvenile Study With Iptacopan Dosing for 52 Weeks

Group no.	Dose level (mg/kg/day)[a]	Concentration (mg/mL)[a]	No. of animals[b]			
			Main study		Recovery study	
			Males	Females	Males	Females
1/ Vehicle control	0	0	5	5	5	5
2/ LNP023	5	1	5	5	-	-
3/ LNP023	30	6	5	5	-	-
4/ LNP023	150	30	5	5	5	5

Source: Applicant's submission
[a] The dose level and concentration are expressed as the base form. The salt to base ratio of LNP023 is 1.086.
[b] See Table 139 for details on dam and pups nos., and assignment to groups.
Abbreviations: LNP023, iptacopan

Parameter	Method Details

Table 139. Iptacopan Dosing Groups and Animal Allocations in Dams and Pups

Group no.	Dose level (mg/kg/day)[a]	Replicate[b]	Dam no.	Animal no. of F1 pups			
				Main study		Recovery study	
				Males	Females	Males	Females
1/ Vehicle control	0	3, 3R	1	1001, 1002	-	1006[c], 1007	-
		1, 1R	2	-	1501, 1502	-	1506, 1507
		8, 8R	9	1003-1005	-	-	1508-1510
		11	14	-	1503, 1504	-	-
		12, 12R	12	-	1605	1106, 1108-1110	-
2/ LNP023	5	4	6	2001-2003	2501-2503	-	-
		10	11	2004, 2005	2504, 2505	-	-
3/ LNP023	30	5	5	3001, 3002	3501-3503	-	-
		7	10	3003-3005	3504, 3505	-	-
4/ LNP023	150	4, 4R	4	4001, 4002	4501, 4502	-	4506, 4507
		6, 6R	7	-	4503, 4504	4003, 4004, 4006[c], 4007	-
		9, 9R	8	-	4505	-	4508-4510
		13, 13R	13	4105, 4106, 4108	-	4109, 4110	-

Source: Applicant's submission
[a] The dose is expressed as base. The salt to base ratio of LNP023 is 1.086.
[b] Pups were grouped into replicates based on the calendar date of their birth.
[c] Animals nos. 4006 and 1006 were euthanized on PND 33 and 42, respectively, due to gavage trauma.
Abbreviations: F, filial generation; GD, gestation day; HD, high dose; LD, low dose; LNP023, iptacopan; MD, mid dose; no, number; PND, postnatal day; R, replicate

Deviation from study protocol affecting interpretation of results:	The deviations did not impact the integrity of the study.

Source: Reviewer's analysis
Abbreviations: F, filial generation; HD, high dose; LD, low dose; MD, mid dose; NF, national formulary; PND, postnatal day

Table 140. Observations and Results

Parameters	Major Findings
Mortality	There were no iptacopan-related deaths. • The mortality of 2 males (Control #1006 on PND 33, HD #1006 on PND 42) during the dosing period are likely from gavage error based on the findings of lung hemorrhage (with mononuclear inflammation) at necropsy, and they were replaced with spare animals. • During recovery period, one control male (#1108) was prematurely terminated due to moribund clinical signs. At necropsy, the cause of death was determined to be polyarteritis with vascular/perivascular inflammation in multiple organs including heart and aorta. Pericardial fluid accumulation, raised pale foci on the epicardium of the heart, thick pericardium and pale firm foci on the adventitia of the thoracic aorta were observed.
Clinical signs	Iptacopan-related salivation (9/10 in males, 10/10 in females), thin appearance (6/10 males, 10/10 females), and vomitus (white/foamy/liquid,1/10 in males and up to 3/10 females) at HD and sign of emesis with foamy materials in all iptacopan-treated animals (2-3 animals/group) were observed during the dosing period. The skin discoloration in urogenital area (2-3/10) and/or fur thin cover were observed in iptacopan-treated animals at HD.

Parameters	Major Findings
Body weights/body weight gain	Body weight gain (BWG) during preweaning period (PND 28-56) was decreased by 7% and 13% in males and 13% and 24% in females at MD and HD, respectively, compared to controls. During postweaning period (PND 56-392), BWG decreased by 19, 10, and 5% for females at LD, MD, and HD, respectively, compared to controls. BWG was increased by 64% in males and 71% in females at HD after the recovery period.
Food consumption, Ophthalmology, Urinalysis	No iptacopan-related effects observed.
Developmental Parameter: Growth (length/height), Neurological examination	No iptacopan-related effects observed.
ECG	Mild to moderate heart rate increase occurred and corresponding shortening of the PR and QT intervals was observed at 2.5-3.5 hours postdose during Weeks 2, 13 and 52 at HD. There were no iptacopan-related effects on the QTc interval or QRS duration. The changes in quantitative ECG parameters were reversible, not being observed 24 hours postdose or at the end of the recovery.
Hematology	• Red blood cell, hemoglobin and hematocrit levels were mildly decreased compared to controls in males at ≥ MD and females at HD. • Minimal increases in reticulocyte counts in males at ≥ LD and females at MD, and minimal increases in mean corpuscular volume at ≥ MD in males and HD in females were noted compared to controls. • Low numbers of nucleated red blood cells were observed in few dogs at HD at Weeks 26 and 52, but the finding was without any evidence of changes in M:E ratio, nor any proliferation or maturation abnormalities in bone marrow cytological evaluation at HD compared to the controls • The hematologic findings had corresponding microscopic findings of increased hematopoietic cellularity of the bone marrow in males and females at MD and HD • Iptacopan-related changes resolved at the end of recovery period.
Coagulation	Mild increases in fibrinogen were observed in males without dose-relation at Week 13 in HD males and at Week 26 in all iptacopan treated males, which was also observed in MD females at Weeks 26 and 39 compared to the control group. These findings resolved during the recovery period.
Clinical chemistry	• Total bilirubin level was increased dose dependently in females at MD (47%) and HD (60%) at Week 52 and increases by 53% in males was noted at HD compared to control. • Increases in urea (24%) and/or creatinine (20%) in HD females and minimal increases in calcium (3-4%) in HD males and females were noted. • Dose-related minimal to mild increases in phosphorus levels at MD and minimal increases in calcium in males and females at HD. • Iptacopan-related changes at HD did not resolve during/end of the recovery period for the increases of urea in males and females, creatinine in females, and increases in phosphorus and calcium level in males.

Parameters	Major Findings
Organ weights	Iptacopan-related changes in organ weight ratio (% body weight) were noted in liver, heart, thyroid/parathyroid, and prostate in males and heart and thyroid/parathyroid in females at the end of recovery period. At the end of recovery period, the change in thyroid and heart (female only) did not resolve.
Macroscopic findings	Pale foci were observed in one HD female (#4505) with corresponding microscopic findings of fibrosis at the end of dosing period. Following 27-week recovery period, pale foci in the heart of a HD male was noted with corresponding microscopic finding of fibrosis.

Table 141. Percent Difference of Organ Weight Ratio (% Body Weight) Compared to Controls After Iptacopan Treatment for 52 Weeks and Recovery Period for 27 Weeks

		Liver	Heart	Thyroid/Parathyroid	Prostate
Dosing period					
Male	MD	+9	+14	+3	+1
	HD	+29	+32	+74	-25
Female	MD	*	+22	+15	-
	HD	*	+42	+32	-
Recovery period					
Male	HD	*	+6	+51	-21
Female	HD	*	+27	+21	-

Source: Reviewer's analysis
* No noteworthy findings, - not applicable
Abbreviations: HD, high dose; MD, mid dose

Parameters	Major Findings
Microscopic findings	Iptacopan-related microscopic findings were observed: • Heart: minimal to mild fibrosis at HD was noted • Aorta: minimal to mild mineralization (dose related incidence in females), Special stain (Von Kossa) showed no dose-relation (Table 142). • Bone marrow: minimal increase of hematopoietic cellularity was noted at MD and HD • Thyroid: Dose-related follicular cell hypertrophy was noted with dose-dependent incidence • Liver: minimal to mild Kupffer cell pigment was noted at MD and HD with dose-relation.

Table 142. Microscopic Findings in Juvenile Dogs After Iptacopan Treatment for 52 Weeks

Tissue/Finding	Sex	Males				Females			
	Dose (mg/kg/day)	0	5	30	150	0	5	30	150
Heart	Number examined	5	5	5	5	5	5	5	5
Fibrosis									
	Total number affected	0	0	0	2	0	0	0	2
	Minimal	0	0	0	2	0	0	0	1
	Mild	0	0	0	0	0	0	0	1
Aorta (base of the heart)	Number examined	5	5	5	5	5	5	5	5
Mineralization									
	Total number affected	1	2	3	1	1	1	2	3
	Minimal	1	2	2	1	1	1	2	2
	Mild	0	0	1	0	0	0	0	1
Bone marrow	Number examined	5	5	5	5	5	5	5	5
Increased cellularity, hematopoietic									
Total number affected		1	1	4	4	1	0	4	4
Minimal		1	1	4	4	1	0	4	4
Thyroid gland	Number examined	5	5	5	5	5	5	5	5
Hypertrophy, follicular cell									
	Total number affected	1	1	2	4	1	1	1	4
	Minimal	1	1	2	4	1	1	1	4
Adrenal gland	Number examined	5	5	5	5	5	5	5	5
Vacuolation, cortical, zona glomerulosa									
	Total number affected	0	0	0	1	0	0	0	2
	Minimal	0	0	0	1	0	0	0	2
Liver	Number examined	5	5	5	5	5	5	5	5
Pigment, Kupffer cell									
	Total number affected	0	0	1	3	0	0	3	4
	Minimal	0	0	1	1	0	0	3	3
	Mild	0	0	0	2	0	0	0	1

Source: Applicant's submission

Table 143. Von Kossa Staining for Mineral in Aorta of Juvenile Dogs After Iptacopan Treatment for 52 Weeks

Tissue/Finding	Sex	Males				Females			
	Dose (mg/kg/day)	0	5	30	150	0	5	30	150
Aorta (base of the heart) - Von Kossa staining	Number examined	5	5	5	5	5	5	5	5
Positive (mineralization)									
	Total number affected	4	4	4	3	4	3	5	3
	Minimal	4	4	2	3	4	3	5	2
	Mild	0	0	2	0	0	0	0	1

Source: Applicant's submission

Parameters	Major Findings
Male reproductive organ and spermatogenic cycle evaluation	Minimal to moderate testicular hypospermatogenesis increased with dose-dependency in MD and HD and lumen cellular debris in the epididymides (minimal to mild) of HD. The round spermatids and spermatocytes in all stages of spermatogenesis were likely from testicular hypospermatogenesis. Also, vacuolation, disruption of normal cellular architecture in the tubules and/or exfoliated and multinucleated germ cells were observed.

Table 144. Macroscopic Findings in Testes and Epididymis in Juvenile Dogs After Iptacopan Treatment for 52 Weeks

Tissue/Finding	Sex	Males			
	Dose (mg/kg/day)	0	5	30	150
Testes	Number examined	5	5	5	5
Hypospermatogenesis					
	Total number affected	2	2	5	5
	Minimal	2	1	5	1
	Mild	0	1	0	3
	Moderate	0	0	0	1
Epididymis	Number examined	5	5	5	5
Cellular debris, lumen					
	Total number affected	0	1	0	4
	Minimal	0	0	0	2
	Mild	0	1	0	2

Source: Applicant's submission

Hormone Analysis	• Pituitary-testis axis in males: Minimal transient increase was noted in the androgens androstenedione, testosterone and dihydrotestosterone at HD in Week 2 only without iptacopan-related changes in LH and FSH. • Pituitary-thyroid axis in males and females: A transient increase in T3 plasma concentrations was observed at HD in treatment Weeks 2 and 4 in absence of any iptacopan-related changes in T4 and TSH.
NT-proBNP	• Increased NT-proBNP plasma levels were observed in females, and also in MD and HD males with lower magnitude starting in Week 2 until the end of dosing Week 51, compared to controls.
Blood immunophenotyping	• Total lymphocyte counts as well as in the absolute counts and relative percentages of total T helper T, cytotoxic T and B lymphocytes were not affected by iptacopan treatment in weeks 39, 52, 64 and 79. • The lower absolute count values observed in iptacopan treated animals were within normal variability.
T-cell dependent antibody response (TDAR)	No iptacopan-related change was noted in the primary and secondary anti-KLJ IgM and IgG responses from Weeks 46 to 52 (dosing) and 74 to 80 (recovery)
AP activity	AP activity was inhibited by 84% and 97% at MD and HD, respectively, 24 hours post-dose.

Parameters	Major Findings
Toxicokinetic	Iptacopan was detected in plasma. The systemic exposure ($AUC_{0\text{-}24h}$ and C_{max}) increased with dose increment and the increase was approximately dose proportional. There was no evidence of sex difference (<2-fold) or accumulation in systemic exposure to iptacopan. T_{max} ranged between 0.5-3 hours. **Table 145. Toxicokinetic Parameters in Juvenile Dogs With Iptacopan Treatment for 52 Weeks** Source: Applicant's submission Abbreviations: $AUC_{0\text{-}24}$, area under the concentration-time curve from time $_{0\text{-}24\ h}$; D, day; C_{max}, maximum plasma concentration; Cmax/D, maximum plasma concentration per day; h, hour; T_{max}, time to maximum concentration; M, male; F, female; MF, average of male and female; PND, postnatal day

Dose Level (mg/kg/day)	Interval	Sex	Cmax (µg/mL)	Cmax/D [(µg/mL/ (mg/kg/day)]	Tmax (h)	AUC0-24 (h*µg/mL)	AUC0-24/D [(h*µg/mL) (mg/kg/day)]
5 (Group 2)	PND 28	M	4.04	0.808	1.70	39.9	7.97
		F	3.95	0.791	1.30	36.3	7.27
		MF	4.00	0.799	1.50	38.1	7.62
	Week 13 (PND 117)	M	4.37	0.874	0.700	35.1	7.03
		F	4.65	0.930	0.700	35.4	7.08
		MF	4.51	0.902	0.700	35.3	7.06
	Week 52 (PND 390)	M	5.95	1.19	0.700	50.1	10.0
		F	5.78	1.16	0.600	46.1	9.22
		MF	5.87	1.17	0.650	48.1	9.62
30 (Group 3)	PND 28	M	23.5	0.782	1.80	226	7.53
		F	23.2	0.774	1.80	207	6.91
		MF	23.3	0.778	1.80	217	7.22
	Week 13 (PND 117)	M	22.7	0.758	1.00	163	5.45
		F	20.3	0.677	0.900	136	4.54
		MF	21.5	0.717	0.950	150	4.99
	Week 52 (PND 390)	M	26.2	0.874	0.900	182	6.07
		F	26.3	0.877	0.800	167	5.57
		MF	26.3	0.875	0.850	175	5.82
150 (Group 4)	PND 28	M	77.9	0.520	2.64	848	5.65
		F	73.9	0.493	2.33	797	5.32
		MF	76.1	0.507	2.50	827	5.51
	Week 13 (PND 117)	M	92.1	0.614	1.80	811	5.41
		F	73.1	0.487	1.40	664	4.43
		MF	82.6	0.551	1.60	738	4.92
	Week 52 (PND 390)	M	83.1	0.554	1.80	841	5.61
		F	92.2	0.614	1.60	928	6.19
		MF	87.7	0.584	1.70	885	5.90

Source: Reviewer's analysis
Abbreviations: AP, alternative pathway; $AUC_{0\text{-}24}$, area under the concentration-time curve from time $_{0\text{-}24\ h}$; BWG, body weight gain; C_{max}, maximum plasma concentration; ECG, electrocardiogram; FSH, follicular stimulating hormone; HD, high dose; IgG, immunoglobulin G; IgM, immunoglobulin M; KLH, keyhole limpet hemocyanin; LD, low dose; LH, luteinizing hormone; MD, mid dose; M.E, myeloid: erythroid ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PND, postnatal day; PR, PR interval; QT, QT interval; QTc, corrected QT interval; QRS, QRS complex; TDAR, T-cell dependent ant body response; T_{max}, time to maximum concentration; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, Thyroxine

13.1.5.6. Impurities/Degradants

Impurities

Two impurities ((b) (4) and (b) (4)) are both proposed at limits of not more than (b) (4)% and (b) (4)% in the drug substance and product, respectively.

- (b) (4) and (b) (4) are considered qualified based on their presence at adequate clinical exposure margins in nonclinical toxicology studies.

Another impurity ((b) (4)) is specified to be present in the drug substance and drug product at not more than (b) (4)% and (b) (4)%, respectively.

- (b) (4) is a process-related impurity and a potential degradation product.
- (b) (4) was not detected in the drug substance batches used in tox studies.
- (b) (4)
- The proposed (b) (4)% specification limit thus appears appropriate.

One impurity ((b) (4)) produced positive response(s) indicating genotoxicity potential.

- (b) (4) found to be positive in the TA98 strain in an Ames assay and induced micronuclei in vitro in human peripheral blood lymphocytes in the absence of S-9.
- However, (b) (4) was negative in a 4-week mammalian peripheral blood erythrocyte Pig-a gene mutation assay with micronucleus test.
- The results of this assessment were negative and (b) (4) is considered a non-genotoxic impurity and will be limited to a specification supported by the available nonclinical data.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Not applicable

14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding

Study DMPK R1600148 assessed the in vitro plasma protein binding of [^{14}C] iptacopan in human and mouse plasma (wild type and factor B knockout type). Human plasma protein

binding of iptacopan was concentration dependent with the unbound fraction (f_u) of 1.1 to 23.4% over the concentration range of 100 to 10,000 ng/mL.

14.1.2. Distribution in Red Blood Cells

Study DMPK R1500362 assessed the in vitro blood distribution and plasma protein binding of [^{14}C] iptacopan, including stability in blood and plasma of rat, dog, and human, and the binding of [^{14}C] iptacopan to isolated human plasma proteins. At the range of 10 ng/mL to 10,000 ng/mL, the mean (±SD) fraction plasma (fp) range was 93.3±1.3% to 24.3±0.3%, respectively, and the mean (concentration in blood/plasma [Cb/Cp]) range was 0.6 to 2.1 respectively. The total plasma protein binding was concentration dependent (1.23 to 25.4%), similar to that observed in study DMPK R1600148 (see Section 14.1.1 above) and human studies (see Section 14.2). Importantly, binding of iptacopan to isolated plasma proteins for isolated human serum albumin, α1-acid-glycoprotein, and lipoproteins was not concentration dependent indicating that the dose dependance might be mediated through different plasma proteins, probably immunoglobulins and the target plasma protein factor B. Iptacopan mean f_u (±SD) values on human serum albumin, α1-acid-glycoprotein, and lipoproteins were 71.6±3.3, 90.7±0.3, 84.0±0.8, respectively, and are presented here for completeness.

14.1.3. Metabolism Characterization

In Vitro Potential as Substrate

Study DMPK R1500516 assessed the human liver enzymes involved in the metabolism of [^{14}C] iptacopan in human liver microsomes (HLM), human hepatocytes, cytosol, and S9 fractions**.** The contribution by individual human cytochrome P450 (CYP450) enzymes to the metabolic clearance (CL) was assessed in combination with selective chemical enzyme inhibitors. Kinetics parameters (maximum enzyme velocity and intrinsic affinity constant according to Michaelis-Menten method [K_m]) of the in vitro metabolism in HLM of iptacopan were also determined. Incubations with iptacopan in HLM along with incubations of selective enzyme inhibitors demonstrated that CYP2C8 plays a key role in oxidative metabolism of iptacopan, with a lower contribution of other CYP enzymes (Table 146). Besides oxidative metabolism, iptacopan was metabolized by direct glucuronidation, which contributed to the total metabolism in human hepatocytes. Maximum enzyme velocity was 90.3 pmol/min/mg, K_m was 163.3 µM, and Cl_{int} was 0.6 µL/mg/min.

Table 146. In Vitro Evaluation Summary of Iptacopan as a Substrate of Human CYP Enzymes

Enzyme	Inhibitor	Concentration [µM]	Percent Activity
CYP3A4	Azamulin	5	95
CYP3A4	Ketoconazole	1	91
CYP2D6	Quinidine	2	100
CYP2C19	Loratidine	2	111
CYP2E1	DETC	100	78
CYP2C9	Sulfaphenazole	5	104
CYP2C8	Montelukast	2	53
CYP2B6	Ticlopidine	10	98

Enzyme	Inhibitor	Concentration [μM]	Percent Activity
CYP1A2	Furafylline	10	101

Source: Table 6-4, page 24-25 of Study 1500516 report
Abbreviations: CYP, cytochrome P450; DETC, diethyldithiocarbamic acid

Study DMPK R1500300 aimed to continue the assessment of hepatic metabolism of iptacopan in human hepatocyte biotransformation pathways. Metabolites of [^{14}C] iptacopan in 6-hour incubations with human hepatocytes at 10 μM substrate concentration were structurally characterized by mass spectrometry. Metabolism pathways involved (1) N-dealkylation (M1), (2) O-deethylation (M2, M9), (3) oxidation (M3, M4, M5, M6, M7), and (4) acyl glucuronidation (M8, M9). The highest percent of radioactivity, 88.7%, was attributed to iptacopan. The most abundant metabolite was M8 and its isomers with 1.85% of radioactivity, followed by M2 with 1.37%. All other metabolites had ≤1% of radioactivity.

Study DMPK R1600579 characterized the CYP450 enzymes involved in the primary oxidative metabolism of iptacopan in recombinant enzymes. Briefly, incubations were carried out in tris(hydroxymethyl)aminomethane buffer (50 mM, pH 7.5) at 37°C with 100 mM $MgCl_2$ (5mM final concentration). Recombinant human CYPs were preincubated for 3 minutes at 37°C. The reaction was started by the addition of a fresh 10 mM solution of nicotinamide adenine dinucleotide phosphate (1 mM final concentration). The enzymatic reactions were stopped and precipitated by the addition of an equal volume of acetonitrile. After at least 30 minutes at -80°C, the samples were centrifuged at 25000 × g for 15 minutes. Radiometry was performed on a liquid scintillation counter using the supernatant. CYP2C8 was the major enzyme contributing to hepatic oxidative metabolism with a fraction metabolized (fm) of ~98%, followed by a minor involvement (~2%) of CYP2D6. DMPK R1500514 assessed the formation of covalent drug protein adducts upon metabolic activation of [^{14}C] iptacopan in human microsomes as well as human hepatocytes. Results indicated a low formation of reactive metabolites of iptacopan, and consequently, a minor formation of covalent drug-protein adducts. For human liver microsomes and human hepatocytes, protein adduct formation were below the predefined thresholds. Study DMPK R1600140 assessed the human uridine diphosphate glucuronosyltransferase (UGT) isoenzymes involved in the direct glucuronidation of iptacopan to M8 using human recombinant UGTs in microsomes. After 1 hour, M8 amounted to about 2 to 2.5% of total radioactivity in the incubations with UGT1A1 and 1.5 to 2% with UGT1A8, but amounted to only 0.5% with UGT1A3. Study DMPK R1600698 assessed UGT-mediated clearance of iptacopan in HLM and identified UGTs involved in direct glucuronidation. These results were in line with those from the recombinant UGT mapping study, DMPK R1600140, where UGT1A1 was considered the major enzyme involved in direct glucuronidation.

In Vitro Potential as Inhibitor

Study DMPK R1300641 assessed the time-dependent inhibition by iptacopan of CYP1A2, CYP2C9, CYP2D6, and CYP3A4/5 up to a concentration of 100 μM in HLM. Phenacetin, diclofenac, bufuralol, and midazolam were used as substrates for CYP1A2, CYP2C9, CYP2D6, and CYP3A4/5. The results indicated that iptacopan is not a time-dependent inhibitor of these enzymes. Study DMPK R1500321 further assessed the reversible inhibition by iptacopan of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 up to a concentration of 100 μM in HLM. Phenacetin, coumarin, bupropion, amodiaquine, diclofenac, S-mephenytoin, bufuralol, and chlorzoxazone were used as substrates for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. Both

midazolam and testosterone were used as substrates for CYP3A4/5. The results indicate that iptacopan is not a reversible inhibitor of these enzymes. Study DMPK R1900589 assessed the time-dependent inhibition by iptacopan for CYP2B6, CYP2C8, and CYP2C19. Bupropion, amodiaquine, S-mephenytoin were used as substrates for CYP2B6, CYP2C8, and CYP2C19. Iptacopan showed time-dependent inhibition of CYP2C8 (Ki = 179 μM). No time-dependent inhibition of CYP2B6 and CYP2C19 by iptacopan was found up to a concentration of 100 μM. Iptacopan is not expected to inhibit CYP2C8 based on its Ki value and expected clinical concentration. Hence no dose adjustment is necessary when coadministered with CYP2C8 substrates. Study DMPK R1500936 assessed the potential of iptacopan to inhibit human UGT1A1 enzyme activity in pooled human liver microsomes using the probe substrate estradiol. The result did not show UGT1A1 inhibition potential in HLM up to 100 μM.

In Vitro Potential as Inducer

Study DMPK R1600704 assessed the potential for iptacopan to induce CYP1A2, CYP2B6, CYP2C9, and CYP3A4 enzyme activities and mRNA levels in primary human hepatocytes. Rifampin, phenobarbital, and omeprazole were used as positive controls for CYP3A/2C induction, CYP2B6 induction, and CYP1A2 induction, respectively. Treatment of hepatocytes from three donors with up to 100 μM iptacopan did not lead to significant induction (defined as a ≥2-fold concentration-dependent increase over vehicle control) of CYP1A2, CYP2B6, and CYP2C9 gene expression and CYP2B6, CYP2C9, and CYP3A4 activity. CYP1A2 activity was induced to 2.4-fold at the highest concentration evaluated of 100 μM in hepatocytes from donor 3 but was accompanied by a 1.3-fold induction of gene expression. CYP3A4 gene expression was induced >2-fold in all three donors, but only at the highest concentration evaluated of 100 μM. The steady-state concentration is not expected to reach 100 μM in the general population at the proposed clinical dose of 200 mg twice daily (BID), hence the induction potential does not appear to be clinically relevant.

14.1.4. Transporter Characterization

In Vitro Potential as Substrate

Study DMPK R1700975 assessed the hepatobiliary disposition of iptacopan using sandwich cultured human hepatocytes and showed that iptacopan is subject to active transport. Study DMPK R1500336 assessed the cellular uptake of iptacopan in suspensions of cryopreserved human hepatocytes. The contribution by transporters was assessed in combination with selective chemical enzyme inhibitors. The results indicated that iptacopan is a substrate of the OATP family in human hepatocytes but not OCT1. Study DMPK R1500730 assessed the intestinal transport of iptacopan using the gastrointestinal Caco-2 cell line. The results indicated that iptacopan is a substrate for the efflux transporter P-gp. Study DMPK R1800300 further assessed the in vitro transporter phenotyping of iptacopan with the human BCRP and MRP2 and with the human OATP1B1 and OATP1B3 transporters. The results indicated that iptacopan is a substrate of BCRP, MRP2, OATP1B3, and, to a lesser extent, OATP1B1. Study DMPK R2000245 assessed iptacopan as substrate of human OAT1, OAT2, OAT3, and OCT2 transporters. The results indicated that iptacopan is not a substrate of OAT1, OAT2, OAT3, and OCT2.

In Vitro Potential as Inhibitor

Study DMPK R1500532 assessed the inhibition potential of iptacopan on uptake transporters OATP1B1 and OATP1B3 using recombinant HEK293 cells. The probe substrate was estradiol-17β-D-glucuronide. Iptacopan was found to be an inhibitor of OATP1B1 (Ki=24.9 μM) and OATP1B3 (Ki >392.7 μM). Study DMPK R1500533 assessed the inhibition potential of iptacopan on human adenosine triphosphate-binding cassette transporter using recombinant MDCKII and LLC-PK1 cells. The probe substrate was digoxin and 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine-2. Based on R1500533 alone, iptacopan was not found to be an inhibitor of P-gp or of BCRP up to 400 μM. Study DMPK R1600716 assessed the interaction of iptacopan with human BCRP and MDR1 (P-gp) in a vesicle-based assay. Iptacopan did not inhibit BCRP-mediated E3S accumulation in vesicles. However, iptacopan was found to inhibit P-gp transport with Ki of 27.7 μM in R1600716. Study DMPK R1500958 assessed the inhibition potential of iptacopan on MRP2 recombinant baculovirus-infected Sf9 cells. The probe substrate was estradiol-17β-D-glucuronide. Based on R1500958, iptacopan was not found to be an inhibitor of MRP2 up to 260 μM. Study DMPK R1600717 assessed the interaction of iptacopan with OCT1 and OCT2 in HEK293 cells. Metformin was used as the probe substrate. Iptacopan was found to be an inhibitor of OCT1 (Ki=321 μM) and OCT 2 (Ki=359 μM). Study DMPK R1709014 assessed the inhibition potential of iptacopan on the human BSEP transporter and the human OAT1, OAT3, MATE1, and MATE2-K uptake transporters. The results indicated that iptacopan does not inhibit BSEP, MATE2-K, or OAT1. However, iptacopan inhibits MATE1 (Ki=400 μM) and OAT3 (Ki=173 μM). Finally, study DMPK R2000210 assessed the inhibition potential of iptacopan on MATE1, MATE2-K, OAT1, OAT3, OCT1, and OCT2. This study further confirmed that iptacopan is an inhibitor of MATE1, OAT3, and OCT1. No half maximal inhibitory concentration could be calculated for MATE2-K, OAT1, and OCT2. Overall, these studies showed that treatment with iptacopan does not inhibit BCRP, MRP2, BSEP, OAT1, and MATE2-K, but it inhibits P-gp, OATP1B1, OATP1B3, MATE1, OCT1, OCT2, and OAT3 in vitro. See clinical drug-drug interaction (DDI) study details under Section 14.2.

14.2. In Vivo Studies

The Applicant conducted five clinical pharmacology studies. In addition, the Applicant submitted four pharmacometrics reports, a physiologically-based pharmacokinetic (PBPK) modeling report, and a pharmacogenomic assessment report. The study design and main results of the five clinical pharmacology studies are described in this section. Pharmacometrics, pharmacogenomics, and PBPK reviews are discussed in Sections 14.5, 14.6, and 14.7, respectively.

Study CLNP023X2101: A Single and Multiple Ascending Dose Study to Assess the Safety, Tolerability, PK, PD, and Food Effect of Iptacopan in Healthy Subjects

Study Design

The Applicant conducted study CLNP023X2101, a randomized, subject-blinded, placebo-controlled study to assess the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and food effect (FE) of iptacopan following (1) a single ascending dose (part 1), (2) 14 days of multiple ascending dose (part 2), and (3) a single dose two-period crossover FE cohort.

One hundred healthy male and female subjects 18 to 56 years of age were enrolled in the study, out of which 78 were dosed with iptacopan (42 in part 1, 24 in part 2, and 12 in part 3). The 7 single ascending dose levels in part 1 were 5, 10, 25, 50, 100, 200, and 400 mg. The 4 multiple ascending dose levels in part 2 were 25 mg BID, 50 mg BID, 100 mg BID, and 200 mg BID over 14 days. In part 3, subjects received a single 100 mg oral dose in the morning of day 1 of both treatment periods, either under fasting conditions or 5 minutes after consuming a high-fat breakfast (fed conditions). Blood was collected to assess iptacopan PK predose and up to 96 hours (part 1 and 3), and 72 hours (part 2) postdose. Urine was collected at predose and on days 1 and 7 between 0 and 8, 8 and 24, and 24 and 48 hours postdose. Human plasma protein binding of iptacopan was assessed from samples at 2, 12, and 48 hours postdose.

Results

Following single oral doses of 5, 10, 25, 50, 100, 200 and 400 mg in healthy adults (part 1), the median time to maximum plasma concentration (t_{max}) ranged from 0.5 to 3 hours (Table 147). Mean (percent coefficient of variation [CV%]) C_{max} ranged from 466 (15.1%) to 5070 (25.9%) ng/mL. Mean (CV%) $AUC_{0-\infty}$ ranged from 5300 (24.2%) to 61200 (25.9%) ng·hr/mL (Table 147 and Figure 13).

Following multiple oral doses of 25 mg BID, 50 mg BID, 100 mg BID, and 200 mg BID, t_{max} ranged from 0.7 to 3 hours (Table 148). Mean (CV%) C_{max} ranged from 1100 (15.2%) to 4120 (26.3%) ng/mL. Mean (CV%) AUC_{0-tau} ranged from 9150 (14.5%) to 25600 (16.8%) ng·h/mL (Table 148 and Figure 14). Mean terminal elimination $t_{1/2}$ was approximately 25 hours. Multiple 200 mg BID doses over a 14-day duration resulted in an accumulation ratio of 1.4, based on AUC_{0-tau} (Table 148. Iptacopan PK was less than dose proportional from 25 mg to 400 mg. However, over the dose range of 100 mg BID and 200 mg BID, iptacopan PK appeared to approach dose-proportionality based on dose-normalized AUC_{0-tau} from study CLNP023X2101 part 2 (Figure 16).

Following single oral doses of 100 mg under fasting and fed conditions, the exposure of iptacopan did not change to a clinically meaningful degree with the 90% confidence intervals (CIs) contained within 0.8 to 1.25 for the ratio of geometric means of $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} (Table 149 and Figure 15). The mean percent (CV%) iptacopan recovered in urine ranged from 12.6% (32.9%) to 14.1% (30.1%). The mean renal clearance (CL_r) following administration of single 100 mg dose was approximately 0.6 L/h.

Overall, the mean fraction unbound from study CLNP023X2101 samples ranged from 0.68% to 22.2% within concentrations of 126 ng/mL to 6790 ng/mL, which indicated that the fraction unbound was concentration dependent (Figure 17).

Table 147. Iptacopan PK Parameters on Day 1 in Study CLNP023X2101 Part 1 Single Ascending Dose

PK Parameters	Mean (CV%)						
Dose (mg)	5	10	25	50	100	200	400
N	6	6	6	6	6	6	6
$AUC_{0-\infty}$ (h·ng/mL)	5300 (24.2)	8440 (24.6)	12700 (23)	17500 (21.3)	25600 (31.5)	36500 (33.2)	61200 (25.9)
C_{max} (ng/mL)	466 (15.1)	714 (19)	994 (21.2)	1370 (11.4)	1980 (23.2)	3230 (26.2)	5070 (25.9)
t_{max} (h)[a]	1 (0.7, 2.4)	1 (0.7, 1.5)	1.1 (0.7, 2.5)	1.2 (0.7, 3)	1 (0.7, 2)	1.13 (0.5, 2.5)	1.25 (0.75, 2.5)
$t_{1/2}$ (h)	14 (17)	15.2 (14.6)	15.5 (33.5)	18.4 (27.9)	13.5 (19)	18 (55.7)	17.3 (17.6)

Source: page 4, Table 4-1, Study CLNP023X2101-am1 Report
[a] Median (minimum, maximum).
Abbreviations: $AUC_{0-\infty}$, area under the drug concentration-time curve extrapolated to infinity; C_{max}, maximum plasma concentration; CV%, percent coefficient of variation; N, number of subjects; PK, pharmacokinetic; t_{max}, time to treatment concentration; $t_{1/2}$, half-life

Table 148. Iptacopan PK Parameters on Day 14 in Study CLNP023X2101 Part 2 Multiple Ascending Dose

PK Parameters	Mean (CV%)			
Dose	25 mg BID	50 mg BID	100 mg BID	200 mg BID
N	6	6	6	6
AUC_{0-tau} (h·ng/mL)[a]	9150 (14.5)	11500 (11.8)	14400 (12.9)	25600 (16.8)
C_{max} (ng/mL)	1100 (15.2)	1530 (17.5)	2250 (18.7)	4120 (26.3)
t_{max} (h)[b]	1.5 (0.9, 2)	1.4 (1, 3)	1.5 (0.7, 2.5)	2 (0.7, 3)
$t_{1/2}$ (h)	18.4 (29.9)	23.8 (41.1)	22.4 (13.3)	25 (44.2)
CL/F (L/h)	2.78 (15.4)	4.41 (12.7)	7.02 (12)	7.96 (13.5)
Vz/F (L)	74.2 (35.4)	146 (34.9)	226 (15)	288 (49.1)
RA	1.51	1.44	1.63	1.38

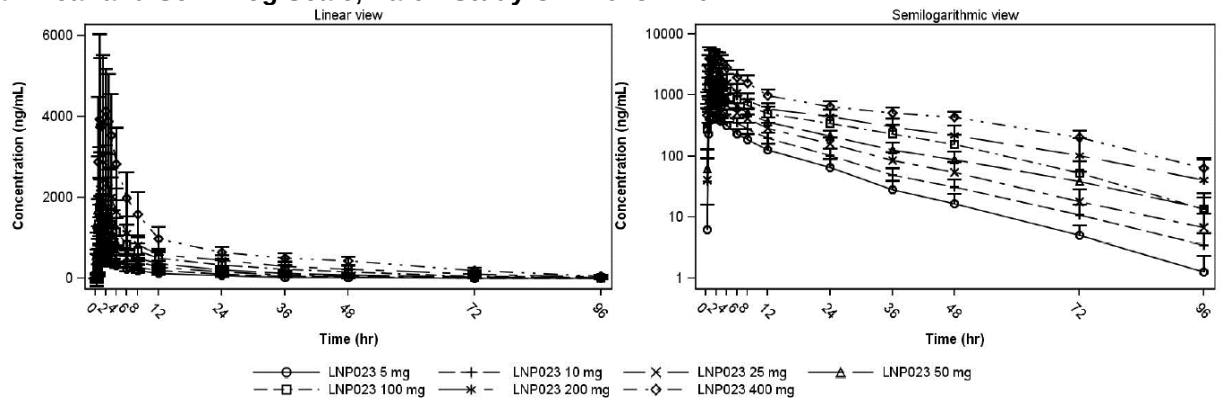
Source: page 4, Table 4.1, CLNP023X2101-am2 Report
[a] tau, 12 h
[b] Median (minimum, maximum)
Abbreviations: AUC_{0-tau}, area under the drug concentration-time curve from time zero to the end of the dosing interval; BID, twice daily; CL/F, apparent total body clearance of drug calculated after extra-vascular administration; C_{max}, maximum plasma concentration; CV%, percent coefficient of variation; N, number of subjects; PK, pharmacokinetic; RA, accumulation ratio based on AUC(0-tau); tau, dosing interval; t_{max}, time to treatment concentration; $t_{1/2}$, half-life; Vz/F, apparent volume of distribution during the terminal phase after extra-vascular administration

Table 149. Iptacopan PK Parameters Following Single 100 mg Oral Administration Under Fed and Fasted Condition in Study CLNP023X2101 Part 3

Parameter	Oral 100 mg Iptacopan	N	Geometric Mean	Ratio of Geometric Mean (Fed:Fasted) (90% CI)
$AUC_{0-\infty}$ (ng·h/mL)	Fed	12	22958.8	0.89 (0.82-0.96)
	Fasted	12	25940.4	
$AUC_{0-tlast}$ (ng·h/mL)	Fed	12	22460.3	0.9 (0.83-0.97)
	Fasted	12	25015.3	
C_{max} (ng/mL)	Fed	12	1726.7	0.97 (0.82-1.14)
	Fasted	12	1784	
T_{max} (h)[a]	Fed	12	1.76 (0.7, 4)	
	Fasted	12	1.26 (0.7, 4)	

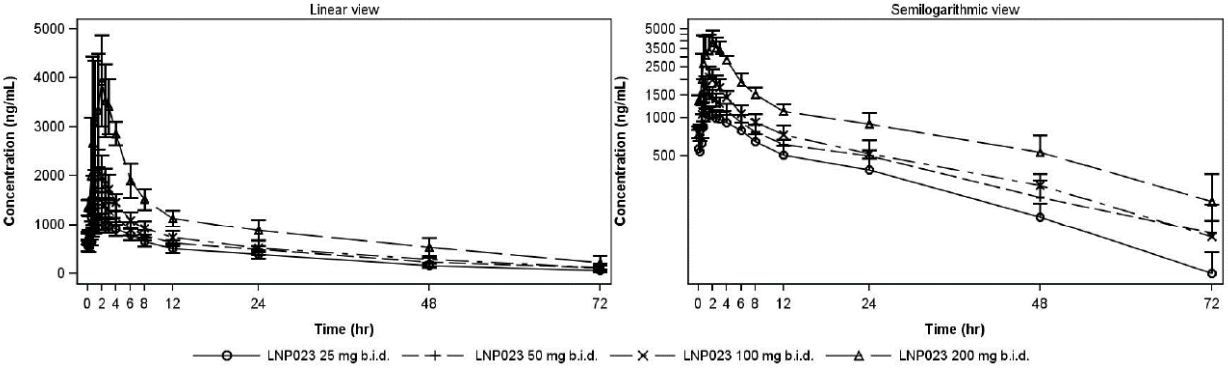
Source: page 86-87 Table 11-9 and 11-10 of Study CLNP023X2101-p01 Report
[a] Median (minimum, maximum)
Abbreviations: $AUC_{0-\infty}$, area under the drug concentration-time curve extrapolated to infinity; $AUC_{0-tlast}$, area under the drug concentration curve from time 0 to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; N, number of subjects; PK, pharmacokinetic; T_{max}, time to treatment concentration

Figure 13. Mean Iptacopan Plasma Concentration-Time Profiles Following Oral Administration on a Linear and Semi-Log Scale, Part 1 Study CLNP023X2101



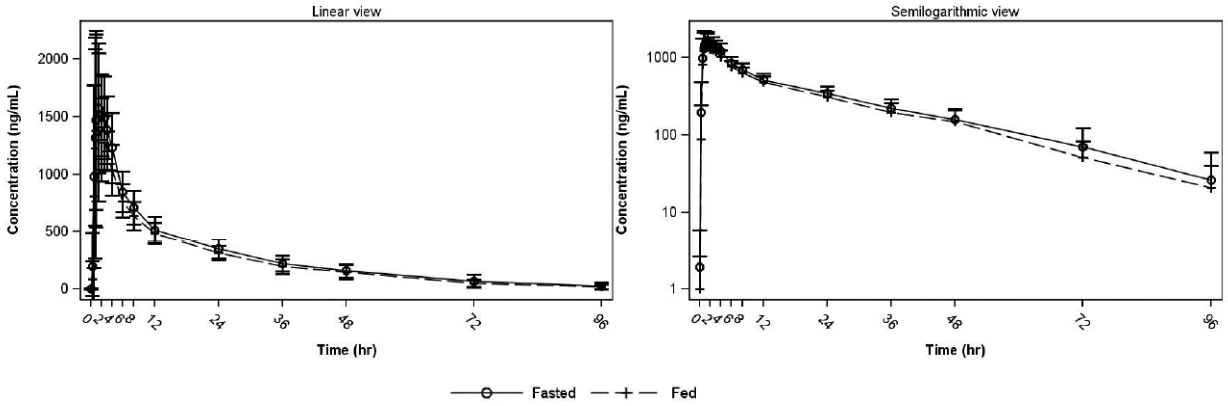
Source: page 76, Figure 11-1, Study CLNP023X2101-p01 Report
Abbreviations: hr, hour; LNP023, iptacopan

Figure 14. Mean Iptacopan Plasma Concentration-Time Profiles Following Oral Administration on a Linear and Semi-Log Scale for Day 14, Part 2 Study CLNP023X2101



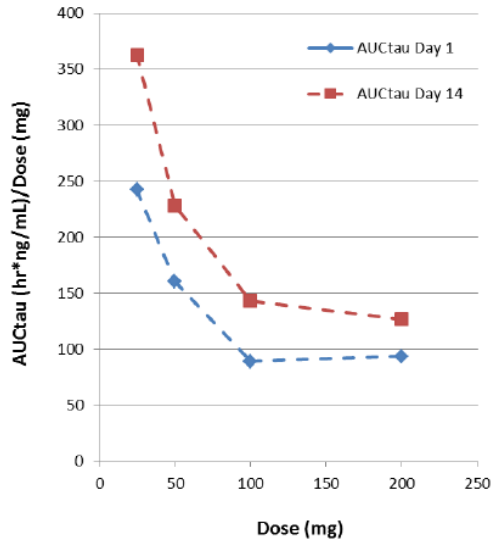
Source: Page 81-82, Figure 11-2, Study CLNP023X2101-P01 Report
Abbreviations: BID, twice daily; hr, hour; LNP023, iptacopan

Figure 15. Mean Iptacopan Plasma Concentration-Time Profiles Following Oral Administration Under Fed and Fasted Condition on a Linear and Semi-Log Scale for Day 1, Part 3 Study CLNP023X2101



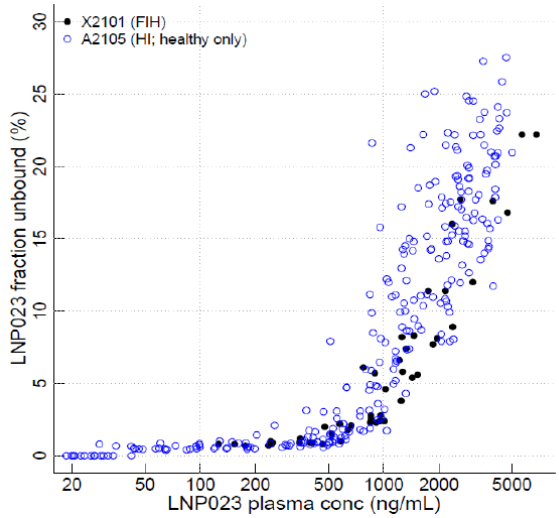
Source: Page 85-86, Figure 11-3, Study CLNP023X2101-p01 Report
Abbreviations: hr, hour

Figure 16. Dose Normalized $AUC_{0\text{-}Tau}$ After Multiple Ascending Doses Versus Dose



Source: Page 39, Figure 3-2, Summary of Clinical Pharmacology
Note: tau = 12 hr
Abbreviations: AUC_{tau}, area under the drug concentration-time curve during the dosing interval; $AUC_{0\text{-}tau,}$ area under the drug concentration-time curve from time zero to the end of the dosing interval; hr, hour; tau, tubulin associated unit

Figure 17. Unbound Fraction of Iptacopan Versus Plasma Concentration in Human Samples, Studies CLNP023X2101 and CLNP023A2105



Source: Page 41, Figure 3-3, Summary of Clinical Pharmacology
Abbreviations: conc, concentration; HI, hepatic impairment; FIH, first in human; LNP023, iptacopan

Study CLNP023A2101: An Open-Label Study to Assess the Absorption, Distribution, Metabolism and Excretion (ADME) of Iptacopan Following a Single Oral Dose of [^{14}C] Iptacopan in Healthy Male/Female Subjects

Study Design

The Applicant conducted study CLNP023A2101, a single-center, open-label study to assess the absorption, distribution, metabolism, and excretion (ADME) of iptacopan following a single oral dose of 100 mg containing approximately 3.7 MBq (100 µCi) of [^{14}C] iptacopan.

Six healthy male and female subjects 18 to 55 years of age were enrolled in the study. Blood collection was at predose and up to 216 hours postdose. Urine collection was at predose, between 0 and 6, 6 and 12, and 12 and 24 hours for the first 24 hours, and then every 24 hours for up to day 26 postdose. Feces collection was every 24 hours for up to day 26 postdose. A single dose treatment on day 1 was followed by a 9-day confinement period (discharge on day 10). If radioactivity recovered in excreta was more than 90% or the combined urinary and fecal excretion was below 1% of the administered dose for 2 consecutive days, and the value of total radioactivity in plasma was below 5% of C_{max}, subjects did not have to return to the clinic for overnight 24-hour visits on days 13 to 14, 17 to 18, 21 to 22, and/or 25 to 26. The cumulative percentage of radioactivity excreted in urine and feces was calculated.

Results

None of the subjects had to return to the study site for additional overnight visits. The mean percent (SD) total recovery of administered radioactivity was approximately 96.4% (1.63) of the administered dose, of which approximately 71.5% (2.79) was excreted in feces and approximately 24.8% (1.71) was excreted in urine over 216 hours.

Two metabolites (M8, M9) were identified in plasma. The most abundant was M8 (acyl glucuronide), which accounted for 8% of radioactivity. A second acyl glucuronide (M9) was present in lower abundance (5.1% of radioactivity). Iptacopan was the largest circulating

component in plasma, accounting for approximately 83% of radioactivity. Seven drug related species were identified in urine. The most abundant was iptacopan, with 17.9%. The most abundant metabolites were M1 (N-dealkylation) and M9, which represented 3.8% and 1.6% of the dose, respectively. The other metabolites detected in urine (P3.1, M2, M6, and M8) were minor, each representing ≤0.4% of the dose. Seven metabolites were identified in feces. The most abundant was M2 (O-deethylation), which represented 27% of the dose. Other abundant components were iptacopan and M7 (deoxidation and dehydrogenation [carboxylation]), representing 16.8 and 8.3%, respectively, of the dose. The other metabolites detected in feces (M11, M6, M12, and M13) were minor, each representing ≤4.2% of the dose. Mean elimination $t_{1/2}$ was similar for total radioactivity in plasma and whole blood at approximately 16 hours. The geometric mean ratio (GMR) of whole blood total radioactivity to plasma total radioactivity was 0.6 for $AUC_{0-\infty}$. According to the results of this study and the in vitro studies (see above DMPK R1500516 and DMPK R1500300), the acyl glucuronide metabolites are M8 and M9. Hence iptacopan undergoes phase 2 metabolism through glucuronidation.

Study CLNP023X1102: A Randomized, Subject-Blinded, Placebo-Controlled, and Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Orally Administered Iptacopan in Japanese Healthy Male Subjects

Study Design

The Applicant conducted study CLNP023X1102, a randomized, subject-blinded, placebo-controlled study to assess the safety, tolerability, PK, and PD of iptacopan in healthy Japanese subjects.

Thirty healthy male subjects 20 to 45 years of age were enrolled in the study. The study consisted of three sequential dose-escalating cohorts of 25, 100, and 400 mg administered as single doses. Blood was collected to assess iptacopan PK predose and up to 96 hours. Urine collection was at predose and between 0 and 8, 8 and 24, 24 and 48, 48 and 72, 72 and 96 hours postdose. Blood samples were collected to evaluate the effect of genomic polymorphism for allele frequencies of relevant metabolizing enzymes and transporters on iptacopan exposure. Human plasma protein binding of iptacopan was assessed from samples at 2 and 12 hours postdose.

Results

Following single oral doses of 25, 100, and 400 mg in healthy Japanese male adults, the median t_{max} ranged from 1 to 3 hours (Table 150). Mean (CV%) C_{max} ranged from 1160 (21.9%) to 7990 (17.1%) ng/mL. Mean (CV%) $AUC_{0-\infty}$ ranged from 12500 (26.4) to 73500 (19.5) ng·h/mL (Table 150 and Figure 18). In general, iptacopan PK in Japanese subjects appeared less than dose proportional, consistent with non-Japanese subjects. Although at the 25 mg and the 100 mg doses, iptacopan $AUC_{0-\infty}$ in Japanese subjects appeared similar to that in non-Japanese subjects (Table 150), at a single dose of 400 mg, $AUC_{0-\infty}$ appeared higher by approximately 20% in Japanese subjects (Table 150). An exploratory pharmacogenomic analysis was conducted to understand the association of CYP2C8 variants and the difference in exposure observed between the two groups. See Section 14.6 for the pharmacogenetics assessment.

The mean percent of iptacopan recovered in urine ranged from 16.2 to 31.9% in the dose range of 25 mg to 400 mg. The mean CL_r of iptacopan ranged from 0.3 L/h to 1.7 L/h.

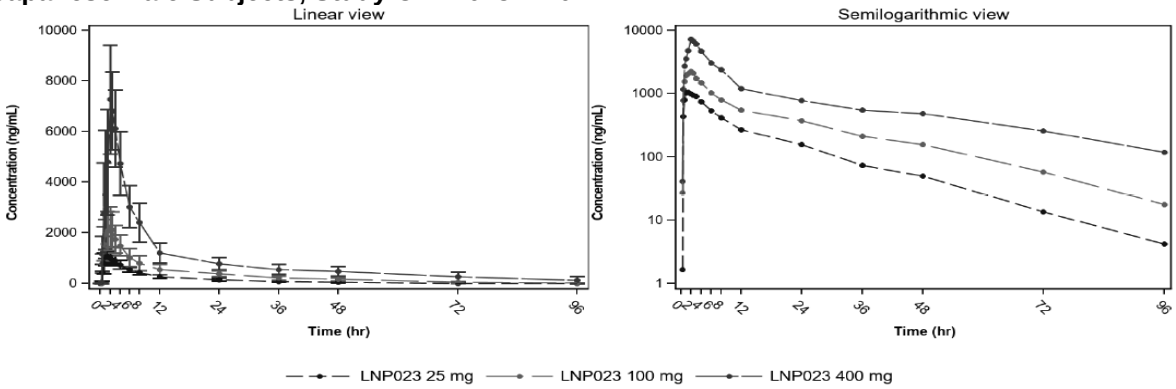
Overall, the mean fraction unbound from study CLNP023X1102 samples ranged from 0.72% to 49.2% within concentrations of 127 ng/mL to 7660 ng/mL, which indicated that the fraction unbound was also concentration dependent in this population.

Table 150. Iptacopan PK Parameters in Study CLNP023X1102

PK Parameters	Mean (CV%)		
Dose (mg)	25	100	400
N	8	8	8
$AUC_{0-\infty}$ (h·ng/mL)	12500 (26.4)	28700 (31.9)	73500 (19.5)
C_{max} (ng/mL)	1160 (21.9)	2460 (29.8)	7990 (17.1)
T_{max} (h)[a]	1.5 (1, 3)	1.7 (1, 2.5)	2.2 (1, 3)
$T_{1/2}$ (h)	13.2 (16.3)	15.1 (24.1)	24.7 (63.2)
CL/F (L/h)	2.12 (24.2)	3.80 (31.8)	5.63 (19.5)
Vz/F (L)	39.5 (21.1)	79.7 (27.3)	155 (30.6)

Source: page 43, Table 11-1, Study CLNP023X1102 Report
[a] Median (minimum, maximum)
Abbreviations: $AUC_{0-\infty}$, area under the drug concentration-time curve extrapolated to infinity; CL/F, apparent total body clearance of drug calculated after extra-vascular administration; C_{max}, maximum plasma concentration; CV%, percent coefficient of variation; h, hour; N, number of subjects; PK, pharmacokinetic; T_{max}, time to treatment concentration; $T_{1/2}$, half-life; Vz/F, apparent volume of distribution during the terminal phase after extra-vascular administration

Figure 18. Mean Iptacopan Plasma Concentration-Time Profiles on a Linear and Semi-Log Scale in Japanese Male Subjects, Study CLNP023X1102



Source: Page 44, Figure 11-1, Study CLNP023X1102 Report
Abbreviations: hr, hour; LNP023, iptacopan

Study CLNP023A2105: Single Dose, Open-Label Study to Investigate the Pharmacokinetics and Safety of Iptacopan in Subjects With Mild, Moderate and Severe Hepatic Impairment Compared to Matched Control Healthy Subjects With Normal Hepatic Function

Study Design

The Applicant conducted study CLNP023A2105, a single dose, open-label study to assess the safety and PK in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) compared to matched control healthy subjects with normal hepatic function.

Thirty-eight male and female subjects 18 to 75 years of age were enrolled in the study. Eight subjects were dosed in the mild and moderate hepatic impairment groups each, while 6 subjects were dosed in the severe hepatic impairment group and 16 subjects were dosed in the normal

hepatic function group. All subjects received a single oral dose of 200 mg. Blood was collected to assess total and unbound iptacopan PK predose and up to 240 hours postdose.

Results

Following administration of a single dose of 200 mg iptacopan, mean total iptacopan C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ did not change to a clinically relevant degree in any hepatic impairment group compared to the normal reference group (Figure 19). However, the GMR of unbound C_{max} in participants with mild, moderate, and severe hepatic impairment relative to the normal reference group was 1.38, 1.67, and 2.11, respectively (Table 151 and Figure 20). In addition, the GMR of unbound $AUC_{0\text{-}\infty}$ in participants with mild, moderate, and severe hepatic impairment relative to the normal reference group was 1.48, 1.58, and 3.71, respectively (Table 151 and Figure 20). The GMR of unbound $AUC_{0\text{-}tlast}$ was consistent with that of unbound $AUC_{0\text{-}\infty}$ for the respective hepatic impairment groups relative to the normal reference group (Table 151). The Applicant hypothesized that the increase in unbound plasma iptacopan could be due to decreased liver production of factor B in hepatic impairment. Factor B is the plasma target of iptacopan. Since factor B levels were not measured in this study, other determinants of the observed higher unbound exposure of iptacopan cannot be ruled out.

The clinical safety of steady-state exposures greater than those achieved with the 200 mg BID dose is unknown. The Applicant did not propose any dose adjustments for any hepatic impairment group or limit the use in the severe hepatic impairment group. The Applicant proposed to use the safety data from single doses up to 1200 mg used in study CLNP023A2107 to support the absence of dose adjustment for patients with hepatic impairment. The Applicant stated that clinical context in which iptacopan would be used in a severe hepatic impairment patient would likely be life-threatening; thus, benefit would likely outweigh any potential hypothetical risk. Concerns with higher unbound exposure on infection risk are addressed with the Applicant's proposed labeling risk evaluation and mitigation strategy of vaccination and prophylactic antibiotic use. Furthermore, the Applicant stated that off-target effects include preclinical toxicity in dog testis tubular degeneration and that the AUC at the lowest-observed-adverse-effect level for dogs was double the clinical AUC exposure. However, the Applicant did not address the exposure relationship with clinical safety measures, including platelet count, cholesterol, follicle stimulating hormone (FSH), thyroid stimulating hormone, triiodothyronine (T3), dihydrotestosterone, absolute reticulocyte count, and bilirubin.

The clinical pharmacology team sent an information request to the Applicant to perform exposure-safety modeling to understand the relationship with observed clinical exposure in the phase 2 and 3 studies, with safety measures up to 6 months of iptacopan treatment. In general, the observed exposure-safety relationship for platelet count and cholesterol appears to be largely related to the treatment effect, that is, whether the subjects received or did not receive iptacopan. In general, the exposure-safety modeling shows that the iptacopan exposure relationship to safety measures is dose independent. See Section 14.5 for pharmacometrics analysis.

The exposure-safety relationship showed that the observed concentrations in subjects with PNH covered the expected increases in mild and moderate hepatic impairment. The clinical pharmacology team found that dose adjustment is not necessary for subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment.

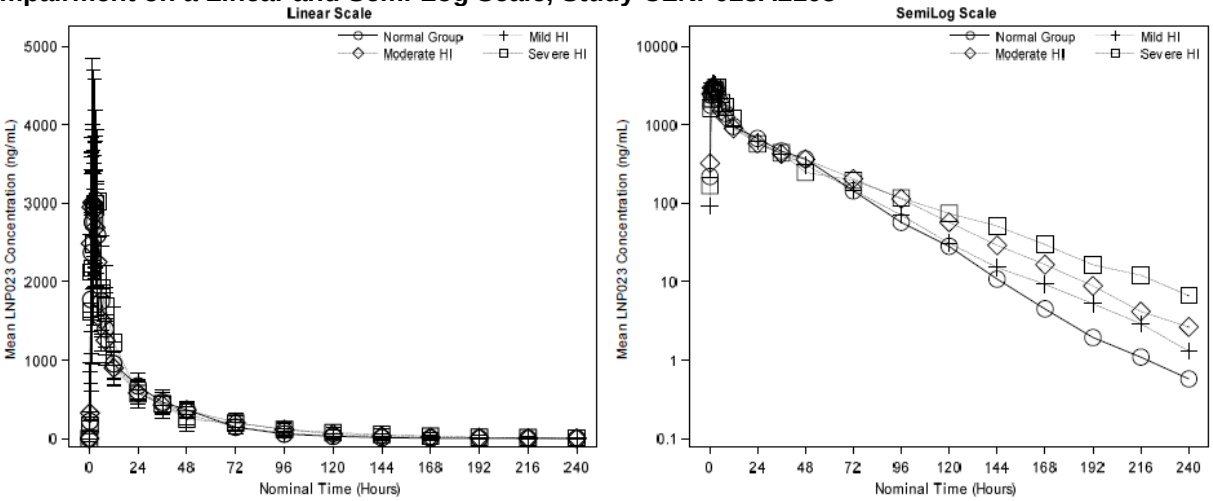
With regard to severe hepatic impairment, the increase in unbound exposures was well beyond the clinically observed exposures and were not covered by the available exposure-safety relationship. The clinical pharmacology team also found dose adjustments for severe hepatic impairment not feasible due to (1) the poor predictability of the PK behavior at steady state attributable to the nonlinear PK and lower hepatic factor B production in patients with hepatic impairment, and (2) the availability of only one strength of 200 mg. Therefore, the team does not recommend the use of iptacopan in patients with severe hepatic impairment.

Table 151. PK Parameters of Unbound Iptacopan Following Single 200 mg Oral Administration in Subjects With Hepatic Impairment - Study CLNP023A2105

Parameter	Oral 200 mg Iptacopan	N	Geometric Mean	Ratio of Geometric Mean (Test: Reference) (90% CI)
Unbound $AUC_{0-\infty}$ (ng·h/mL)	Mild HI (Child-Pugh A) (Test)	8	5490	1.48 (1.27, 1.73)
	Moderate HI (Child-Pugh B) (Test)	8	5860	1.58 (1.35, 1.85)
	Severe HI (Child-Pugh C) (Test)	6	13800	3.71 (3.08, 4.47)
	Normal Group (Reference)	16	3710	
Unbound $AUC_{0-tlast}$ (ng·h/mL)	Mild HI (Child-Pugh A) (Test)	8	5480	1.48 (1.26, 1.73)
	Moderate HI (Child-Pugh B) (Test)	8	5850	1.58 (1.35, 1.85)
	Severe HI (Child-Pugh C) (Test)	6	13800	3.72 (3.09, 4.47)
	Normal Group (Reference)	16	3700	
Unbound C_{max} (ng/mL)	Mild HI (Child-Pugh A) (Test)	8	920	1.38 (1.11, 1.71)
	Moderate HI (Child-Pugh B) (Test)	8	1120	1.67 (1.35, 2.08)
	Severe HI (Child-Pugh C) (Test)	6	1410	2.11 (1.63, 2.73)
	Normal Group(Reference)	16	669	

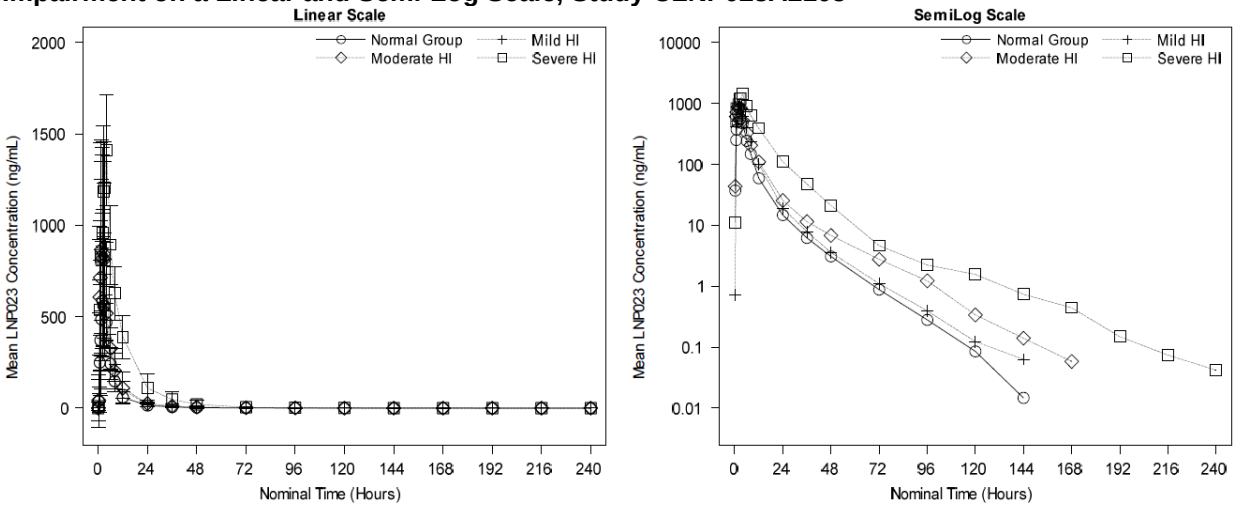
Source: page 69, Table 11-5 of Study CLNP023A2105Report
Abbreviations: $AUC_{0-\infty}$, area under the drug concentration-time curve extrapolated to infinity; $AUC_{0-tlast}$, area under the drug concentration curve from time 0 to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; HI, hepatic impairment; N, number of subjects; PK, pharmacokinetic

Figure 19. Mean Total Iptacopan Plasma Concentration-Time Profiles in Subjects With Hepatic Impairment on a Linear and Semi-Log Scale, Study CLNP023A2105



Source: Page 52, Figure 11-3, Study CLNP023A2105 Report
Abbreviations: HI, hepatic impairment; LNP023, iptacopan

Figure 20. Mean Unbound Iptacopan Plasma Concentration-Time Profiles in Subjects With Hepatic Impairment on a Linear and Semi-Log Scale, Study CLNP023A2105



Source: Page 65, Figure 11-17, Study CLNP023A2105 Report
Abbreviations: HI, hepatic impairment; LNP023, iptacopan

Study CLNP023A2104: Open-Label, Three-Cohort, Two-Period, Fixed Sequence Study to Investigate the Interaction of Clopidogrel and Cyclosporine, on the Iptacopan PK and to Assess the Effect of Multiple Oral Doses of Iptacopan on the PK of Digoxin and Rosuvastatin in Healthy Subjects

Study Design

The Applicant conducted study CLNP023A2104, an open-label, three-cohort, two-period, fixed sequence study to assess the DDI between clopidogrel (moderate CYP2C8 inhibitor) in cohort 1 or cyclosporine (P-gp, BCRP, OATP1B1, and OATP1B3 inhibitor) in cohort 2 on iptacopan PK. In cohort 3, the effect of multiple oral doses of iptacopan on the PK of digoxin (P-gp substrate) and rosuvastatin (BCRP, OATP1B1, and OATP1B3 substrate) in healthy subjects was assessed.

Fifty-six healthy male and female subjects 18 to 55 years of age were enrolled in the study. Cohort 1 enrolled 18 subjects, cohort 2 enrolled 21 subjects, and cohort 3 enrolled 17 subjects. In cohort 1, participants received either 100 mg of iptacopan alone or in combination with 300 mg of clopidogrel (loading dose) followed by 75 mg of clopidogrel once daily. PK sampling in plasma was up to 96 hours. In cohort 2, participants received 100 mg of iptacopan alone or in combination with 175 mg cyclosporine twice daily. PK sampling in plasma was up to 96 hours. In cohort 3, participants received a morning single dose of 0.25 mg digoxin and 10 mg rosuvastatin (administered as a two-drug cocktail) alone or in combination with 200 mg iptacopan twice daily. PK sampling in plasma was up to 10 days.

Results

Effect as Victim

In cohort 1, the GMR (90%CI) of total iptacopan C_{max}, $AUC_{0-\infty}$, $AUC_{0-tlast}$ following coadministration of a single oral dose of 100 mg iptacopan and 75 mg BID of clopidogrel relative to iptacopan alone was 1.05 (0.97, 1.14), 1.36 (1.28, 1.45), and 1.33 (1.26, 1.4), respectively.

In cohort 2, the GMR (90%CI) of total iptacopan C_{max}, $AUC_{0-\infty}$, $AUC_{0-tlast}$ following coadministration of a single oral dose of 100 mg iptacopan and 175 mg BID of cyclosporine relative to iptacopan alone was 1.41 (1.35, 1.47), 1.5 (1.42, 1.59), and 1.46 (1.39, 1.52), respectively.

Clopidogrel is considered a moderate CYP2C8 inhibitor according to public FDA CYP tables, not a strong CY2C8 inhibitor. Hence the interaction between clopidogrel and iptacopan might have not captured the worst-case scenario for CYP2C8 inhibition. The clinical pharmacology team sent an information request to the Applicant to assess the effect of strong CYP2C8 inhibition (e.g., with gemfibrozil) on iptacopan. The Applicant submitted a revised PBPK model to simulate the effect of multiple doses of gemfibrozil on iptacopan PK. The Applicant's revised PBPK model showed that the GMR for iptacopan C_{max} and $AUC_{0-\infty}$ did not increase to a clinically meaningful degree, with GMR ranging from (b) (4) to (b) (4). However, the PBPK results are implausible because of the observed higher iptacopan exposures with clopidogrel, a moderate CYP2C8 inhibitor. After review of the PBPK modeling, structural limitations were found for the PBPK model (see Section 14.7) that limited its use for assessing the drug interaction with a strong CYP2C8 inhibitor.

Gemfibrozil (a strong CYP2C8 inhibitor) is known to have a larger effect than clopidogrel on CYP2C8 substrate exposure. For example, the concomitant administration of gemfibrozil 600 mg twice a day for 5 days with a single 100 mg dose of daprodustat (a known CYPC28 substrate) resulted in an 18.6-fold increase in $AUC_{0-\infty}$ and a 3.9-fold increase in C_{max} of daprodustat on Day 4 of gemfibrozil administration, while AUC and C_{max} are expected to increase at least 4-fold and 3-fold, respectively, following concomitant administration of daprodustat with clopidogrel 75 mg once daily. Therefore, in the absence of more data, there is uncertainty that a strong CYP2C8 inhibitor may increase the exposure of iptacopan to levels beyond the current clinical experience. Therefore, the clinical pharmacology team recommends new Section 7 labeling text to not recommend the use of iptacopan in the presence of a strong CYP2C8 inhibitor (e.g., gemfibrozil).

Finally, the effects of clopidogrel and cyclosporine on the exposure of iptacopan as assessed in study CLNP023A2104 were found not to be clinically meaningful. The increase in exposure was within the current clinical experience and the exposure-safety relationship did not show iptacopan exposure-dependent changes in safety parameters. Therefore, the clinical pharmacology team found that dose adjustments are not necessary for subjects coadministered iptacopan and a moderate CYP2C8 inhibitor or a P-gp, BCRP, OATP1B1, or OATP1B3 inhibitor.

Effect as Perpetrator

In cohort 3, the GMR (90%CI) of digoxin C_{max}, $AUC_{0-\infty}$, and $AUC_{0-tlast}$ following coadministration of a single oral dose of 0.25 mg digoxin and 200 mg BID of iptacopan relative to digoxin administered alone was 1.08 (0.94, 1.24), 1.02 (0.93, 1.12), and 1 (0.9, 1.11), respectively.

In cohort 3, the GMR (90%CI) of rosuvastatin C_{max}, $AUC_{0-\infty}$, and $AUC_{0-tlast}$ following coadministration of a single oral dose of 10 mg rosuvastatin and 200 mg BID of iptacopan relative to rosuvastatin administered alone was 1 (0.87, 1.15), 1.01 (0.91, 1.12), and 1.3 (0.93, 1.16), respectively.

In general, iptacopan did not change the PK of P-gp, BCRP, OATP1B1, and OATP1B3 substrate to a clinically meaningful degree at the tested dose of 200 mg BID.

14.3. Bioanalytical Method Validation and Performance

Bioanalytical methods were reviewed for iptacopan in plasma ((b) (4)-MS-851), ultrafiltrate ((b) (4)-MS-1486), and urine ((b) (4)-MS-852) (Table 152 and Table 153). The methods consist of either solid phase extraction (ultrafiltration used the Ultrafiltration Centrifree device) or protein precipitation followed by dilution of the supernatant and analysis of diluted sample extract by a liquid chromatography-tandem mass spectrometry technique. The methods were suitable for the determination of iptacopan in plasma, ultrafiltrate, and urine. The methods were cross-validated between test sites (Table 154). A summary of analytical methods used in iptacopan clinical studies is presented in Table 155. All methods were validated, which satisfied the method validation criteria in accordance with the FDA guidance for industry *Bioanalytical Method Validation and Study Sample Analysis* (November 2022). The performance of the assay was considered acceptable for sample analysis.

Table 152. Summary of Method Validation Reports for the Plasma (DMPK R1501031, DMPK R1600743, DMPK R1900470) and Ultrafiltrate (DMPK R2200309) Analytical Assays

Method ID	DMPK R1501031	DMPK R1600743	DMPK R1900470	DMPK R2200309 (ultra-filtrate)
Linearity (by linear regression)	1.00 to 2000 ng/mL	1.00 to 2000 ng/mL	1.00 to 2000 ng/mL	0.2 to 599 ng/mL
Weighting factor	$1/X^2$	$1/X^2$	$1/X^2$	$1/X^2$
Inter-day accuracy (Bias %) (from 3 analytical runs on 3 validation days) at LLOQ	-1.6%	3.0%	3.0%	3.5%
Inter-day accuracy (Bias %) (from 3 analytical runs on 3 validation days) at above LLOQ	-2.0 to 5.3%	-1.3 to 3.3%	1.1 to 5.4%	-1.6 to 1.4%
Inter-day precision (CV %) (from 3 analytical runs on 3 validation days) at LLOQ	7.0%	9.7%	4.6%	8.7%
Inter-day precision (CV %) (from 3 analytical runs on 3 validation days) at above LLOQ	2.5 to 3.0%	3.3 to 5.8%	1.9 to 2.6%	3.5 to 7.2%
Post-preparative stability in extracts (Auto sampler)	5 days (at 15°C)	64 hours (5±3°C)	167 hours (at 2 to 8°C)	264 hours (5±3°C), 12 hours at RT
Short-term stability in spiked human plasma	7 days at RT	10 hours at RT	25 hours at RT	13 hours at RT
Freeze-thaw stability of spiked human plasma	4 freeze thaws cycles (≤ -15°C and ≤ -60°C)	5 freeze thaws cycles (-20 ± 5 and -78± 8°C)	5 freeze thaws cycles at -30°C to -10°C and -80°C to -60°C	5 freeze thaws cycles (20± 5 and -78± 8°C)
Long-term stability in spiked human plasma at ≤-15°C	179 days	1010 days	182 days	94 days
Long-term stability in spiked human plasma at ≤-70°C	179 days	1010 days	182 days	94 days
Method ID	**DMPK R1501031**	**DMPK R1600743**	**DMPK R1900470**	**DMPK R2200309 (ultra-filtrate)**
Interference from Hemolysis or Lipemic plasma	No	No	No	No for hemolysis plasma. Test in Lipemic plasma was not performed.
Stability in fresh human blood	2h at RT and on ice	2h at RT and on ice	2h at RT and on ice	Not performed
Stability duration information mean always "at least". e.g., At least 2 hours at RT				

Source: Table 1-7 Summary of biopharmaceutics Studies and Associated Analytical Methods
Abbreviations: C°, celsius; CV%, percent coefficient of variation; ID, identification; DMPK, drug metabolism and pharmacokinetics, LLOQ, lower limit of quantification; RT, room temperature

Table 153. Summary of Method Validation for the Urine Analytical Assays (DMPK R1600744, DMPK R1900470a)

Method Id	DMPK R1600744	DMPK R1900470a
Linearity (by linear regression)	10.0 to 10000 ng/mL	10.0 to 10000 ng/mL
Weighting factor	$1/X^2$	$1/X^2$
Inter-day accuracy (Bias %) (from 3 analytical runs on 3 validation days) at LLOQ	0.0%	2.0%
Inter-day accuracy (Bias %) (from 3 analytical runs on 3 validation days) at above LLOQ	-2.6 to 6.0%	-4.0 to 5.3%
Inter-day precision (CV %) (from 3 analytical runs on 3 validation days) at LLOQ	3.5%	5.8%
Inter-day precision (CV %) (from 3 analytical runs on 3 validation days) at above LLOQ	1.9 to 3.0%	2.3 to 3.3%
Post-preparative stability in extracts (Auto sampler)	148 hours (at 5±3°C)	120 hours (at 2 to 8°C)
Short-term stability in spiked human urine	13 hours at RT	41 hours at RT and wet ice
Freeze-thaw stability of spiked human plasma	5 freeze thaws cycles (-20± 5 and -78± 8°C)	5 freeze thaws cycles (-30 to - 10°C and -80 to -60°C)
Long-term stability in spiked human plasma at ≤-15°C	832 days	175 days
Method Id	**DMPK R1600744**	**DMPK R1900470a**
Long-term stability in spiked human plasma at ≤-70°C	828 days	175 days
Stability duration information mean always "at least". e.g., At least 2 hours at RT		

Source: Table 1-8 Summary of biopharmaceutics Studies and Associated Analytical Methods
Abbreviations: C°, celsius; CV%, percent coefficient of variation; DMPK, drug metabolism and pharmacokinetics, Id, identification; LLOQ, lower limit of quantification; RT, room temperature

Table 154. Summary of Method Cross Validation Across Analytical Sites

Matrix	BA sites	Method ID cross validated methods	Sample Type	Cross check data reported in the following studies	Iptacopan concentration range (ng/mL)
Plasma	Novartis US (ref lab) versus (b) (4) (test Lab)	DMPK R1501031 (Novartis) against DMPK R1600743 (b) (4)	28 Study samples from CLNP023X2101	DMPK R1600743	0 to 2360 (ref. Lab)
Plasma	(b) (4) (ref. Lab) versus (b) (4) (b) (4) (test Lab)	DMPK R1600743 (b) (4) against DMPK R1900470 (b) (4)	24 spiked QC samples	DMPK R1900470	3 to 1600 (ref. lab)
Urine	Novartis US (ref. lab) versus (b) (4) (test lab)	DMPK R1501031 (Novartis) against DMPK R1600744 (b) (4)	15 spiked QC samples	DMPK R1600744	10 to 7500 (ref. Lab)
Urine	(b) (4) (ref. Lab) versus (b) (4) (b) (4) (test Lab)	DMPK R1600744 (b) (4) against DMPK R1900470a (test Lab)	24 spiked QC samples	DMPK R1900470a	30 to 8000 (ref. lab)

Source: Table 1-9 Summary of biopharmaceutics Studies and Associated Analytical Methods
Abbreviations: BA, bioanalytical; DMPK, drug metabolism and pharmacokinetics; ID, identification; QC, quality control; ref, reference; US, United States

Table 155. Summary of Analytical Methods Used in Iptacopan Clinical Studies

Analyte	Matrix	LLOQ (ng/mL)	Method validation report	BA laboratory	Study	BA data report
LNP023	Plasma	1	DMPK R1600743	(b) (4)	Study CLFG316X2201	DMPK RCLFG316X2201
LNP023	Plasma	1	DMPK R1600743		Study A2101	DMPK RCLNP023A2101a
LNP023	Plasma	1	DMPK R1600743		Study A2301	DMPK RCLNP023A2301
LNP023	Urine		DMPK R1600744		Study A2301	DMPK RCLNP023A2301a
LNP023	Plasma	1	DMPK R1900470		Study A2301	DMPK RCLNP023A2301b
LNP023	Urine	10	DMPK R1900470a		Study A2301	DMPK RCLNP023A2301b
LNP023	Plasma	1	DMPK R1600743		Study B12301	DMPK RCLNP023B1301
LNP023	Plasma	1	DMPK R1600743		Study B12001B	DMPK RCLNP023B12001B-int
LNP023	Plasma	1	DMPK R1600743		Study X2101	DMPK RCLNP023X2101a
LNP023	Urine	10	DMPK R1600744		Study X2101	DMPK RCLNP023X2101b
LNP023	Plasma	1	DMPK R1501031	Novartis (EH)	Study X2101	DMPK RCLNP023X2101
LNP023	Plasma	1	DMPK R1600743	(b) (4)	Study X1102	DMPK RCLNP023X1102
LNP023	Urine	10	DMPK R1600744		Study X1102	DMPK RCLNP023X1102a
LNP023	Plasma	1	DMPK R1600743		Study X2202	DMPK RCLNP023X2202
LNP023	Urine	10	DMPK R1600744		Study X2202	DMPK RCLNP023X2202a
LNP023	Plasma	1	DMPK R1600743		Study X2203	DMPK RCLNP023X2203
LNP023	Urine	10	DMPK R1600744		Study X2203	DMPK RCLN023X2203c
LNP023	Plasma	1	DMPK R1900470		Study X2203	DMPK RCLN023X2203d
LNP023	Urine	10	DMPK R1900470a		Study X2203	DMPK RCLN023X2203d
LNP023	Plasma	1	DMPK R1600743		Study A2104	DMPK RCLNP023A2104
LNP023	Urine	10	DMPK R1600744		Study A2104	DMPK RCLNP023A2104a
LNP023	Plasma	1	DMPK R1600743		Study A2105	DMPK RCLNP023A2105
Analyte	**Matrix**	**LLOQ (ng/mL)**	**Method validation report**	**BA laboratory**	**Study**	**BA data report**
LNP023	Unbound LNP023 in ultra-filtrated plasma	0.2	DMPK R2200309	(b) (4)	Study A2105	DMPK RCLNP023A2105a
LNP023	Plasma	1	DMPK R1600743		Study A2107	DMPK RCLNP023A2107
LNP023	Plasma	1	DMPK R1600743		Study X2201	DMPK RCLNP023X2201
LNP023	Plasma	1	DMPK R1600743		Study X2204	DMPK RCLNP023X2204
LNP023	Plasma	1	DMPK R1600743		Study C12302	DMPK RCLNP023C12302-int
LNP023	Plasma	1	DMPK R1600743		Study C12301	DMPK RCLNP023C12301-int
LNP023	Plasma	1	DMPK R1900470		Study C12301	DMPK RCLNP023C12301a-int

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: BA, bioanalytical; CN, China; DMPK, drug metabolism and pharmacokinetics, EH, East Hanover; LLOQ, lower limit of quantification; LNP023, iptacopan

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

Population PK Analysis

This population PK analysis included PK data from studies in subjects with C3 glomerulopathy (C3G), immunoglobulin A nephropathy (IgAN), and PNH. The analysis was conducted on the following studies:

- X2201, PoC in subjects with PNH, iptacopan in addition to eculizumab (final data)
- X2202, phase 2 in subjects with C3G (final data)
- X2203, phase 2 in subjects with IgAN, part 1 and part 2 (final data)
- X2204, phase 2 in subjects with PNH, iptacopan as monotherapy (final data)
- C12301 (APPOINT-PNH), phase 3 in treatment-naïve subjects with PNH (data cutoff: July 31, 2022)
- C12302 (APPLY-PNH), phase 3 in subjects with PNH who are anti-C5-experienced (eculizumab or ravulizumab) (data cutoff: July 31, 2022)

The population PK analysis was restricted to iptacopan 100 and 200 mg BID. This restriction was applied due to a negative correlation between dose and bioavailability at doses lower than 100 mg, and the focus of the analysis was on the therapeutic dose range. A model including all available iptacopan doses was tested as a sensitivity analysis.

The final modeling dataset (doses 100 and 200 mg BID) consisted of 159 (68%) subjects with PNH, 48 (21%) subjects with IgAN, and 27 (12%) subjects with C3G. The number of subjects by study and treatment arm is listed in Table 156. The demographic information is summarized in Table 157.

Table 156. Number of Subjects and PK Concentrations Per Study and Treatment in Dataset for Model Building

Study	Treatment	Nb of subjects	Nb of samples	Nb of samples BLOQ
X2201 (PNH, LNP + SoC)	X2201-200mg (PNH)	10	288	1
	X2201-50mg-200mg (PNH)	5	48	0
X2202 (C3G)	X2202-10-25-100-200mg (C3G transpl.)	11	169	0
	X2202-10-25-100-200mg (C3G)	16	261	0
X2203 (IgAN)	X2203-100mg (IgAN)	22	260	9
	X2203-200mg (IgAN)	26	328	1
X2204 (PNH, LNP monotherapy)	X2204-25mg-100mg (PNH)	7	107	0
	X2204-50mg-200mg (PNH)	5	84	0
C12301 (PNH APPOINT)	C12301 200 mg (PNH)	40	286	0
C12302 (PNH APPLY)	C12302 200 mg (PNH)	62	480	0
	C12302 Anti-C5 treatment 200 mg (PNH)	30	128	0

Source: Lnp023-population-pk-model, Table 7-1
Notes: All data from the 100 mg and 200 mg bid cohorts was used for modeling, irrespective of whether or not the subjects received SoC.
Abbreviations: BID, twice daily; BLOQ, below the limit of quantification; C3G, C3 glomerulopathy; IgAN, immunoglobulin A nephropathy; Nb, number; LNP, iptacopan; PK, pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria, SoC, standard of care

Table 157. Demographics of Individuals in Population PK Modeling Dataset

Study	N	Orig. body weight (kg)	Age (years)	eGFR (mL/min/1.73m^2)	N (%) Female	N (%) Chinese	N (%) Japan	N (%) other Asian
X2201	15	77.4 (50-120)	45 (24-78)	94.5 (29.1-134)	6 (40)	0 (0)	0 (0)	0(0)
X2202	27	66 (43.6-112)	24 (18-70)	58.8 (27.4-134)	9 (33.3)	0 (0)	0 (0)	0(0)
X2203	48	71.4 (41.7-120)	34.5 (19-70)	48.1 (28.5-125)	22 (45.8)	9 (18.8)	3 (6.2)	12 (25)
X2204	12	55.8 (34.9-82.6)	35.5 (20-62)	116 (59.8-141)	6 (50)	2 (16.7)	0 (0)	10 (83.3)
C12301	40	69.2 (46.5-100)	38.5 (18-81)	105 (35.2-143)	17 (42.5)	20 (50)	0 (0)	7 (17.5)
C12302	92	68.2 (40-118)	53 (20-84)	93.4 (32.9-142)	64 (69.6)	2 (2.2)	9 (9.8)	7 (7.6)

Source: Lnp023-population-pk-model, Table 7-3
Median (min-max) are provided for baseline weight, baseline age and baseline eGFR
Abbreviations: eGFR, estimate glomerular filtration rate; Lnp023, iptacopan; max, maximum; min, minimum; N, number of subjects; Orig., original; PK. pharmacokinetic

The final base model (mod5/1cpt_1orderAbs_tlag_propErr.mlxtran) was a one-compartment model with first-order absorption, lag-time, and first order elimination. Correlation between apparent clearance (CL/F) and central volume (Vc/F) could not be estimated as it tended to 1 when included.

Besides body weight, which was already included in the base model, additional covariates listed in Table 158 were explored. Body weight (34.9 to 120 kg), baseline estimated glomerular filtration rate (eGFR; 27.4 to 143 mL/min/1.73m^2), ethnicity (Chinese, Japanese, non-China/Japan Asian, and others), and covariates on CL/F were retained in the final model, indicating increasing CL/F with increasing body weight and baseline eGFR, and decreasing CL/F in Chinese and other Asians (Chinese and Japanese excluded) compared to other ethnic groups. FDA requested additional covariate analysis for race based on the classification described in FDA guidance for industry and Food and Drug Administration staff: *Collection of Race and Ethnicity Data in Clinical Trial* (October 2016). Asians (n=81) were estimated to have decreased CL/F compared with Whites (n=145), Blacks (n=6), and other races (n=2), the effect of which was within the range of estimated effects in the 3 ethnicity sub categories (Chinese, Japanese, non-China/Japan Asian). The PK parameters of the final population PK model are summarized in Table 159.

Table 158. Parameter Estimates of Covariates in the Population PK Model With All Relevant Covariates Tested

Covariate	Parameters	Reason for investigation
Body weight	CL/F, Vc/F, Q/F, Vp/F	Clinical interest
Age	CL/F	Clinical interest
Sex	CL/F	Clinical interest
Ethnicity[1]	CL/F	Clinical interest
eGFR[2]	CL/F	Clinical interest
Disease (PNH, IgAN, C3G)	CL/F	Clinical interest
PNH population (naïve versus experienced)	CL/F	Clinical interest

Source: Lnp023-population-pk-model, Table 6-1
[1] Ethnicity: Chinese, Japanese, Asian, and rest of the world if enough data available in each category
[2] eGFR: estimated glomerular filtration rate.
Abbreviations: C3G, C3 glomerulopathy; CL/F, apparent clearance; eGFR, estimate glomerular filtration rate; IgAN, immunoglobulin A nephropathy; Lnp023, iptacopan; PK, pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria; Q/F, apparent intercompartmental clearance; Vc/F, apparent central volume; Vp/F, apparent peripheral volume of distribution

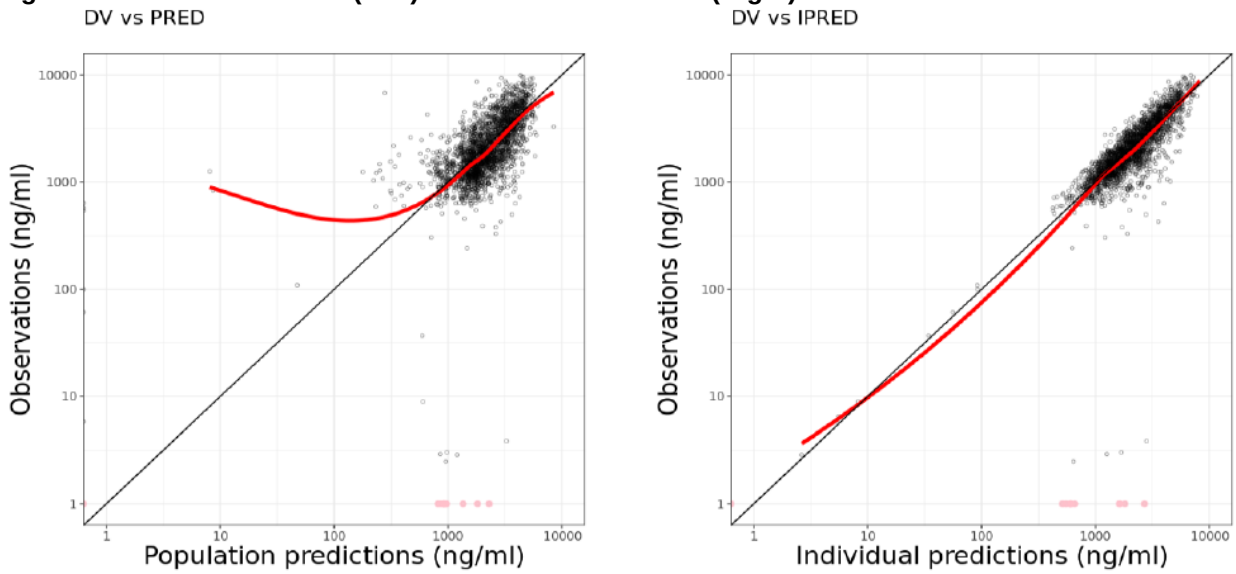
Table 159. Parameter Estimates of the Final Population PK Model

Parameter	Estimate (RSE*)	Shrinkage	p-value
Structural parameters			
CL/F (L/d)	138 (3%)		
Absorption lag time, Tlag (d)	0.0132 (12%)		
Vc/F	1.59 (12%)		
Absorption rate constant ka (1/d)	1.53 (4%)		
Inter-individual variability, standard deviations			
IIV on CL/F	0.296 (5%)	13%	
IIV on Tlag	0.645 (14%)	83%	
IIV on Vc/F	0.542 (18%)	94%	
IIV on ka	0.529 (6%)	26%	
Covariate effects			
Ethnicity (China) on CL/F	-0.314 (20%)		3.4e-07
Ethnicity (other Asian, not China nor Japan)	-0.187 (33%)		0.0021
Ethnicity (Japan) on CL/F	-0.15 (64%)		0.12
Baseline eGFR on CL/F	0.345 (14%)		9.9e-13
Weight on CL/F	0.278 (34%)		0.0037
Residual variability			
Proportional error	0.307 (2%)		

Source: Lnp023-population-pk-model, Table 7-6
*RSE: relative standard error expressed as percentage; shrinkage was calculated in ggPMX using variance-based definition of shrinkage; IIV: inter-individual variability; covariate effect for body weight was centered at 70 kg; baseline eGFR was centered at 66 mL/min/1.73 m^2 and reference ethnicity was “rest of the world” (i.e., all ethnicities excluding other Asian, Chinese and Japanese).
Abbreviations: CL/F, apparent clearance; eGFR, estimate glomerular filtration rate; IIV, inter-individual variability; ka, absorption rate constant; Lnp023, iptacopan; PK, pharmacokinetics; RSE, relative standard error; Tlag, time prior to the first measurable concentration; Vc/F, apparent central volume

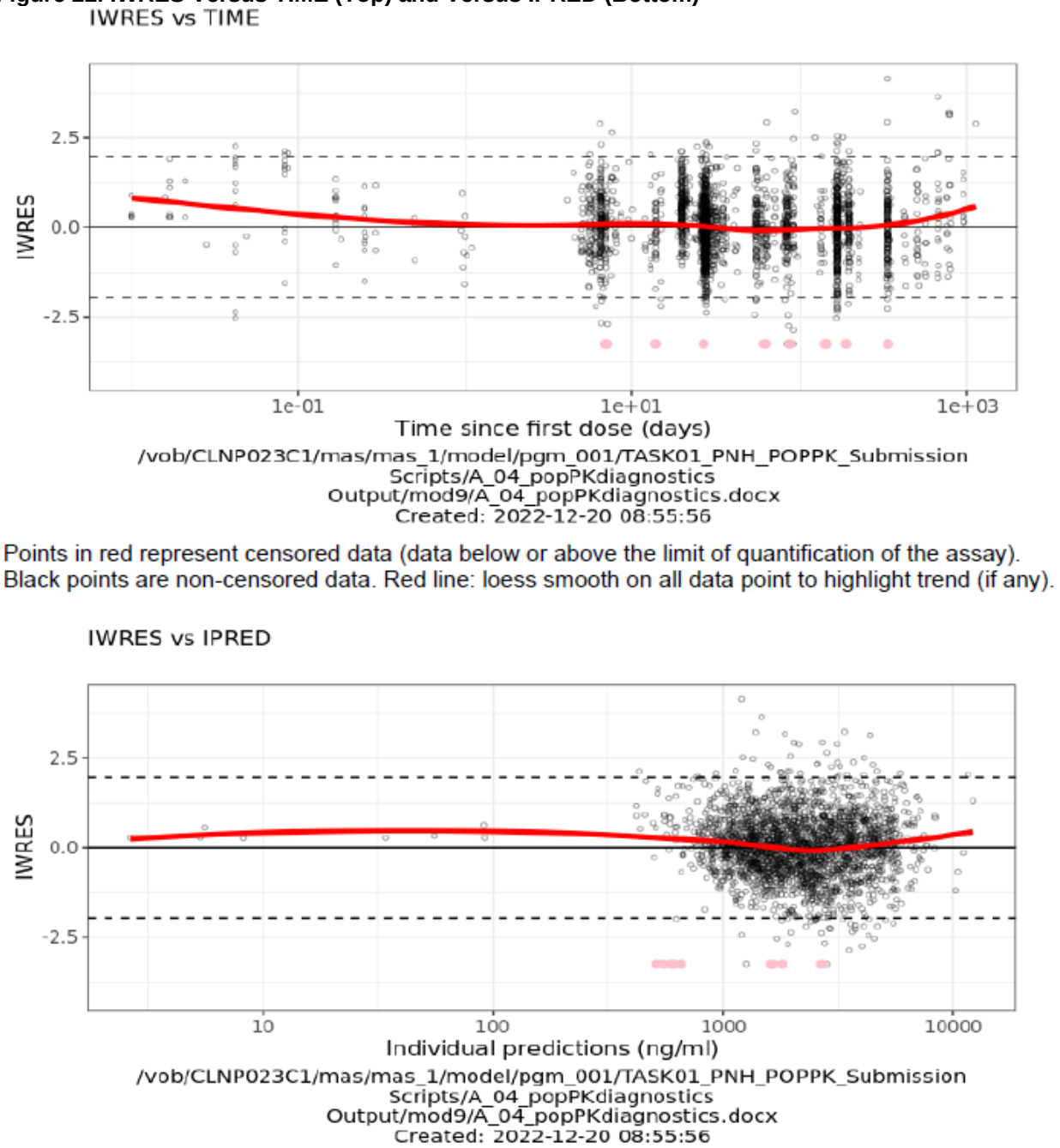
Plots of observed data versus population predictions and versus individual predictions (Figure 21) and plots of individual weighted residuals (IWRES) versus time and versus individual predictions (Figure 22) indicated an acceptable fit overall.

Figure 21. DV Versus PRED (Left) and DV Versus IPRED (Right)



Source: Lnp023-population-pk-model, Figure 7-7
Points in red represent censored data (data below or above the limit of quantification of the assay)
Black points are non-censored data. Red line: loess smooth on all data points to highlight trend (if any)
Abbreviations: DV, observations; IPRED, individual predictions; Lnp023, iptacopan; PRED, predictionsM; vs, versus

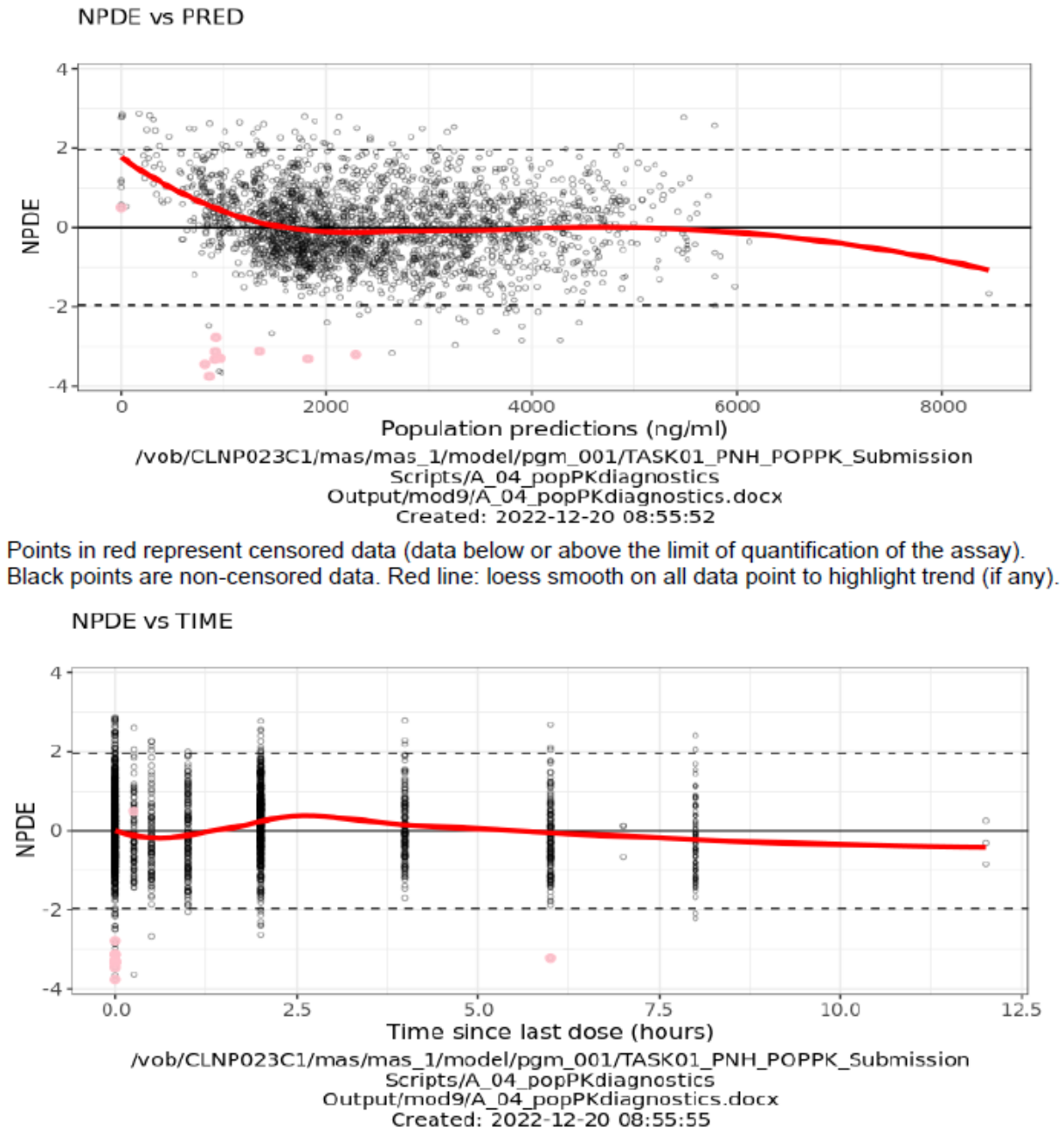
Figure 22. IWRES Versus TIME (Top) and Versus IPRED (Bottom)



Source: Lnp023-population-pk-model, Figure 7-9
Points in red represent censored data (data below or above the limit of quantification of the assay)
Black points are non-censored data. Red line: loess smooth on all data point to highlight trend (if any). Horizontal dashed lines: ±2 Standardized Residuals.
Abbreviations: IPRED, individual predictions; IWRES, individual weighted residuals; Lnp023, iptacopan; PK, pharmacokinetics; vs, versus

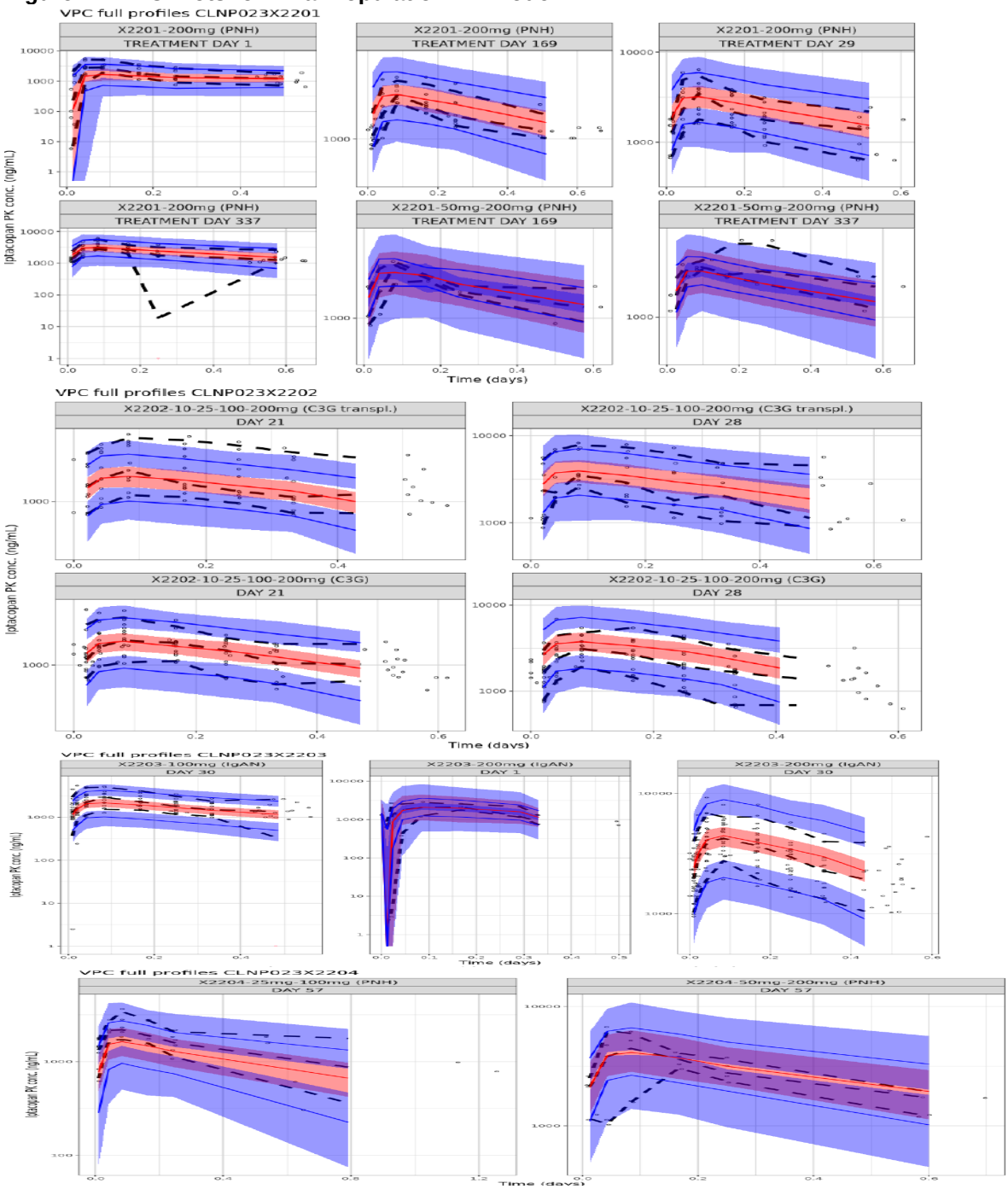
Simulation-based diagnostics, normalized prediction distribution errors (NPDE) and visual predictive check (VPC), were performed to evaluate the predictive performance of the model. Overall, the predictive capability of the final population PK model appears to be acceptable (Figure 23 and Figure 24).

Figure 23. NPDE Versus PRED (Top) and Versus TIME (Bottom)



Source: Lnp023-population-pk-model, Figure 7-8
Points in red represent censored data (data below or above the limit of quantification of the assay).
Black points are non-censored data. Red line: loess smooth on all data point to highlight trend (if any). Horizontal dashed lines: ±2 Standardized Residuals.
Abbreviations: NPDE, normalized prediction distribution errors; Lnp023, iptacopan; pk, pharmacokinetic; PRED, predicted; vs, versus

Figure 24. VPC Plots for Final Population PK Model



Source: Lnp023-population-pk-model, Figure 7-10
Dots: observed data; dash lines: 5th, 50th and 95th percentiles of observed data; solid lines: 5th, 50th and 95th percentiles of model predictions; shaded areas: model-based 90% confidence intervals for respective percentiles. Binning was performed by nominal time.
Abbreviations: C3G, C3 glomerulopathy; Conc, concentration; IgAN, immunoglobulin A nephropathy; Lnp023, iptacopan; PK, pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria; VPC, visual predictive check

A descriptive model enabling inclusion of all phase 2 data (dose levels 10 to 200 mg BID) accounting for the under-dose proportionality was tested as a sensitivity analysis. In this model, the individual relative bioavailability was parametrized with a maximum effect (E_{max}) function

(Equation 1), where F_i is the relative bioavailability for the individual i; F_{pop} is the population parameter for bioavailability; $E0_{pop}$ and $Emax_{pop}$ are relative bioavailability factors at low and high doses, respectively; and $ED50_{pop}$ is the relative bioavailability midpoint. Of note, F_{pop} and $Emax_{pop}$ were fixed to 1. $Dose_j$ is the dose, and j represents each administered dose in phase 2 and phase 3 studies of iptacopan.

Equation 1. Individual Bioavailability

$$F_i = F_{pop} \cdot \left(E0_{pop} + (Emax_{pop} - E0_{pop}) * \left(\frac{Dose_j}{ED50_{pop} + Dose_j}\right)\right) \cdot \exp(\eta_i),$$

The parameter estimates for the final sensitivity population PK model of iptacopan, including all dose levels, are listed in Table 160. Baseline eGFR (27.1 to 143 mL/min/1.73m^2), body weight (34.9 to 120 kg), ethnicity (Chinese, Japanese, non-China/Japan Asian, and others), and indication (PNH, C3G, and IgAN) were covariates for CL. Additional covariate analysis suggested Asians (n=101) had decreased CL/F compared with Whites (n=165), Blacks (n=7), and other races (n=2), the effect of which was within the range of estimated effects in the 3 ethnicity sub categories (Chinese, Japanese, non-China/Japan Asian).

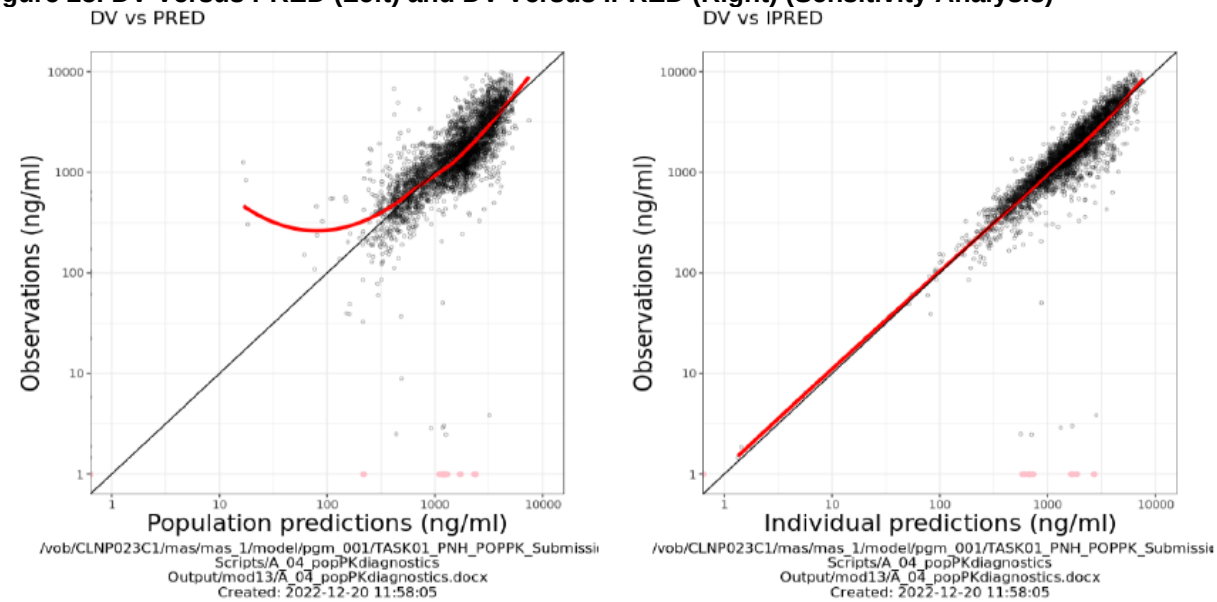
Table 160. Parameter Estimates of the Final Sensitivity Analysis Population PK Model

Parameter	Estimate	Shrinkage	p-value
Structural parameters			
CL/F (L/d)	196 (4%)		
Relative bioavailability factor at low doses, E0	9.04 (5%)		
Relative bioavailability midpoint, ED50 (mg)	12.6 (9%)		
Relative bioavailability factor at high doses, Emax	1 (fixed)		
Relative bioavailability, F	1 (fixed)		
Absorption rate constant, ka (1/d)	1.38 (4%)		
Absorption lag time, Tlag (d)	0.0128 (6%)		
Vc/F (L)	3 (7%)		
Inter-individual variability, standard deviations			
IIV on CL/F	0.299 (5%)	11%	
IIV on ka	0.572 (6%)	22%	
IIV on Tlag	0.446 (12%)	79%	
IIV on Vc/F	0.329 (13%)	93%	
Covariate effects			
Baseline eGFR on CL/F	0.339 (15%)		4.4e-11
Weight on CL/F	0.264 (34%)		0.0032
Ethnicity (*China) on CL/F*	-0.27 (21%)		2.7e-06
Ethnicity (other *Asian, no China nor Japan) on CL/F*	-0.0931 (60%)		0.095
Ethnicity (Japan*) on CL/F*	-0.106 (87%)		0.25
Indication (C3G patients)	0.284 (25%)		5.9e-05
Indication (IgAN patients)	0.0423 (119%)		0.4
Residual variability			
Proportional error	0.306 (1%)		

Source: Lnp023-population-pk-model, Table 7-7
%RSE: relative standard error expressed as percentage; Shrinkage was calculated in ggPMX using variance-based definition of shrinkage.
IIV: inter-individual variability; covariate effect for body weight was centered at 70 kg; baseline eGFR was centered at 65 mL/min/1.73 m^2; reference ethnicity was rest of the world (i.e., all ethnicities excluding other Asian, Chinese and Japanese and reference indication was PNH.
Abbreviations: C3G, C3 glomerulopathy; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; ED50, half maximal effective concentration; IgAN, immunoglobulin A nephropathy; IIV, inter-individual variability; ka, absorption rate constant; PK pharmacokinetics; PNH, paroxysmal nocturnal hemoglobinuria; Tlag, time prior to the first measurable concentration; Vc/F, apparent central volume

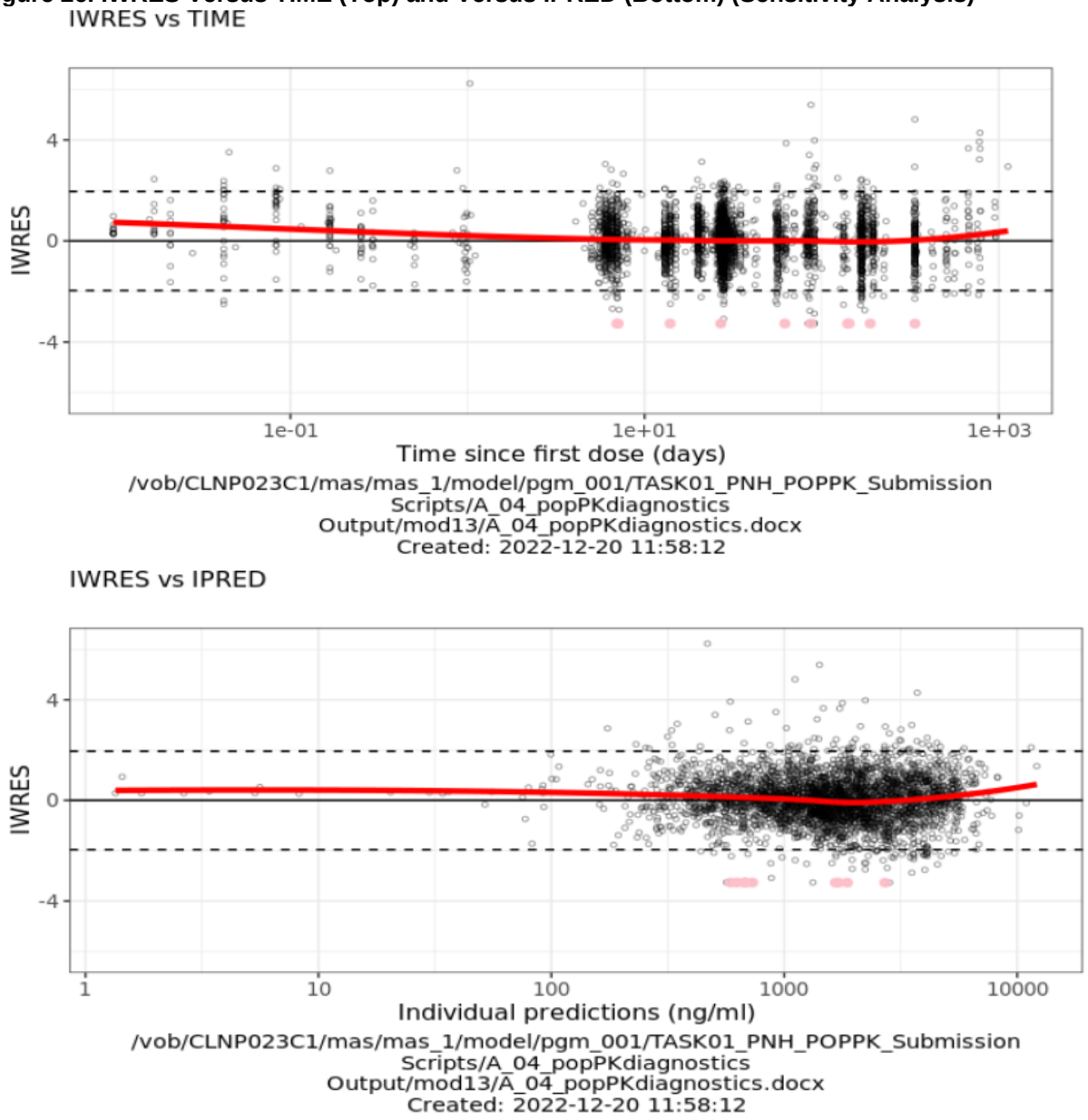
Plots of observed data versus population predictions and versus individual predictions (Figure 25), and plots of individual weighted residuals versus time and versus individual predictions were produced (Figure 26) and indicated an acceptable fit overall. Additionally, simulation-based diagnostics (NPDE and VPCs) were performed to evaluate the predictive performance of the model. Overall, the predictive capability of the sensitivity model appeared to be acceptable (Figure 27 and Figure 28).

Figure 25. DV Versus PRED (Left) and DV Versus IPRED (Right) (Sensitivity Analysis)



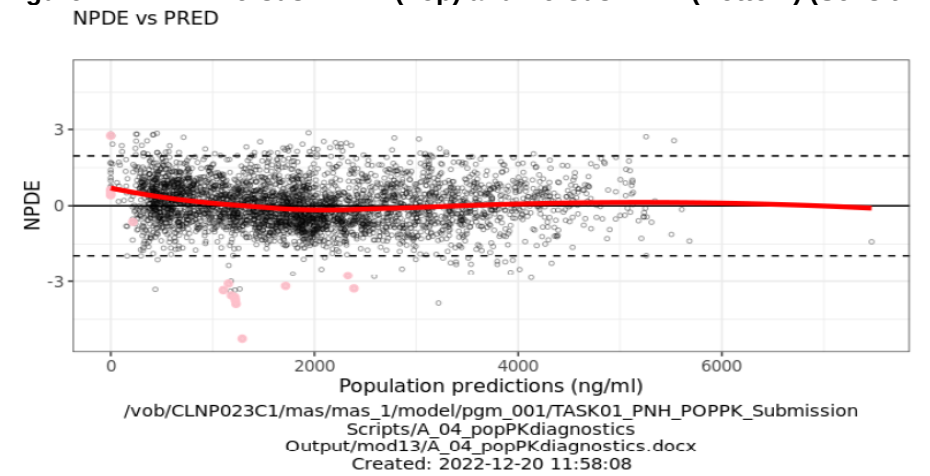
Source: Lnp023-population-pk-model, Figure 7-12
Points in red represent censored data (data below or above the limit of quantification of the assay).
Black points are non-censored data. Red line: loess smooth on all data point to highlight trend (if any).
Abbreviations: DV, observations; IPRED, individual predictions; Lnp023, iptacopan; PRED, predictions

Figure 26. IWRES Versus TIME (Top) and Versus IPRED (Bottom) (Sensitivity Analysis)

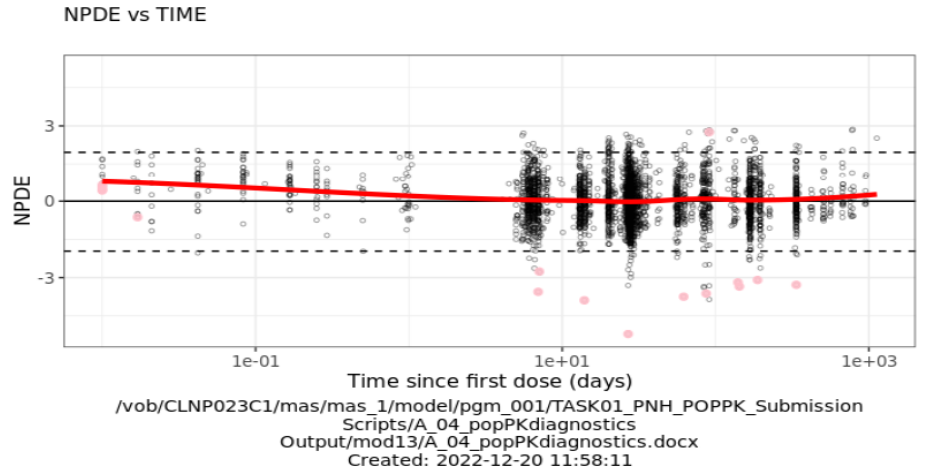


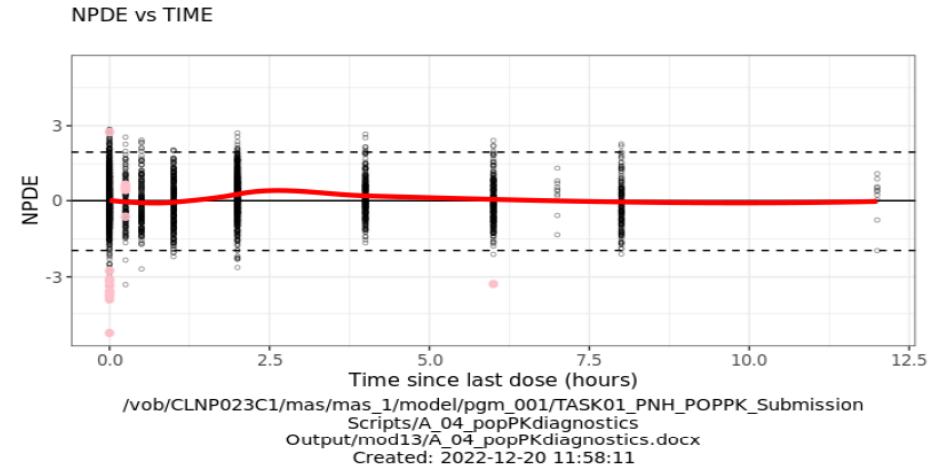
Source: Lnp023-population-pk-model, Figure 7-14
Points in red represent censored data (data below or above the limit of quantification of the assay).
Black points are non-censored data. Red line: loess smooth on all data point to highlight trend (if any). Horizontal dashed lines: ±2 Standardized Residuals.
Abbreviations: IPRED, individual predictions; IWRES, individual weighted residuals; Lnp023, iptacopan; vs, versus

Figure 27. NPDE Versus PRED (Top) and Versus TIME (Bottom) (Sensitivity Analysis)



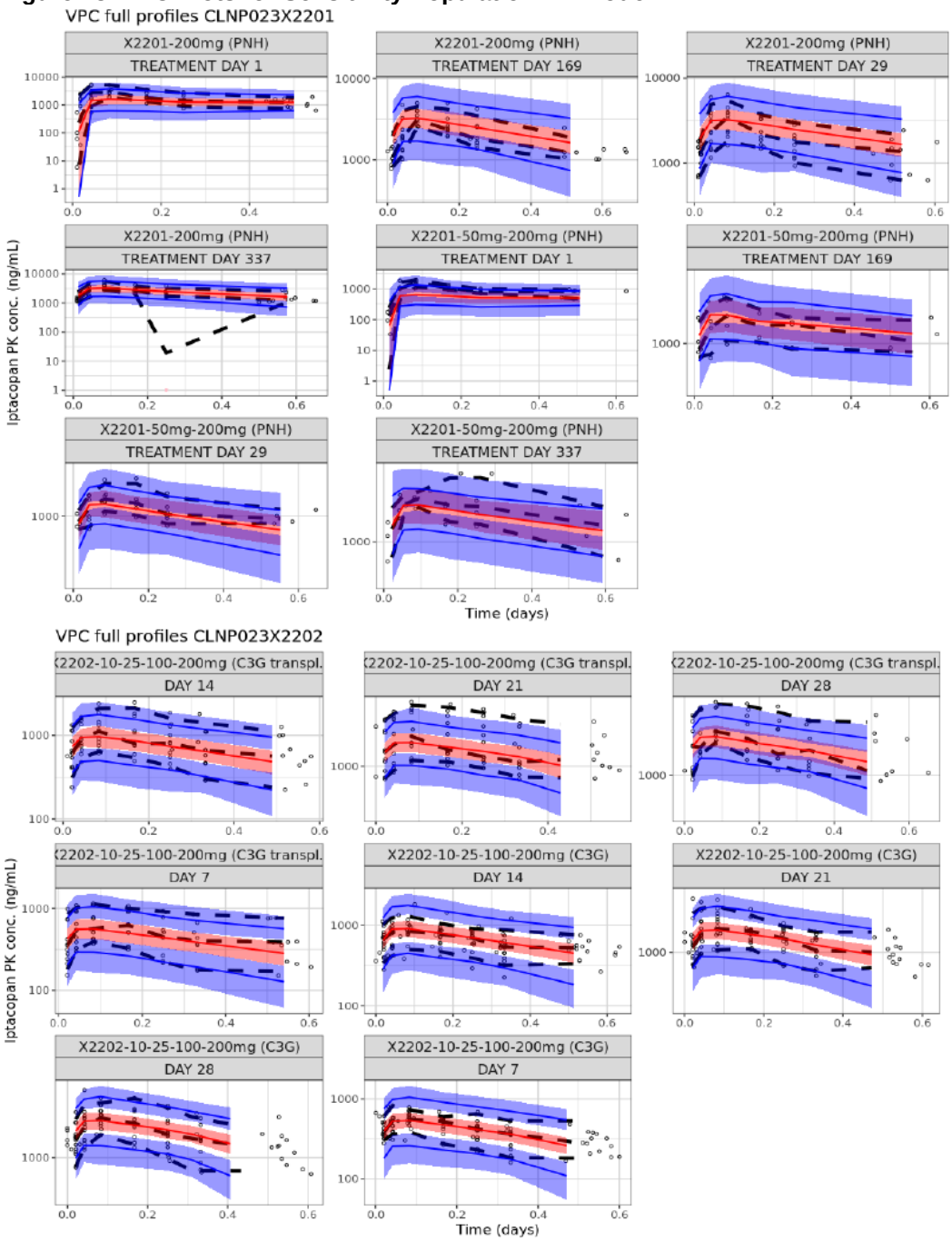
Points in red represent censored data (data below or above the limit of quantification of the assay).
Black points are non-censored data. Red line: loess smooth on all data point to highlight trend (if any

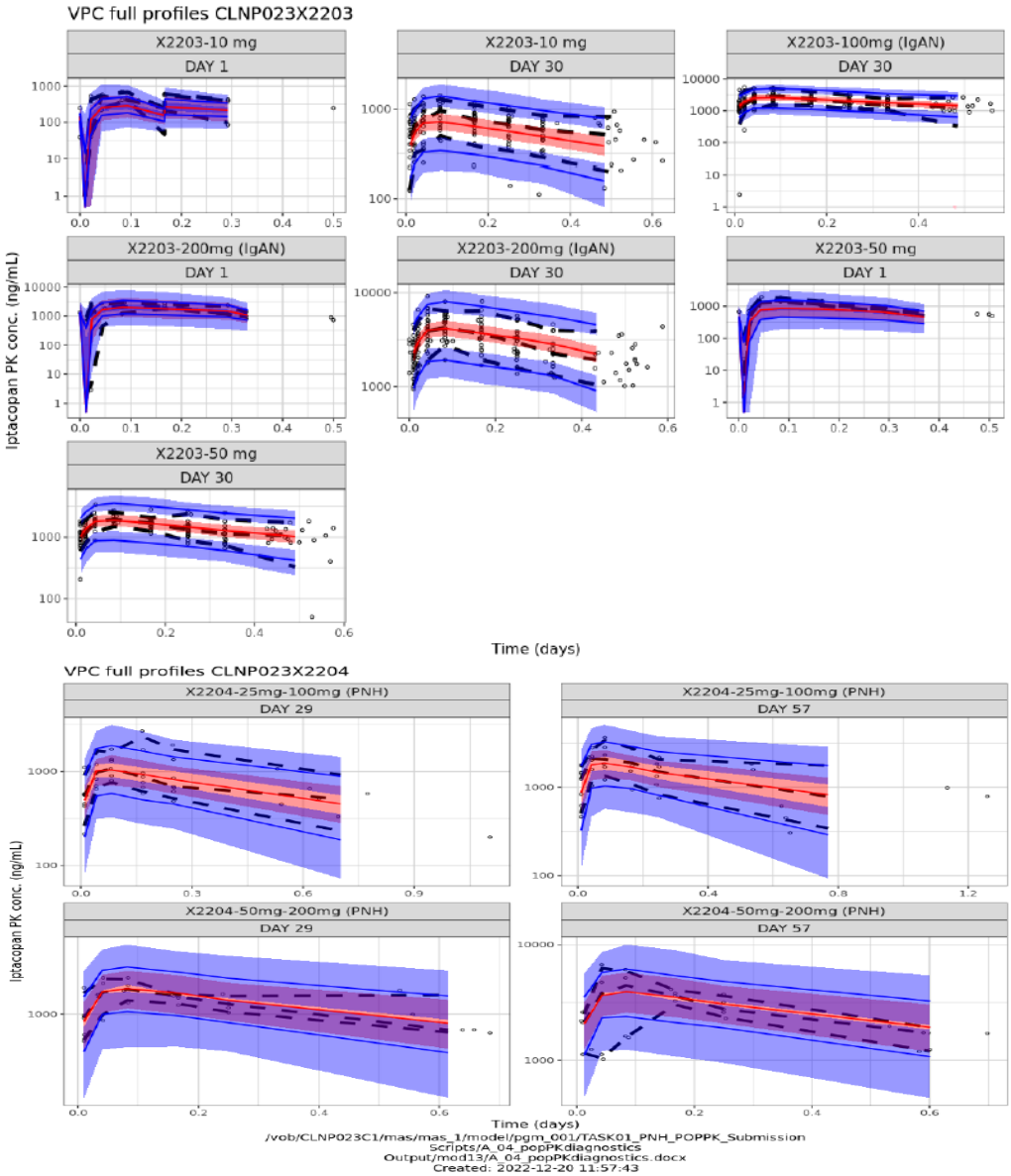




Source: Lnp023-population-pk-model, Figure 7-13
Points in red represent censored data (data below or above the limit of quantification of the assay).
Black points are non-censored data. Red line: loess smooth on all data point to highlight trend (if any). Horizontal dashed lines: ±2 Standardized Residuals.
Abbreviations: NPDE, normalized prediction distribution errors; Lnp023, iptacopan; PRED, predictions; vs, versus

Figure 28. VPC Plots for Sensitivity Population PK Model





Source: Lnp023-population-pk-model, Figure 7-15
Dots: observed data: pink dots are observed BLOQ; dash lines: 5th. 50th and 95th percentiles of observed data: shaded areas: model-based 90% confidence intervals for respective percentiles. Binning was performed by nominal time.
Abbreviations: BLOQ, below the limit of quantification; C3G, C3 glomerulopathy; conc, concentration; IgAN, immunoglobulin A nephropathy; Lnp023, iptacopan; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; VPC, visual predictive check

Reviewer Comment:

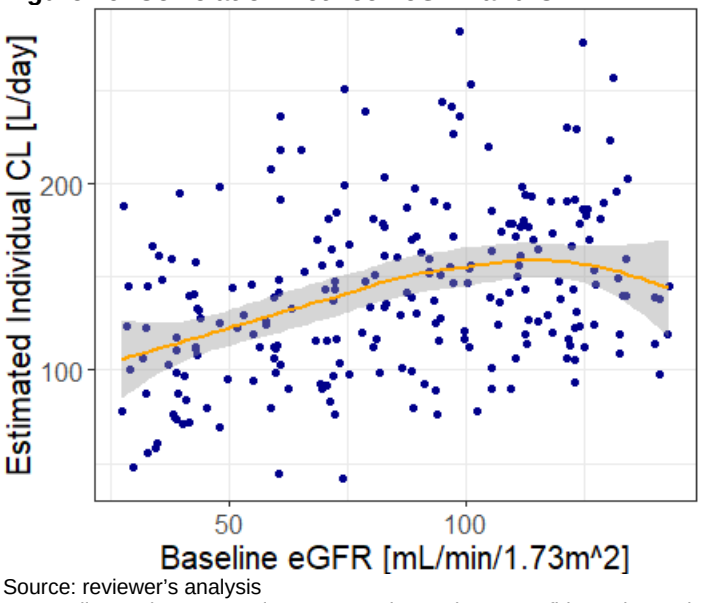
The final population PK model and sensitivity population PK model were reproduced. The model estimated a flip-flop PK for iptacopan. A small apparent volume of distribution was estimated with a large shrinkage in the final model, which may be due to the inappropriate model structure. However, a two-compartment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

To support the labeling statement, a visual inspection was performed for the predicted individual CL and intrinsic factors using the final population PK model. There were trends showing that

CL increased following increases in eGFR (Figure 29) and body weight (Figure 30) and decreases in age (Figure 31). As expected, CL decreased with increased severity of renal impairment (Figure 32). Substantial overlap was observed for model-estimated individual CL/F across all races (Figure 33). No difference in CL was identified between males and females (Figure 34). The effects of the above-mentioned covariates were not considered clinically relevant since (1) the PK exposure associated with the proposed dosage (200 mg BID) was considered lying near the plateau of the PK/PD and exposure-response relationship for efficacy, and (2) no exposure-response correlation was demonstrated for safety outcomes.

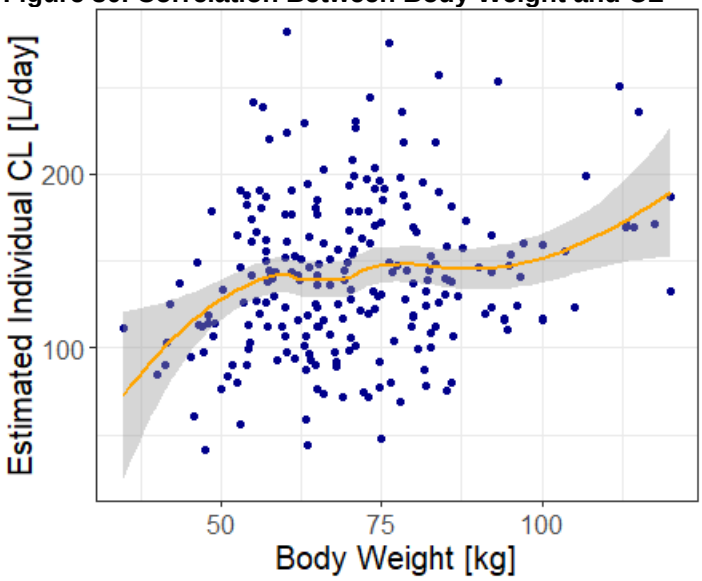
Population PK simulation was performed for the 159 subjects with PNH from CLNP023X2201, CLNP023X2204, CLNP023C12301, and CLNP023C12302 using the individual PK parameters estimated by the final population PK model. The subjects were assumed to have received the 200 mg BID dosing regimen. The mean (SD) of C_{max}, trough concentration (C_{trough}), and average concentration at steady state were 4163 (1330) ng/mL, 1937 (748) ng/mL, and 2949 (996) ng/mL, respectively.

Figure 29. Correlation Between eGFR and CL



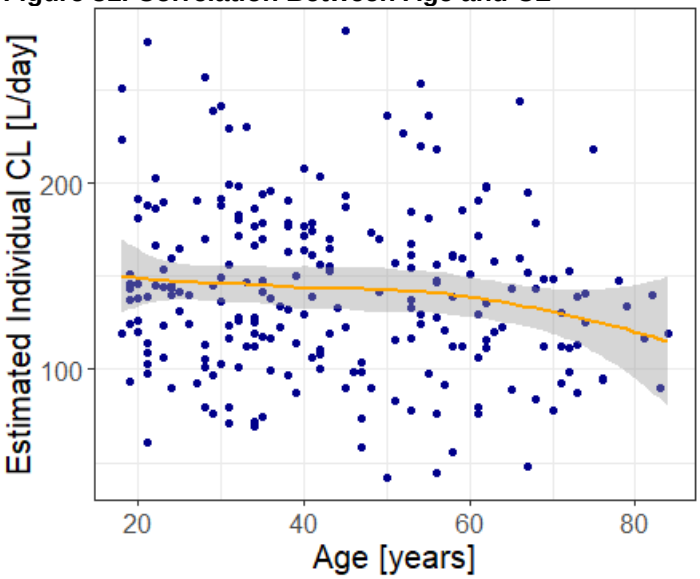
Source: reviewer's analysis
Orange line and grey area: loess regression and 95% confidence interval
Abbreviations: CL, clearance; eGFR, estimated glomerular filtration rate

Figure 30. Correlation Between Body Weight and CL



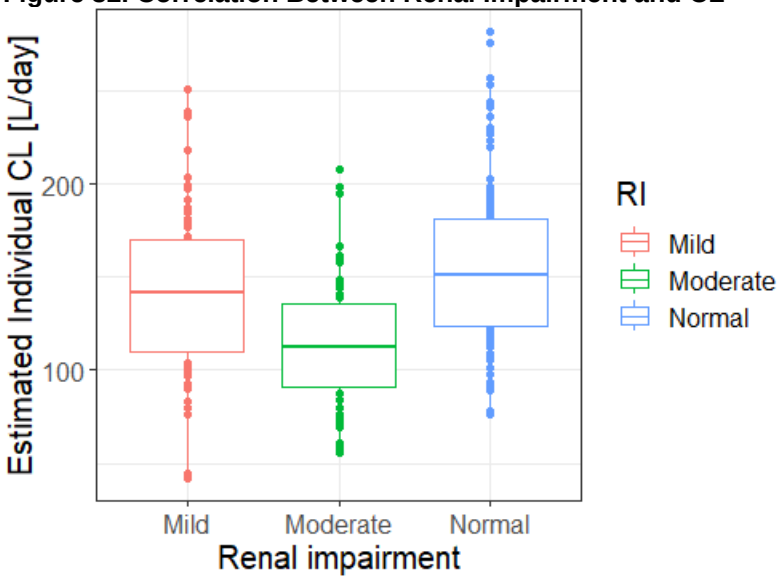
Source: reviewer's analysis
Abbreviations: CL, clearance
Orange line and grey area: loess regression and 95% confidence interval

Figure 31. Correlation Between Age and CL



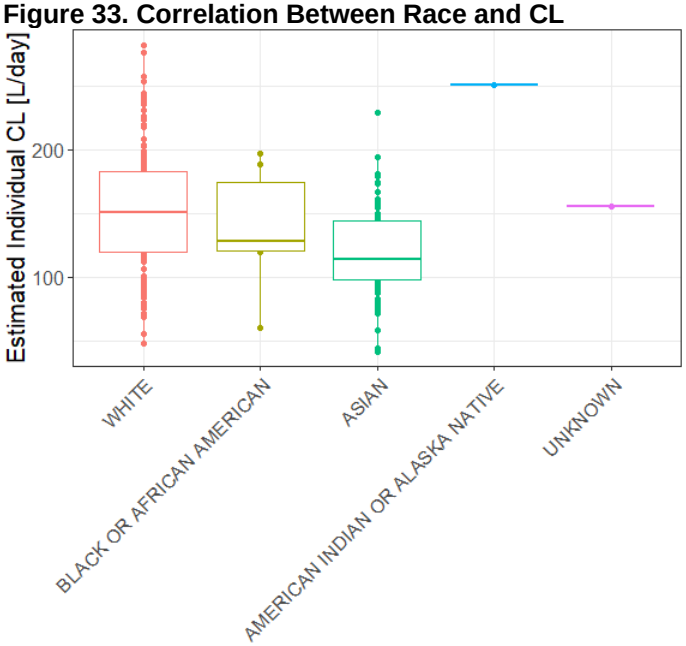
Source: reviewer's analysis
Abbreviations: CL, clearance
Orange line and grey area: loess regression and 95% confidence interval

Figure 32. Correlation Between Renal Impairment and CL



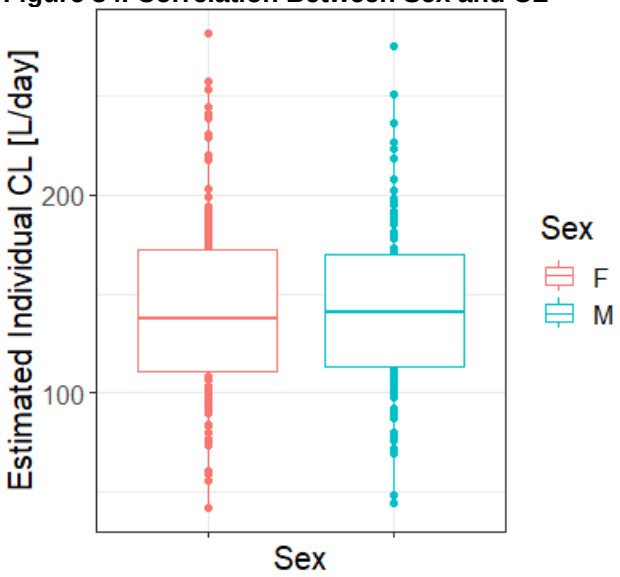
Source: reviewer's analysis
Abbreviations: CL, clearance, RI, renal impairment

Figure 33. Correlation Between Race and CL



Source: reviewer's analysis
Abbreviations: CL, clearance

Figure 34. Correlation Between Sex and CL



Source: reviewer's analysis
Abbreviations: CL, clearance, F, female, M, male

PK/PD Analysis

The analysis was conducted on the following studies:

- CLNP023X2101, first-in-human in healthy volunteers (final data)
- CLNP023X2201, phase 2 in subjects with PNH, iptacopan in addition to eculizumab (final data)
- CLNP023X2202, phase 2 in subjects with C3G (final data)
- CLNP023X2203, phase 2 in subjects with IgAN (final data)
- CLNP023X2204, phase 2 in subjects with PNH, iptacopan as monotherapy (final data)

All iptacopan dose levels were included in the analysis. The modeling dataset contained a total of 247 subjects, with 88 (35.6%) healthy volunteers, 103 (41.7%) subjects with IgAN, 27 (10.9%) subjects with C3G, and 29 (11.7%) subjects with PNH. The demographics of the subjects are summarized in Table 161. The number of subjects by study and treatment arm as well as the number of observations of each biomarker are listed in Table 162.

Table 161. Demographics of Patients in the PKPD Analysis Dataset

Study	N	Weight, kg (median [range])	Age, years (median [range])	Female (%)	Mainland Chinese (%)	Japanese (%)	Asian Others (%)
X2101 (HV)	88	80.2 [60.4-102]	46 [19-55]	8.0	0.0	0.0	1.1
X2201 (PNH experienced)	16	76.2 [50-120]	45 [24-78]	37.5	0.0	0.0	0.0
X2202 (C3G)	27	66 [43.6-112]	24 [18-70]	33.3	0.0	0.0	0.0
X2203 (IgAN)	103	75.3 [39-120]	37 [18-70]	38.8	9.7	4.9	29.1
X2204 (PNH naive)	13	57.2 [34.9-82.6]	35 [20-62]	53.8	15.4	0.0	84.6
Total	**247**	**76.1 [34.9-120]**	**38 [18-78]**	**27.9**	**4.9**	**2**	**17**

Source: lnp023-population-pkpd-model, Table 7-2
Abbreviations: C3G, C3 glomerulopathy; HV, healthy volunteer, IgAN, immunoglobulin A nephropathy; N, number; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

Table 162. Number of Subjects and Number of Biomarker Samples With Time-Matched PK by Study and Treatment Arm

			Wieslab			Plasma Bb*	Plasma sC5b-9*
Study	Treatment	No. of subjects	No. of samples	No. of samples BLOQ	No. of samples ALOQ	No. of samples	No. of samples
X2101 (Healthy volunteers)	Placebo	22	244	0	37	236	236
	LNP023 5mg SD	6	57	0	0	57	57
	LNP023 10mg SD	6	56	3	8	56	56
	LNP023 25mg SD	6	56	8	8	56	56
	LNP023 50mg SD	6	53	13	5	53	53
	LNP023 100mg SD	6	60	24	3	60	60
	LNP023 200mg SD	6	53	22	0	53	53
	LNP023 400mg SD	6	56	25	0	56	56
	LNP023 25mg	6	73	9	3	71	71
	LNP023 50mg	6	72	15	1	69	69
	LNP023 100mg	6	75	18	0	70	70
	LNP023 200mg	6	75	4	2	71	71
X2201 (PNH naive)	LNP023 50mg	6	66	13	0	67	67
	LNP023 200mg	10	113	83	0	114	113
X2202 (C3G)	LNP023 10-25-100-200mg (native kidney)	16	200	116	0	197	197
	LNP023 10-25-100-200mg (transplanted kidney)	11	136	68	2	137	137
X2203 (IgAN)	Placebo	24	185	0	77	183	177
	LNP023 10mg	18	111	3	18	111	108
	LNP023 50mg	17	116	4	8	117	117
	LNP023 100mg	18	135	14	13	134	134
	LNP023 200mg	26	170	62	17	174	168
X2204 (PNH experienced)	LNP023 25mg-100mg	7	87	16	0	86	86
	LNP023 50mg-200mg	6	68	27	0	68	67
Total		**247**	**2317**	**547**	**202**	**2296**	**2279**

Source: lnp023-population-pkpd-model, Table 7-3
*No censored data for this biomarker
Abbreviations: ALOQ, above the limit of quantification; Bb, activated factor B; BLOQ, below the limit of quantification; C3G, C3 glomerulopathy; IgAN, immunoglobulin A nephropathy; LNP023, iptacopan; No., number; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; SD, standard deviation

The response markers for this analysis were Bb, Wieslab assay, and plasma sC5b-9. Soluble C5b-9 is the terminal product of complement activation and is also known as the soluble membrane attack complex or terminal complement complex (TCC). The Wieslab is an ex vivo assay that measures the amount of C5b-9 formation after alternative pathway activation of serum. The activation of the alternative pathway of complement generates the active proteolytic enzyme Bb. Plasma levels of Bb may be elevated in diseases associated with alternative pathway activation.

A direct-response sigmoid E_{max} model was applied for the three biomarkers of interest (Equation 2), where Y(t) is the biomarker response at time t and C(t) is the observed iptacopan concentration at time t; Y(0) = base is the baseline biomarker value before the start of iptacopan treatment; E_{max} is the maximal reduction of the biomarker relative to baseline; half-maximal effective concentration (EC_{50}) is the iptacopan concentration at which the biomarker inhibition is half-maximal; and γ (gamma) is the shape parameter (Hill coefficient).

Equation 2. E_{max} Model for PD Biomarkers

$$Y(t) = Y(0) * \left(1 - \frac{E_{max} C(t)^{\gamma}}{(EC_{50}{}^{\gamma} + C(t)^{\gamma})}\right)$$

Wieslab

Final parameter estimates are shown in Table 163. EC_{50} values appeared similar between all subject populations and lower in healthy volunteers. The typical EC_{50} value in subjects was 657 ng/mL (relative standard error [RSE] = 4%). The maximal reduction of Wieslab was different for all populations. The maximal effect ($100 \times E_{max}$) of the reference group (subjects with IgAN) was 78.3% (RSE = 2%).

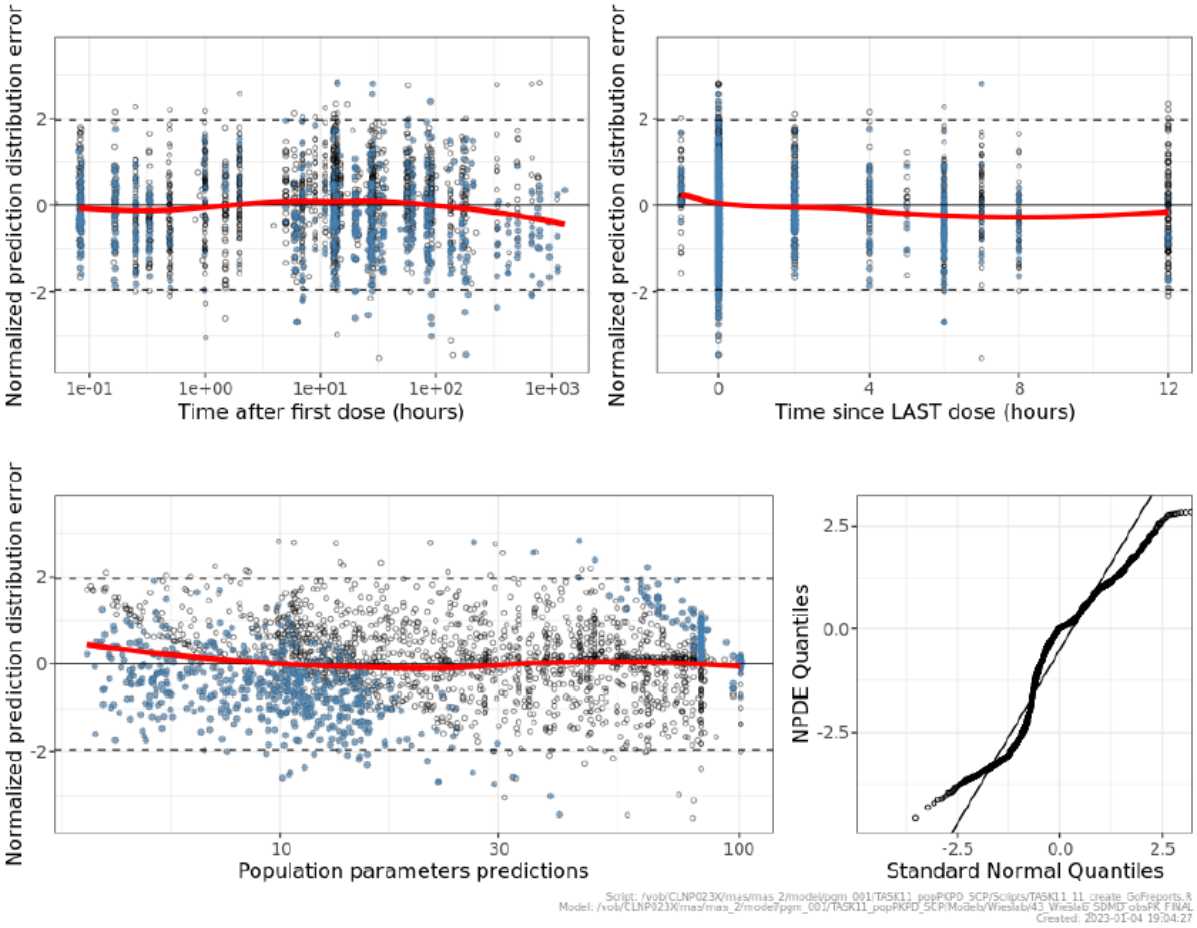
Table 163. Parameter Estimates of Final Wieslab PKPD Model

	Parameter	Value	RSE* (%)	Shrinkage (%)	p-value
Population param.	Base (%)	50.6	1		
	EC50 (ng/ml)	657	4		
	Emax (-)	0.783	2		
	gamma (-)	3.29	5		
IIV	omega_Base	0.209	10	66	
	omega_EC50	0.332	7	45	
	omega_Emax	0.285	20	80	
Covariate effects	beta_Base_logtWIESLABB	0.984	3		<2.2e-16
	beta_EC50_MYPOPTYPE3_Healthy	-0.596	10		<2.2e-16
	beta_Emax_logtWIESLABB_0	1.34	9		<2.2e-16
	beta_Emax_MYPOPTYPE1_C3G_native_kidney	0.43	45		0.025
	beta_Emax_MYPOPTYPE1_C3G_transplanted	0.911	23		2e-05
	beta_Emax_MYPOPTYPE1_Healthy	1.11	12		4.4e-16
	beta_Emax_MYPOPTYPE1_PNH_experienced	-0.244	71		0.16
	beta_Emax_MYPOPTYPE1_PNH_naive	0.207	81		0.22
	Constant residual variability (a)	1.19	17		
	Proportional residual variability (b)	0.195	4		

Source: lnp023-population-pkpd-model, Table 7-8
*RSE: relative standard error
Abbreviations: C3G, C3 glomerulopathy; EC_{50}, half maximal effective concentration; E_{max}, maximum effect; IIV, inter-individual variability; param., parameter; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; RSE, relative standard error

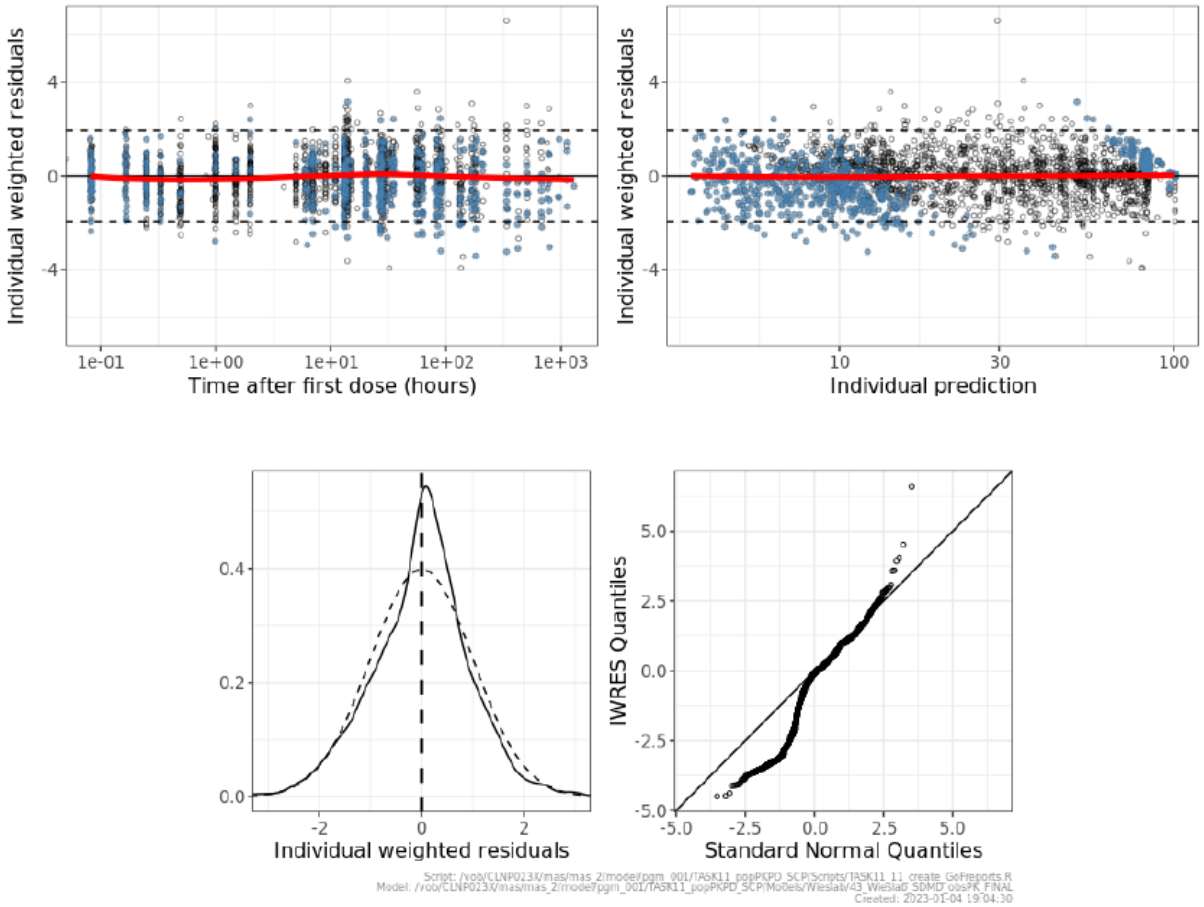
Goodness-of-fit plots showed that the final Wieslab model appeared to be able to describe the data. There were no major trends observed when considering unstratified NPDE versus time, versus time since last dose, and versus prediction (Figure 35). Individual weighted residuals versus time and versus individual predictions (Figure 36) and plots of observed data versus population and individual predictions (Figure 37) also did not show major trends. Visual predictive checks stratified by population type showed that the model appeared to be able to capture the Wieslab time course as well as interindividual variability (Figure 38).

Figure 35. NPDE Panel (NPDE Versus Time, NPDE Versus Time Since Last Dose, and NPDE Versus PRED) for Final Wieslab PKPD Model



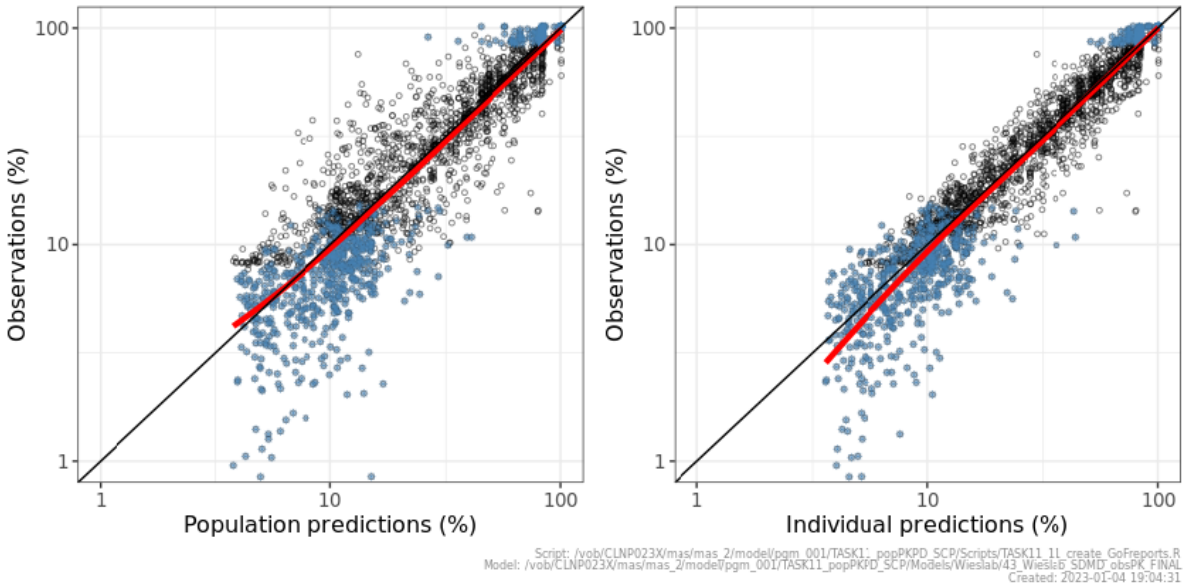
Source: lnp023-population-pkpd-model, Figure 7-11
Points in blue represent censored data (data below or above the limit of quantification of the assay).
Black points are non-censored data. Red line: loess smooth on all data. Horizontal dashed lines: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: NPDE, normalized prediction distribution errors, PD, pharmacodynamic, PK, pharmacokinetic; PRED, predictions

Figure 36. IWRES Panel (IWRES Versus Time, IWRES Versus IPRED) for Final Wieslab PKPD Model



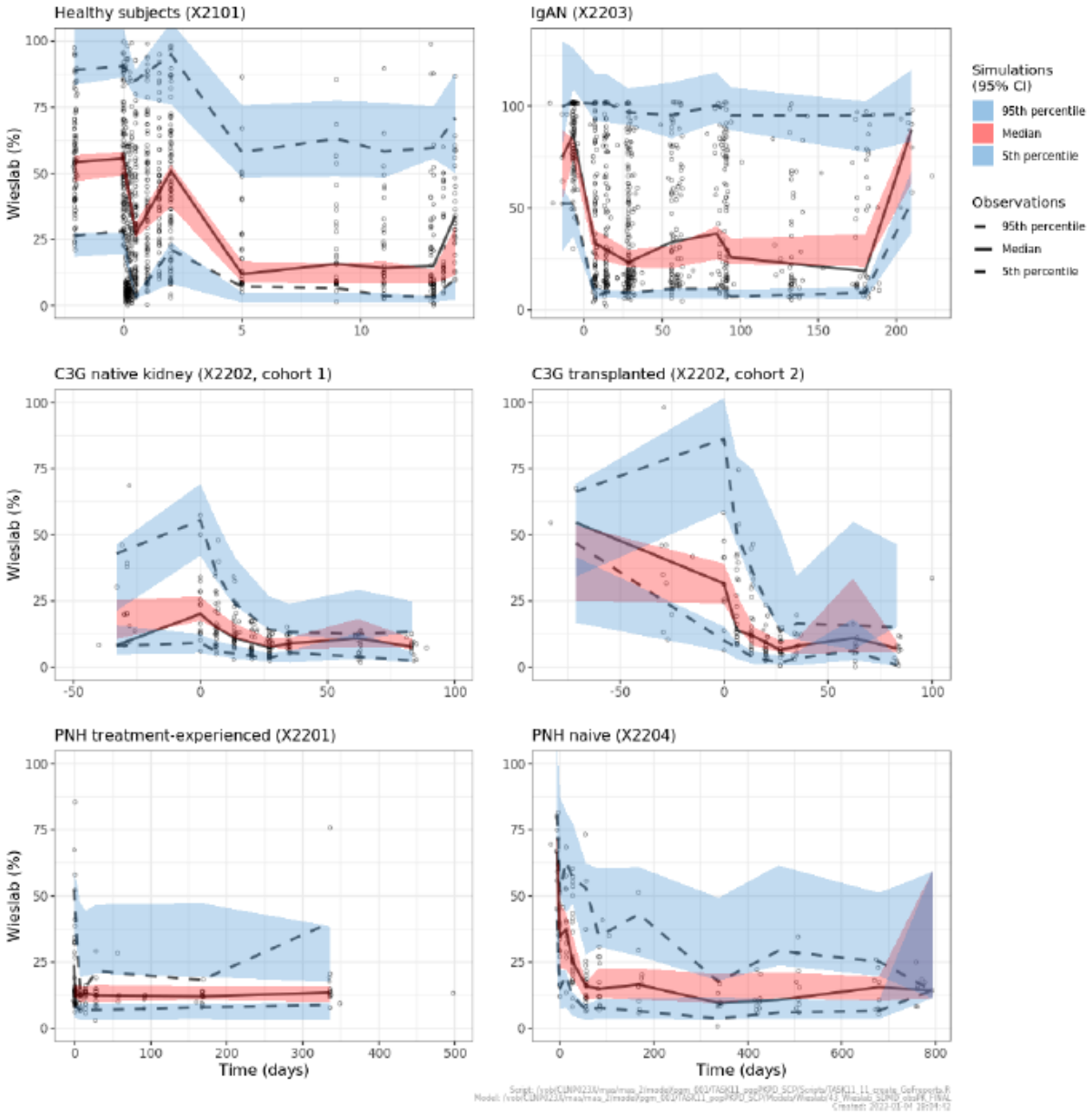
Source: lnp023-population-pkpd-model, Figure 7-14
Points in blue represent censored data (data below or above the limit of quantification of the assay).
Black points are non-censored data. Red line: loess smooth to highlight trend (if any). Horizontal dashed lines: ±2 Standard Residuals. Solid black line: y=x.
Abbreviations: IPRED, individual predictions; IWRES, individual weighted residuals; PD, pharmacodynamic, PK, pharmacokinetic

Figure 37. Observed Data Versus Population and Individual Predictions for Final Wieslab PKPD Model



Source: lnp023-population-pkpd-model, Figure 7-15
Points in blue represent censored data (data below or above the limit of quantification of the assay).
Black points are non-censored data. Red line: loess smooth to highlight trend (if any). Solid black line: y=x.
Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic

Figure 38. VPC Stratified by Population Type for Final Wieslab PKPD Model



Source: lnp023-population-pkpd-model, Figure 7-17
Shaded areas represent 95% confidence intervals for the percentiles. Dots are observations. Percentiles are plotted at the median time point in the bins.
Abbreviations: CI, confidence interval; C3G, C3 glomerulopathy; IgAN, immunoglobulin A nephropathy; PD, pharmacodynamic; PK, pharmacokinetic; VPC, visual predictive check

The final Wieslab model parameters were used to derive the 90% maximal effective concentration (EC_{90}), the iptacopan concentration at which the effect is 90% of the maximum (Table 164). It was assumed that exposures beyond the EC_{90} value are linked with near-maximal biomarker response (maximal efficacy). The final model was further utilized to estimate the exposure-response relationship for Wieslab (Figure 39). In subjects with PNH treatment experience, Wieslab baseline levels were already low due to anti-C5 treatment; however, they continued to decrease upon treatment with iptacopan, with a maximal reduction from baseline of 74% (90% CI [68%, 78%]). In subjects who were treatment-naïve, baseline Wieslab was higher

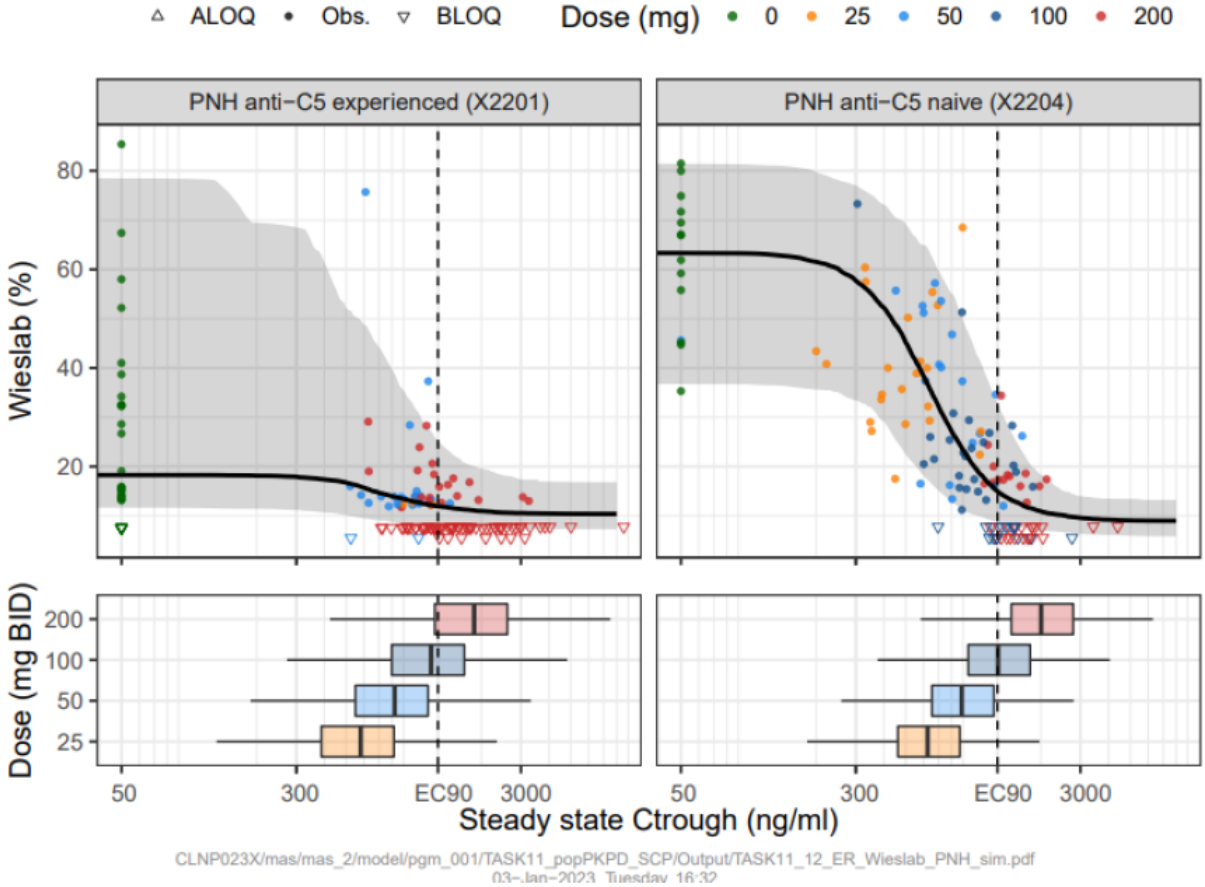
and the inhibitory response was more pronounced, with an E_{max} of 82% (90% CI [78%, 87%]). The estimated EC_{90} was the same for both PNH subpopulations. The model-predicted concentration at which 90% of the maximal Wieslab inhibition would be achieved (EC_{90}) was approximately 1281 ng/mL (90% CI [1207, 1418]). In both PNH subpopulations, this C_{trough} was reached predominantly with the 200 mg BID iptacopan dose.

Table 164. Parameter Estimates [90% Confidence Intervals] of Final Wieslab PKPD Model by Population

Parameter	Healthy subjects	C3G native kidney	C3G transplan-ted	IgAN	PNH experi-enced	PNH naive
EC50 (ng/ml)	362.4 [330.25, 395.63]	657.41 [617.51, 710.12]				
EC90* (ng/ml)	706.08 [653.31, 787.59]	1280.85 [1206.98, 1418.13]				
Emax (-)	0.92 [0.9, 0.93]	0.85 [0.82, 0.88]	0.9 [0.87, 0.93]	0.78 [0.76, 0.81]	0.74 [0.68, 0.78]	0.82 [0.78, 0.87]
γ (-)	3.29 [2.91, 3.55]					

Source: lnp023-population-pkpd-model, Table 7-9
*Parameter EC_x, where x is equal to 90, was derived from EC_{50} and y as $EC_x = EC_{50} * (x/100)^{1/y}$
Emax values reported here only capture the population effect and do not reflect the impact of individual baseline Wieslab levels on Emax
Abbreviations: C3G, C3 glomerulopathy; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration; E_{max}, maximum effect; IgAN, immunoglobulin A nephropathy; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

Figure 39. Exposure-Response of Wieslab Assay in Subjects With PNH



Source: lnp023-population-pkpd-model, Figure 7-20
Black solid line: typical ER curve. Grey area: inter-individual variability for 90% of the population. Vertical dashed line: typical EC90 for Wieslab assay. Boxplots: simulated Ctrough data from popPK model [Population PK Report]. To enable plotting on log-x axis, baseline (pre-treatment) data points were displayed at x=50 to allow adequate visualization. Censored data points are depicted as triangles. Upper looking triangles depict data ALOQ; lower looking triangles depict data BLOQ. Point colors indicate the dose level.
Abbreviations: ALOQ, above limit of quantification; BID, twice daily; BLOQ, below limit of quantification; EC_{90}, 90% maximal effective concentration; ER, exposure-response; C_{trough}, trough concentration; Obs, observations; PNH, paroxysmal nocturnal hemoglobinuria; popPK, population PK

Bb

Final parameter estimates are shown in Table 165. Unlike with the Wieslab model, the estimated EC_{50} and EC_{90} values were the same across all populations, including healthy volunteers.

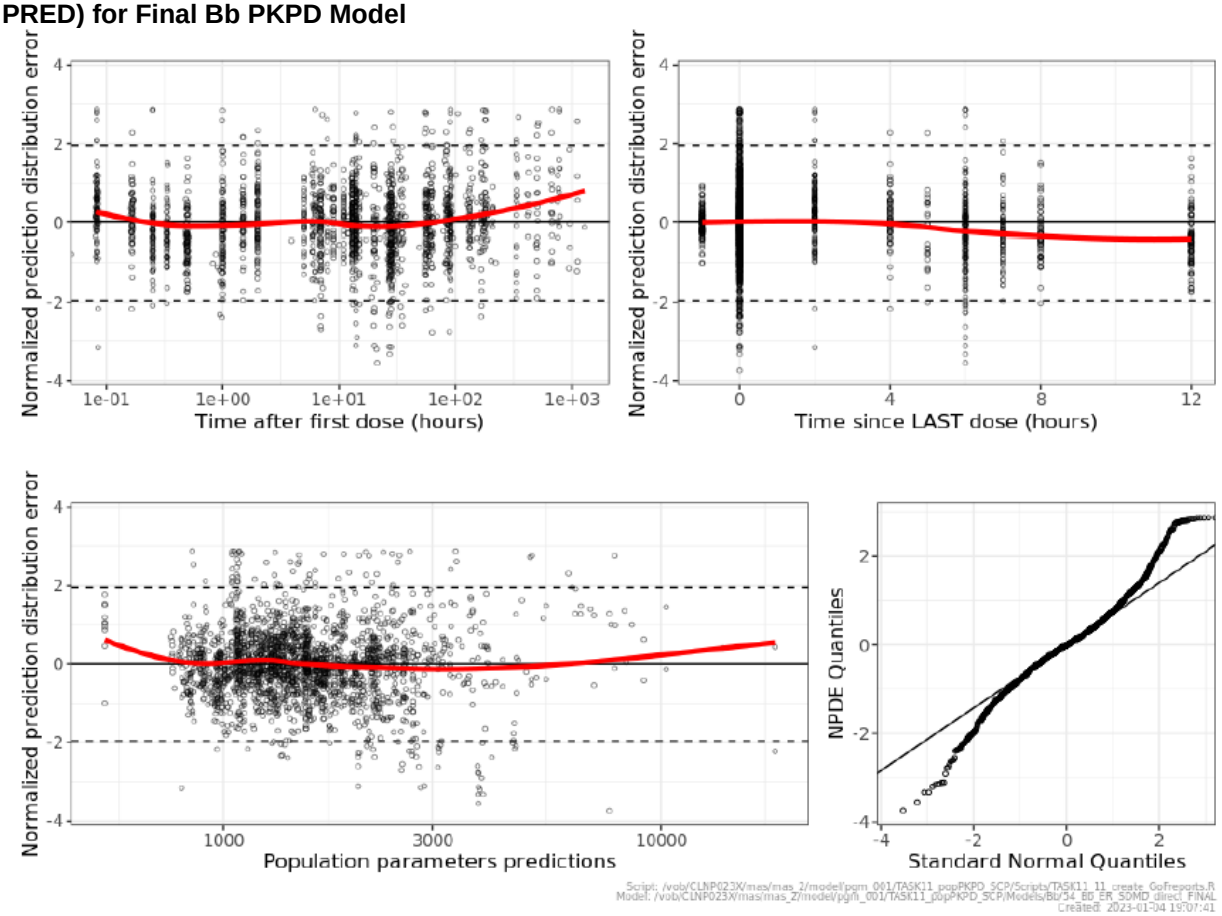
Table 165. Parameter Estimates of Final Bb PKPD Model

	Parameter	Value	RSE *(%)	Shrinkage (%)	p-value
Population param.	Base (ng/ml)	1960	2		
	EC50 (ng/ml)	57.9	17		
	Emax (-)	0.246	8		
	gamma (-)	1	fixed		
IIV	omega_Base	0.0955	10	56	
	omega_Emax	0.527	9	55	
Covariate effects	beta_Base_logtBBB	0.851	3		<2.2e-16
	beta_Base_MYPOPTYPE1_C3G_native_kidney	0.236	21		1.1e-06
	beta_Base_MYPOPTYPE1_C3G_transplanted	0.0825	75		0.18
	beta_Base_MYPOPTYPE1_Healthy	-0.0371	66		0.13
	beta_Base_MYPOPTYPE1_PNH_experienced	-0.116	39		0.0098
	beta_Base_MYPOPTYPE1_PNH_naive	0.204	41		0.015
	beta_Emax_logtBBB	1.14	11		<2.2e-16
	beta_Emax_MYPOPTYPE1_C3G_native_kidney	-0.738	38		0.0084
	beta_Emax_MYPOPTYPE1_C3G_transplanted	0.0323	808		0.9
	beta_Emax_MYPOPTYPE1_Healthy	0.524	29		0.00054
	beta_Emax_MYPOPTYPE1_PNH_experienced	-0.0466	504		0.84
	beta_Emax_MYPOPTYPE1_PNH_naive	1.27	19		2.8e-07
	Residual variability (b)	0.0292	2		

Source: lnp023-population-pkpd-model, Table 7-11
*RSE: relative standard error.
Abbreviations: Bb, activated factor B; C3G, C3 glomerulopathy; EC_{50}, half maximal effective concentration; E_{max}, maximum effect; IIV, inter-individual variability; param., parameter; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; RSE, relative standard error

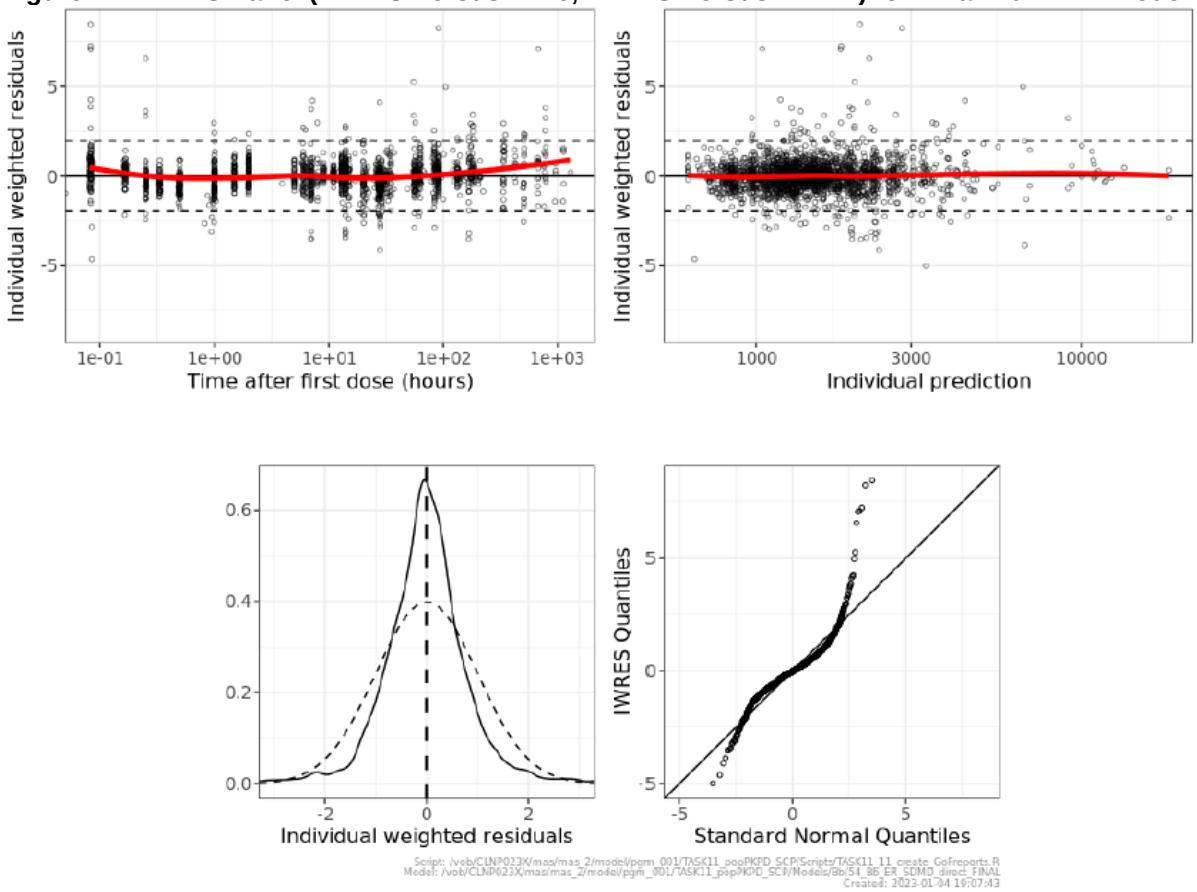
Goodness-of-fit plots showed that the final Bb model appeared to be able to describe the data. There were no major trends observed when considering unstratified NPDE versus time since first dose, versus time since last dose, and versus prediction (Figure 40). Individual weighted residuals versus time and versus individual predictions (Figure 41) and plots of observed data versus population and individual predictions (Figure 42) also did not show major trends. Visual predictive checks stratified by population type showed a good correspondence overall between the model and observed data (Figure 43), with a slight underprediction of the lower quartile of Bb in subjects with IgAN. The variability in both PNH subpopulations was also slightly overpredicted.

Figure 40. NPDE Panel (NPDE Versus Time, NPDE Versus Time Since Last Dose, NPDE Versus PRED) for Final Bb PKPD Model



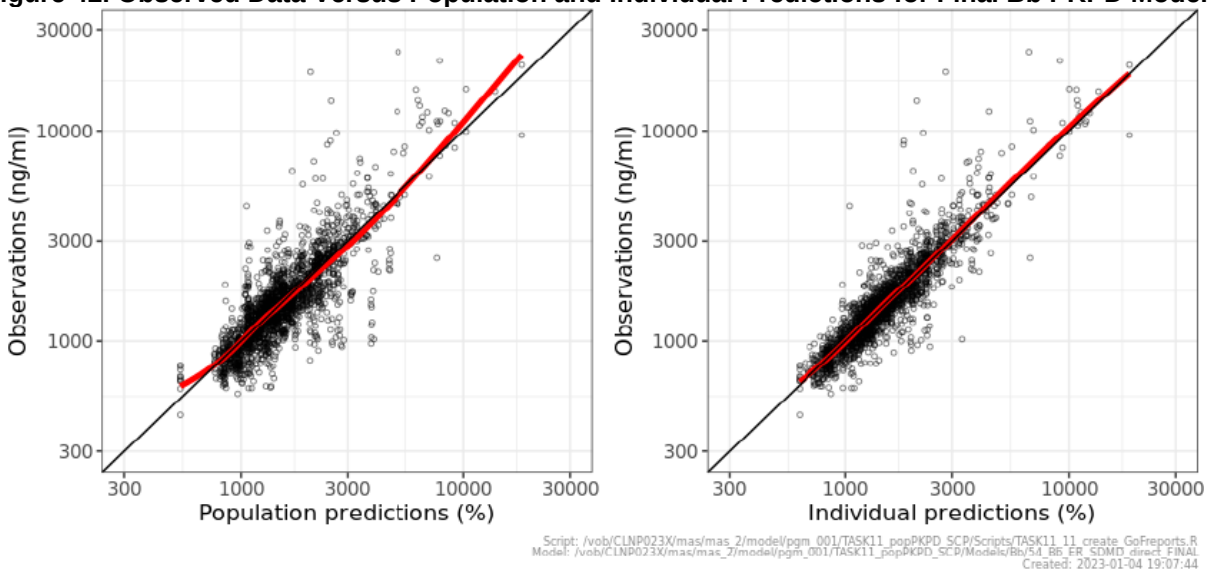
Source: lnp023-population-pkpd-model, Figure 7-23
Black points are non-censored data. Red line: loess smooth. Horizontal dashed line: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: Bb, activated factor B; NDPE, normalized distr bution prediction errors, PD, pharmacodynamics; PK, pharmacokinetics

Figure 41. IWRES Panel (IWRES Versus Time, IWRES Versus IPRED) for Final Bb PKPD Model



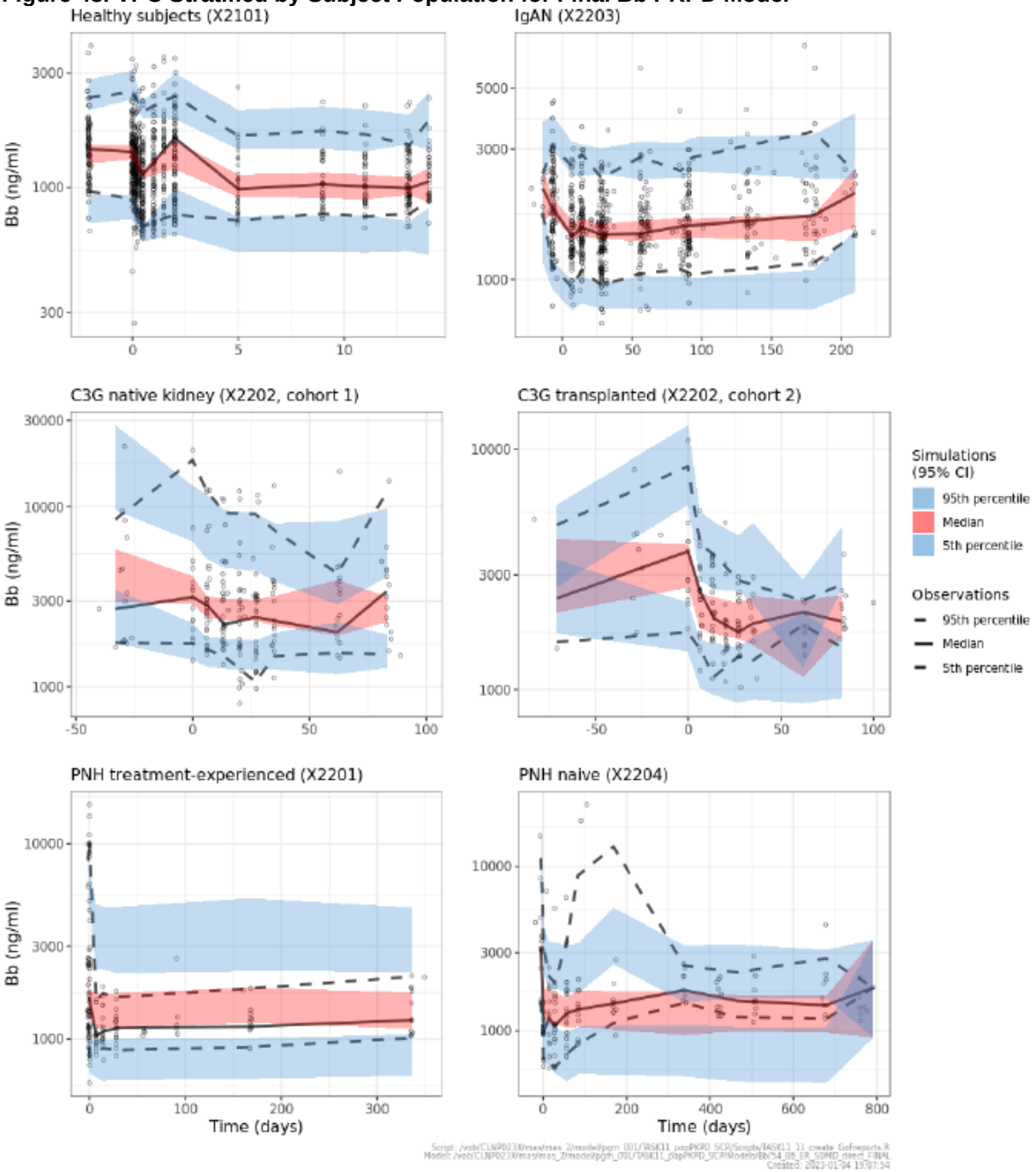
Source: lnp023-population-pkpd-model, Figure 7-26
Black points are non-censored data. Red line: loess smooth. Horizontal dashed line: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: Bb, activated factor B; IPRED, individual predictions; IWRES individual weighted residuals; PD, pharmacodynamics; PK, pharmacokinetics

Figure 42. Observed Data Versus Population and Individual Predictions for Final Bb PKPD Model



Source: lnp023-population-pkpd-model, Figure 7-27
Black points are non-censored data. Red line: loess smooth. Solid black line: y=x.
Abbreviations: Bb, activated factor B; PD, pharmacodynamics; PK, pharmacokinetics

Figure 43. VPC Stratified by Subject Population for Final Bb PKPD Model



Source: lnp023-population-pkpd-model, Figure 7-29
Shaded areas represent 95% confidence intervals for the percentiles. Dots are observations. Percentiles are plotted at the median time point in the bins.
Abbreviations: Bb, activated factor B; CI, confidence interval; C3G, C3 glomerulopathy; IgAN, immunoglobulin A nephropathy; PD, pharmacodynamic; PK, pharmacokinetic; VPC, visual predictive check

The final Bb model parameters were used to derive the EC_{90} (Table 166). The final model was further utilized to estimate the exposure-response relationship for Bb (Figure 44). In subjects with PNH treatment experience, Bb baseline levels were already low, possibly due to prior anti-C5 treatment (very similar to levels in healthy subjects); however, they continued to decrease

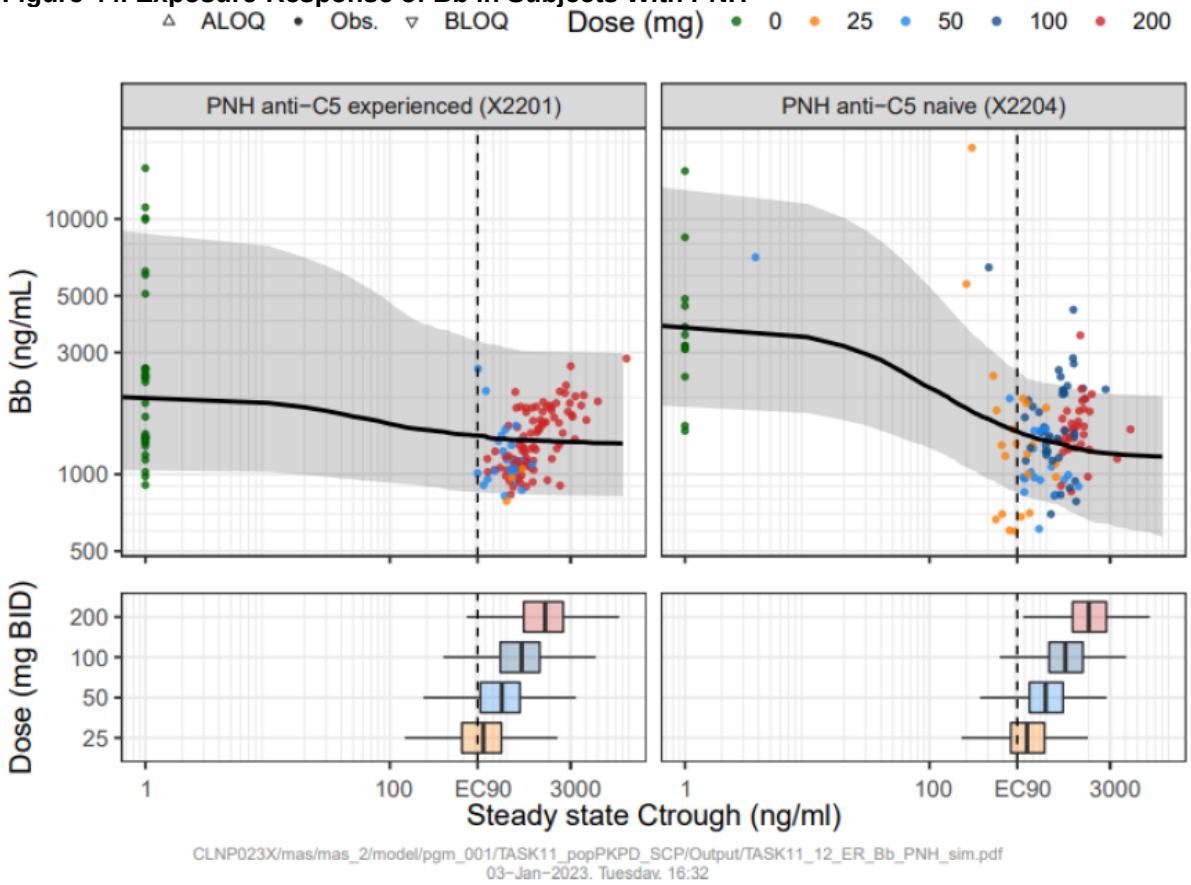
upon treatment with iptacopan, with a typical maximal treatment effect of 24% (90% CI [19%, 29%]) reduction from baseline. In subjects who were treatment naïve, baseline Bb was higher and the inhibitory response was more pronounced, with a typical E_{max} of 54% (90% CI [42%, 67%]). The predicted EC_{90} was approximately 521 ng/mL (90% CI [268, 912]) for both PNH subpopulations, with this C_{trough} already being reached in subjects who received either 50 mg or 100 mg BID iptacopan.

Table 166. Parameter Estimates [90% Confidence Intervals] of Final Bb PKPD Model by Population

Parameter	Healthy subjects	C3G native kidney	C3G transplant	IgAN	PNH experienced	PNH naive
EC50 (ng/ml)	57.91 [29.79, 101.36]					
EC90* (ng/ml)	521.17 [268.11, 912.24]					
Emax (-)	0.36 [0.32, 0.4]	0.14 [0.01, 0.27]	0.25 [0.18, 0.33]	0.25 [0.22, 0.28]	0.24 [0.19, 0.29]	0.54 [0.42, 0.67]
γ (-)	1.00 (fixed)					

Source: lnp023-population-pkpd-model, Table 7-11
*Parameter EC_x, where x is equal to 90, was derived from EC_{50} and γ as $EC_x = EC_{50} *(x/(100-x))^{1/\gamma}$
Emax values reported here only capture the population effect and do not reflect the impact of individual baseline Wieslab levels on Emax
Abbreviations: Bb, activated factor B; C3G, C3 glomerulopathy; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration; E_{max}, maximum effect; IgAN, immunoglobulin A nephropathy; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal ALOQ, above limit of quantification

Figure 44. Exposure-Response of Bb in Subjects With PNH



Source: lnp023-population-pkpd-model, Figure 7-32
Black solid line: typical ER curve. Grey area: inter-individual variability for 90% of the population. Vertical dashed line: typical EC90 for plasma Bb. Boxplots: simulated C_{trough} data from popPK model [Population PK Report]. To enable plotting on log-x axis, baseline (pre-treatment) data points are arbitrarily displayed at x=1 to allow visualization. Point colors indicate the dose level.
Abbreviations: ALOQ, above limit of quantification; Bb, activated factor B; BID, twice daily; BLOQ, below limit of quantification; EC_{90}, 90% maximal effective concentration; ER, exposure-response; C_{trough}, trough concentration; Obs, observations; PNH, paroxysmal nocturnal hemoglobinuria; popPK, population PK

sC5b-9

Final parameter estimates are shown in Table 167. The estimated EC_{50} and EC_{90} values were the same across all populations, including healthy volunteers.

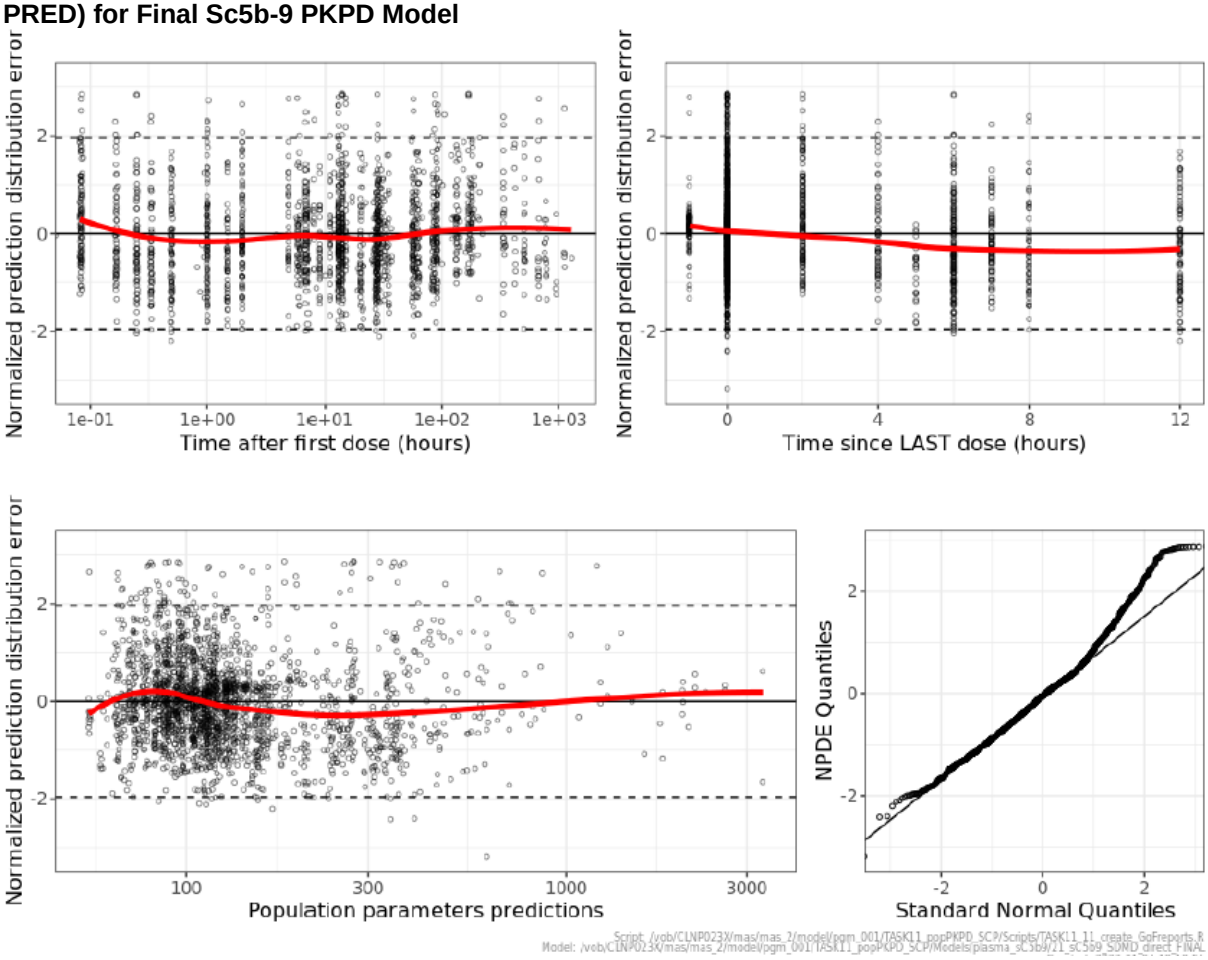
Table 167. Parameter Estimates of Final Plasma Sc5b-9 PKPD Model

	Parameter	Value	RSE* (%)	Shrinkage (%)	p-value
Population param.	Base (ng/ml)	143	2		
	EC50 (ng/ml)	259	8		
	Emax (-)	0.208	9		
	gamma (-)	2.27	12		
IIV	omega_Base	0.128	8	48	
	omega_Emax	0.899	10	54	
Covariate effects	beta_Base_logtSC5B9B	0.883	3		<2.2e-16
	beta_Base_MYPOPTYPE1_C3G_native_kidney	0.302	26		0.00011
	beta_Base_MYPOPTYPE1_C3G_transplanted	0.0747	80		0.21
	beta_Base_MYPOPTYPE1_Healthy	-0.0233	109		0.36
	beta_Base_MYPOPTYPE1_PNH_experienced	0.385	15		7.5e-11
	beta_Base_MYPOPTYPE1_PNH_naive	0.265	21		2.7e-06
	beta_Emax_logtSC5B9B	1.11	9		<2.2e-16
	Residual variability (b)	0.26	2		

Source: lnp023-population-pkpd-model, Table 7-12
*RSE: relative standard error
Abbreviations: C3G, C3 glomerulopathy; EC_{50}, half maximal effective concentration; E_{max}, maximum effect; IIV, inter-individual variability; param., parameter; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; RSE, relative standard error

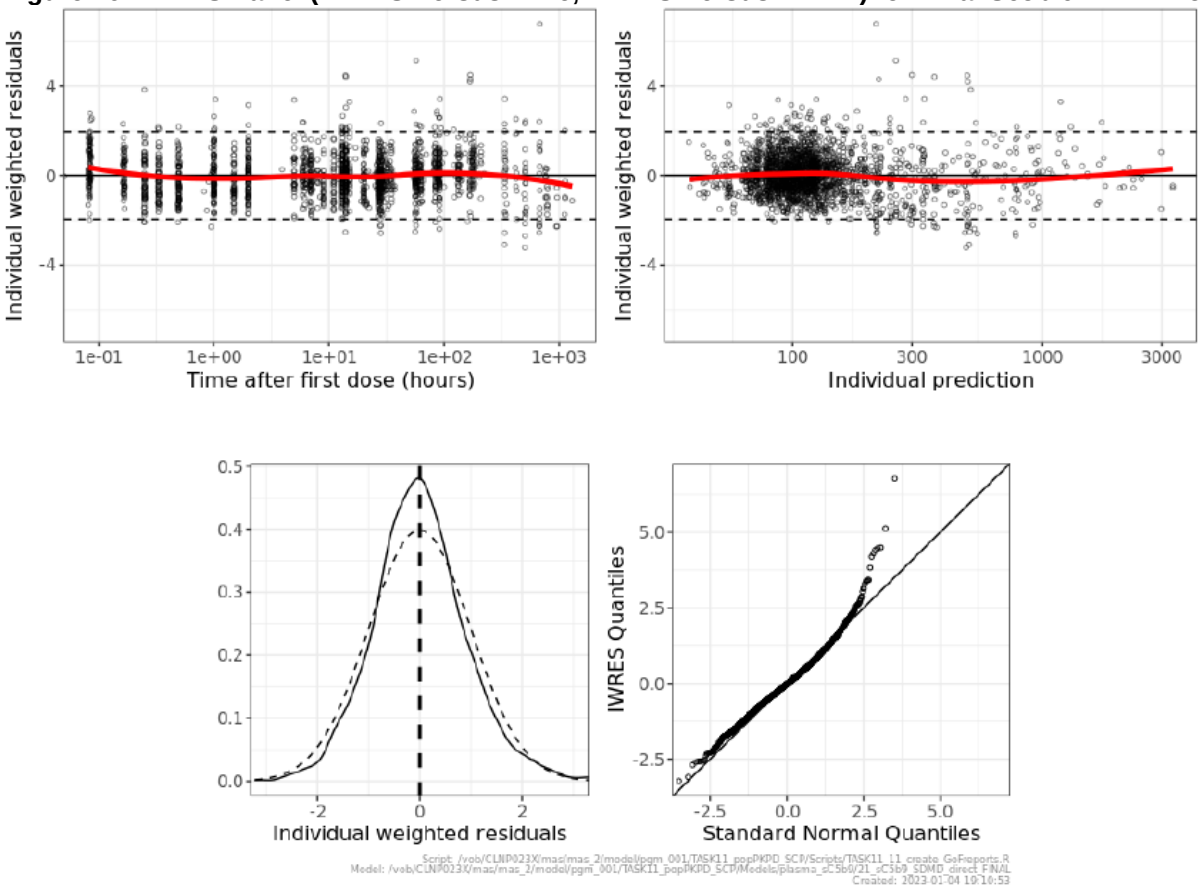
Goodness-of-fit plots showed that the final sC5b-9 model appeared to be able to describe the data. There were no major trends observed when considering unstratified NPDE versus time since first dose, versus time since last dose, and versus prediction (Figure 45). Individual weighted residuals versus time and versus individual predictions (Figure 46) and plots of observed data versus population and individual predictions (Figure 47) also did not show major trends. Visual predictive checks stratified by population type showed an overall good correspondence between the model and observed data (Figure 48) except for the lower quartile of the IgAN population, which was underestimated by the model. Another misfit of the model was observed in the VPC of subjects with C3G native kidney where the median response predicted by the model was higher than the observed data.

Figure 45. NPDE Panel (NPDE Versus Time, NPDE Versus Time Since Last Dose, NPDE Versus PRED) for Final Sc5b-9 PKPD Model



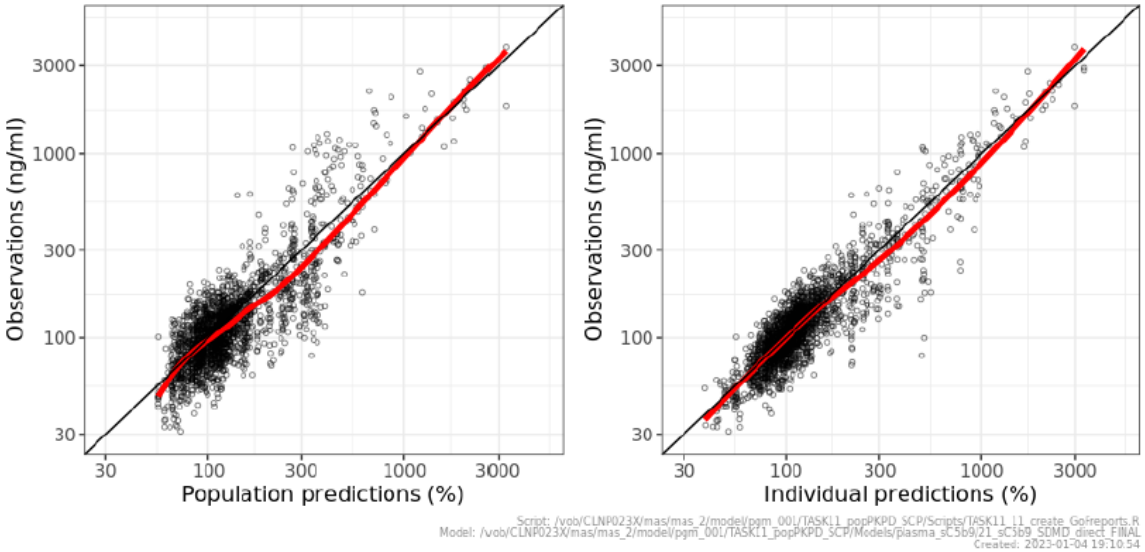
Source: lnp023-population-pkpd-model, Figure 7-35
Black points are non-censored data. Red line: loess smooth. Horizontal dashed line: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: NPDE, normalized prediction distribution errors, PD, pharmacodynamic, PK, pharmacokinetic; PRED, predictions

Figure 46. IWRES Panel (IWRES Versus Time, IWRES Versus IPRED) for Final Sc5b-9 PKPD Model



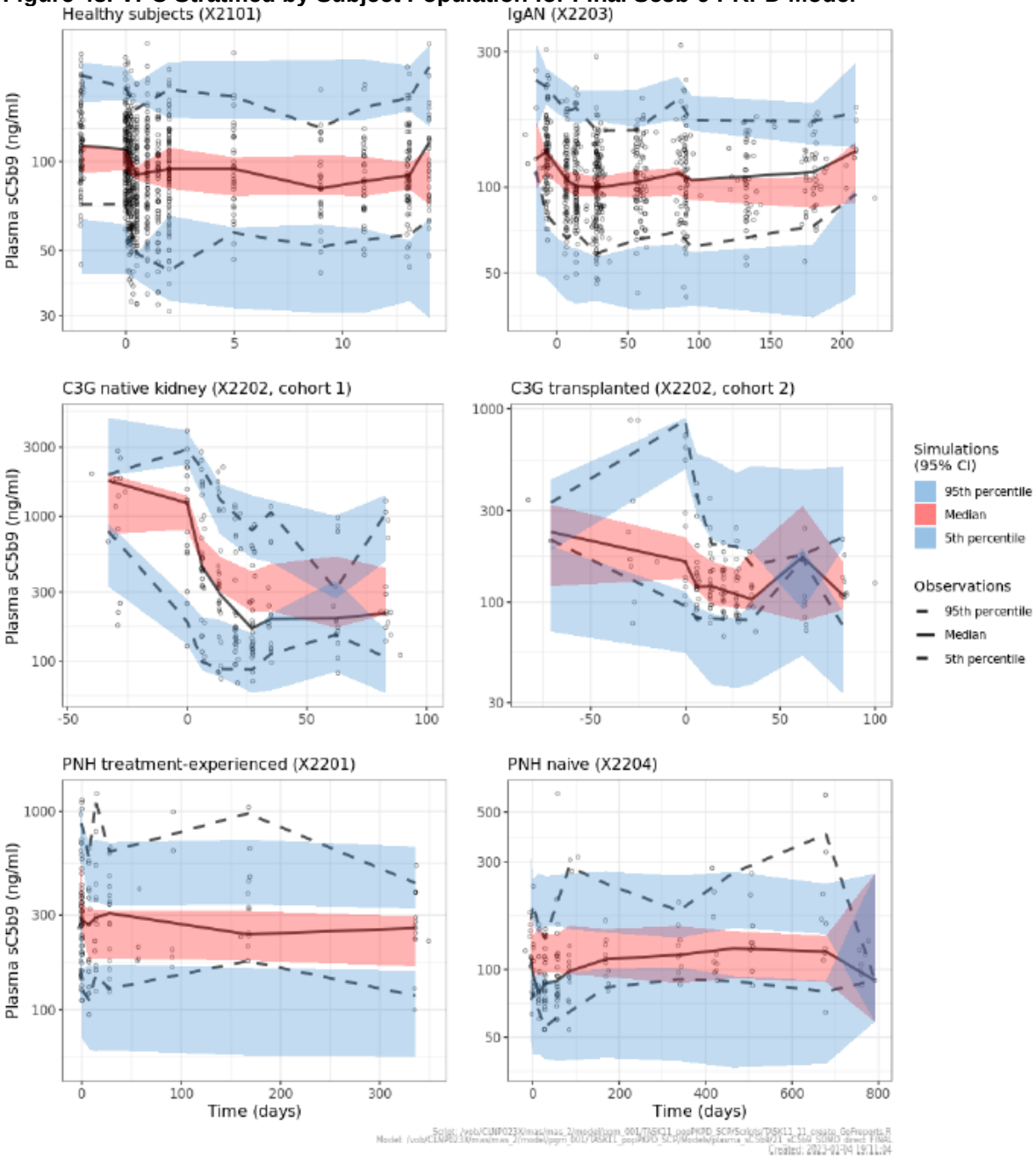
Source: lnp023-population-pkpd-model, Figure 7-38
Black points are non-censored data. Red line: loess smooth. Horizontal dashed line: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: IPRED, individual predictions; IWRES individual weighted residuals; PD, pharmacodynamics; PK, pharmacokinetics

Figure 47. Observed Data Versus Population and Individual Predictions for Final Sc5b-9 PKPD Model



Source: lnp023-population-pkpd-model, Figure 7-39
Blacks point are noncensored data. Red line: loess smooth to highlight trend (if any). Solid black line: y=x.
Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics

Figure 48. VPC Stratified by Subject Population for Final Sc5b-9 PKPD Model



Source: lnp023-population-pkpd-model, Figure 7-41
Shaded areas represent 95% confidence intervals for the percentiles. Dots are observations. Percentiles are plotted at the median time point in the bins.
Abbreviations: CI, confidence interval; C3G, C3 glomerulopathy; IgAN, immunoglobulin A nephropathy; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; VPC, visual predictive check

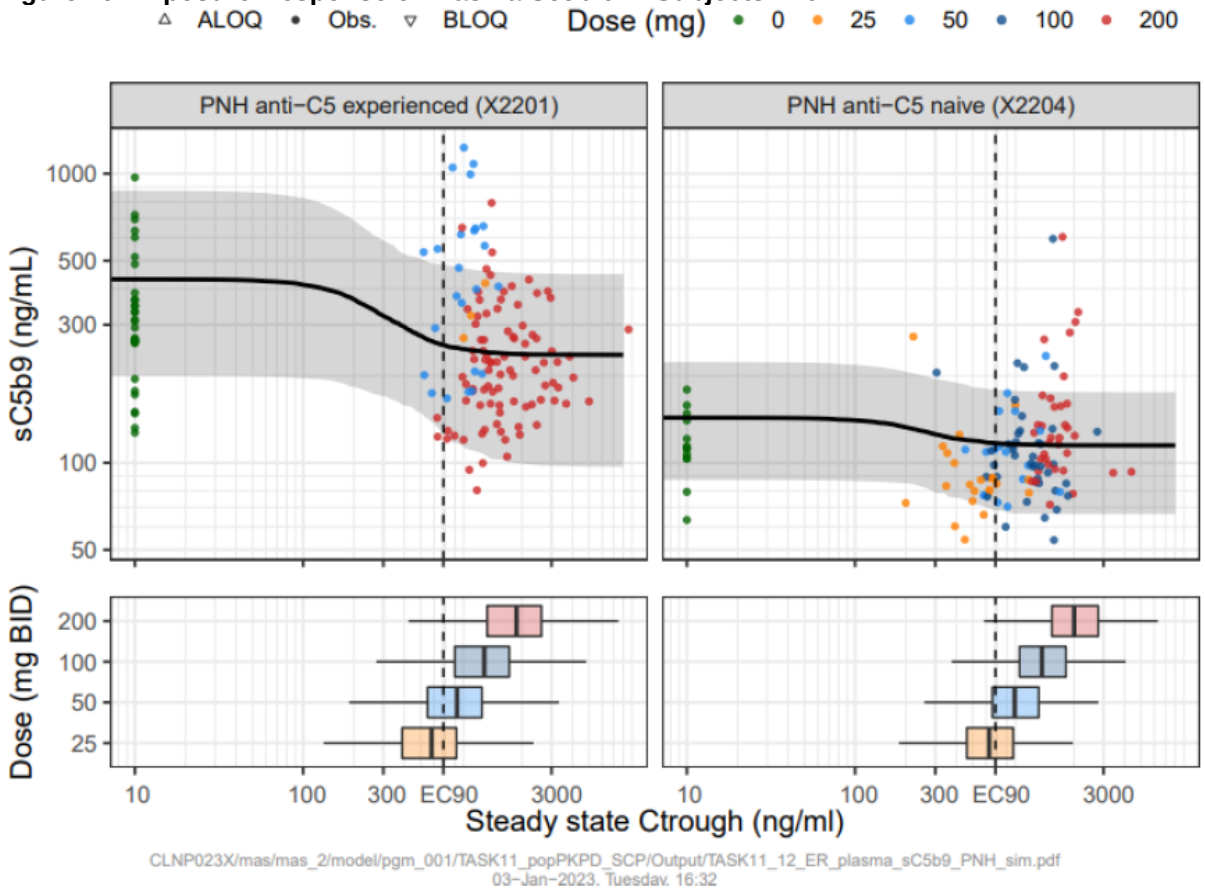
The final sC5b-9 model parameters were used to derive the EC_{90} (Table 168). The final model was further utilized to estimate the exposure-response relationship for sC5b-9 (Figure 49). In both PNH subpopulations, sC5b-9 levels decreased upon treatment with iptacopan. Though baseline sC5b-9 levels were higher in subjects with anti-C5 experience, both subpopulations had the same E_{max} of 21%. The estimated EC_{90} of 682 (90% CI [503, 894]) ng/mL was reached in the majority (>50%) of subjects already with the 50 mg and 100 mg BID iptacopan doses.

Table 168. Parameter Estimates [90% Confidence Intervals] of Final Plasma Sc5b-9 PKPD Model by Population

Parameter	Healthy subjects	C3G native kidney	C3G transplanted	IgAN	PNH experienced	PNH naive
EC50 (ng/ml)	259.29 [217.58, 309.57]					
EC90* (ng/ml)	682.41 [503.19, 893.84]					
Typical Emax (-)	0.21** [0.17, 0.25]					
γ (-)	2.27 [1.71, 3.66]					

Source: lnp023-population-pkpd-model, Table 7-13
*Parameter EC_x, where x is equal to 90, was derived from EC_{50} and γ as $EC_x = EC_{50} * (x/(100-x))^{1/\gamma}$
**Emax was impacted by individual baseline sC5b-9 levels, not reflected in this table.
Abbreviations: C3G, C3 glomerulopathy; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration; E_{max}, maximum effect; IgAN, immunoglobulin A nephropathy; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria

Figure 49. Exposure-Response of Plasma Sc5b-9 in Subjects With PNH



Source: lnp023-population-pkpd-model, Figure 7-44
Black solid line: typical ER curve. Grey area: inter-individual variability for 90% of the population. Vertical dashed line: typical EC90 for plasma sC5b9. Boxplots: simulated Ctrough data from popPK model [Population PK Report]. To enable plotting on log-x axis, baseline (pre-treatment) data points were displayed at x=10 to allow adequate visualization. Point colors indicate the dose level.
Abbreviations: ALOQ, above limit of quantification; BID, twice daily; BLOQ, below limit of quantification; C_{trough}, trough concentration; EC_{90}, 90% maximal effective concentration; ER, exposure-response; Obs, observations; PNH, paroxysmal nocturnal hemoglobinuria; popPK, population PK

Reviewer Comment:

The proposed PK/PD analyses for the three biomarkers (Wieslab assay, Bb, and sC5b-9) appeared to be acceptable. The model-estimated EC_{90} (for both subjects who were previously treated and those who were treatment naïve) were 1280.85, 521.17, and 682.41 ng/mL for Wieslab assay, Bb, and sC5b-9, respectively. Based on the population PK analysis, the steady-state trough concentration for 200 mg BID was approximately 1900 ng/mL, which was higher than the estimated EC_{90} for all 3 biomarkers and located in the plateau phase of the exposure-response relationship for the 3 biomarkers.

Exposure-Response for Efficacy

The analysis was conducted on the following four studies:

- CLNP023X2201, phase 2 in subjects with PNH, iptacopan in addition to eculizumab (final data)
- CLNP023X2204, phase 2 in subjects with PNH, iptacopan as monotherapy (final data)
- CLNP023C12301 (APPOINT-PNH), phase 3 in subjects with PNH who were treatment naïve (data cutoff: November 2, 2022; response data from primary efficacy readout)
- CLNP023C12302 (APPLY-PNH), phase 3 in subjects with PNH who were experienced with anti-C5 treatment (eculizumab or ravulizumab) (PK data cutoff: September 26, 2022; response data from primary efficacy readout)

The modeling dataset (exposure-response dataset) contained a total of 161 subjects with PNH. There were 53 (33%) subjects who were naïve to anti-C5 treatment in the exposure-response dataset, and 108 (67%) subjects who were experienced with anti-C5 treatment. The demographics of subjects are summarized in Table 169. The individual PK parameters estimated from a sensitivity population PK model were applied. Hemoglobin (Hb) and lactate dehydrogenase (LDH) were tested as efficacy response endpoints.

Table 169. Demographics of Patients in the Exposure-Response Analysis for Efficacy

Study	N	Weight, kg (median [range])	Age, years (median [range])	eGFR, mL/min/1.73m² (median [range])	Female (n)	Male (n)	Rest (n)	China (n)	Japan (n)	Asian Other (n)
C12301 (APPOINT-PNH)	40	69.3 [46.5-100]	39 [18-81]	105 [35.2-143]	17	23	13	20	0	7
C12302 (APPLY-PNH)	92	68.2 [40-118]	53 [20-84]	93.4 [32.9-142]	64	28	74	2	9	7
X2201	16	76.2 [50-120]	45 [24-78]	95.1 [29.1-134]	6	10	16	0	0	0
X2204	13	57.2 [34.9-82.6]	35 [20-62]	121 [59.8-141]	7	6	0	2	0	11
PNH anti-C5 experienced	108	70 [40-120]	52.5 [20-84]	94.5 [29.1-142]	70	38	90	2	9	7
PNH anti-C5 naive	53	68 [34.9-100]	38 [18-81]	107 [35.2-143]	24	29	13	22	0	18
Total	**161**	**69.5 [34.9-120]**	**45 [18-84]**	**96.1 [29.1-143]**	**94**	**67**	**103**	**24**	**9**	**25**

Source: Lnp023-modeling-report-exposure, Table 7-2
Abbreviations: eGFR, estimate glomerular filtration rate; N, number; n, number of a category; PNH, paroxysmal nocturnal hemoglobinuria

An indirect response model was applied to describe the dynamics of the efficacy endpoints, Hb and LDH. The response at time t is described as a dynamical system, using an ordinary differential equation describing the "turnover" of the response in terms of an input function at time t ($k_{in}(t)$, also called "production rate") and an output function ($k_{out}(t)$, also called "elimination rate"):

Equation 3. Indirect Response Model for Efficacy Endpoints

$$\frac{dY(t)}{dt} = k_{in}(t) - k_{out}(t)Y(t)$$

The initial conditions were $Y(0) = k_{in}(0)/k_{out}(0) = YBase$, where $YBase$ was the baseline response prior to iptacopan treatment. The treatment effect was incorporated into production rate k_{in} for LDH and into elimination rate k_{out} for Hb:

- Lactate dehydrogenase: $k_{out}(t) = k_{out}$ was a constant with value to be fitted, while $k_{in}(t) = k_{in,1} + S(t)(k_{in,2} - k_{in,1})$ was a function of iptacopan concentrations with $k_{in,1} = k_{out} \times YBase$ and $k_{in,2} = k_{out} \times YTRT$.
- Hemoglobin: $k_{in}(t) = k_{in}$ was a constant with values to be fitted, while $k_{out}(t) = k_{out,1} + S(t)(k_{out,2} - k_{out,1})$ was a function of iptacopan concentrations with $k_{out,1} = k_{in}/YBase$ and $k_{out,2} = k_{in}/YTRT$
- The $YTRT$ was the response at steady state and S(t) was the treatment effect at time t.

Exposure-Response for LDH

The parameter estimates for the final model are listed in Table 170. The estimated EC_{50} [90% confidence interval] value was (~29.8 [26.5, 33.6] ng/mL), and consequently, the EC_{90} value was (~268.3 [238.2, 302.2] ng/mL). With iptacopan treatment, LDH would reach the normal range (<250 U/L) at 237 U/L. Differences in baseline LDH levels by prior treatment status (anti-C5 naïve versus experienced) were captured via the covariate effect of LDH on $YBase$.

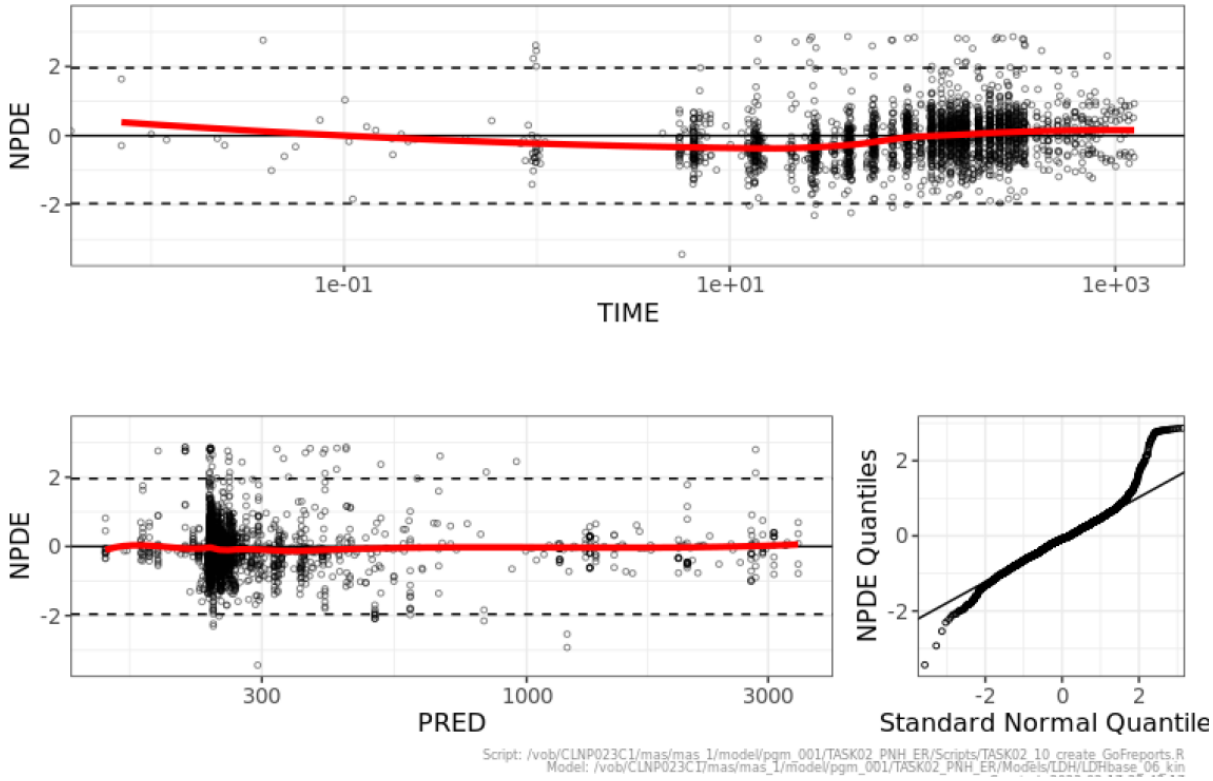
Table 170. Parameter Estimates of Final LDH Model

Parameter	Value	RSE* (%)	Shrinkage (%)	p-value
Structural (population) parameters				
Baseline LDH level (Y_{Base}, U/L)	622.00	2.55		
EC50 (ng/ml)	29.80	7.26		
LDH level on iptacopan treatment (Y_{TRT}, U/L)	237.00	3.29		
LDH degradation rate (k_{out}, 1/day)	0.31	4.58		
Inter-individual variability, IIV (st. dev.)				
IIV Y_{Base} (omega_Base)	0.26	6.40	28	
IIV Y_{TRT} (omega_LevelOnTRT)	0.40	6.11	8	
Covariate effects				
beta_Base_logtLDHB	0.98	2.78		<2.2e-16
Residual variability				
Proportional residual error (b2)	0.24	1.47		

Source: Lnp023-modeling-report-exposure, Table 7-9
*RSE: relative standard error.
Abbreviations: EC_{50}, half-maximal effective concentration; IIV, inter-individual variability; K_{out}, first-order elimination rate constant; LDH, lactate dehydrogenase; RSE, relative standard error; st. dev.; standard deviation; Y_{Base}, baseline response prior to iptacopan treatment; Y_{TRT}, response to iptacopan treatment

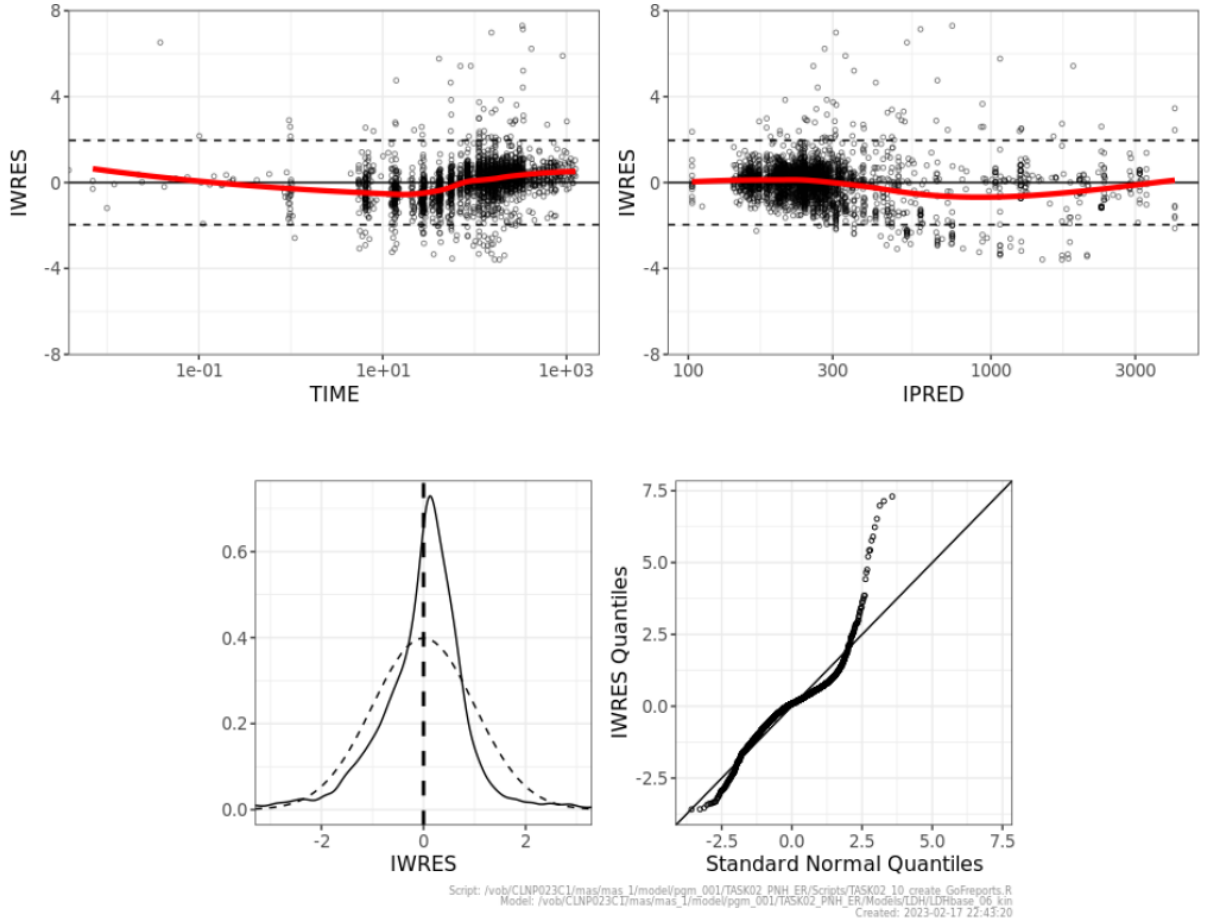
Goodness-of-fit plots showed that the final LDH model appeared to be able to describe the data (Figure 50). There were no major trends observed when considering unstratified NPDE versus time since first dose and versus prediction. Individual weighted residuals versus time and versus individual predictions (Figure 51) and plots of observed data versus population and versus individual predictions (Figure 52) also did not show major trends. Visual predictive checks showed that the model appeared to be able to capture the LDH time course, the steady state level on treatment, as well as interindividual variability structure (Figure 53).

Figure 50. NPDE Panel (NPDE Versus Time, NPDE Versus PRED) for Exposure-Response Model for LDH



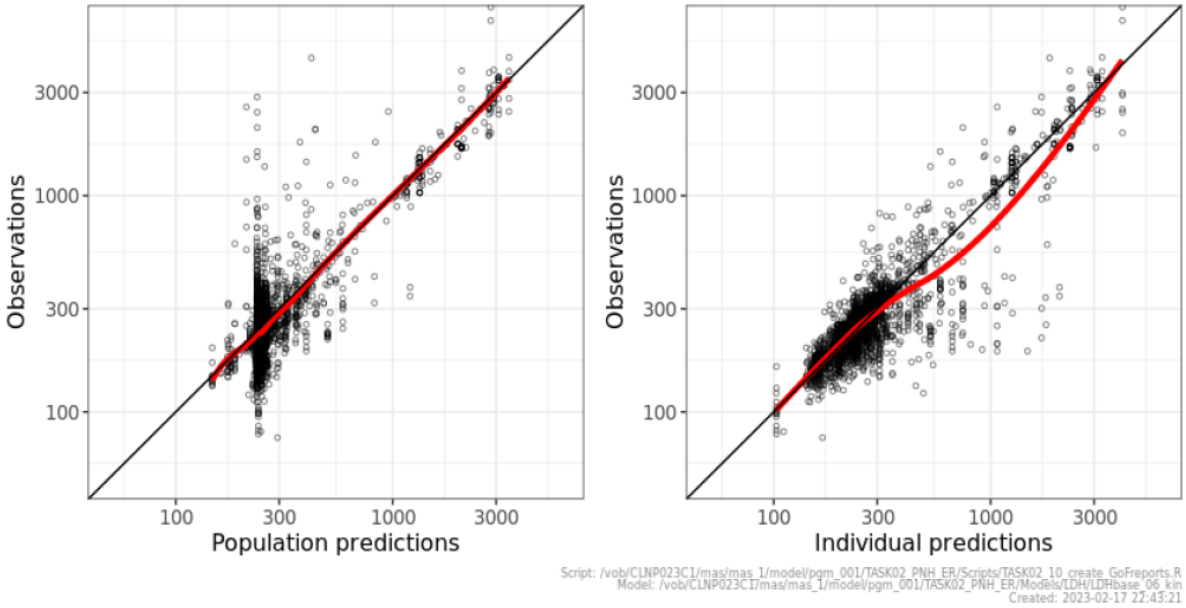
Source: Lnp023-modeling-report-exposure, Figure 7-8
Black points: non-censored data. Red line: loess smooth on all data. Horizontal dashed line: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: NPDE, normalized prediction distribution errors; PRED, prediction; LDH, lactate dehydrogenase

Figure 51. IWRES Panel (IWRES Versus Time, IWRES Versus IPRED) for Exposure-Response Model for LDH



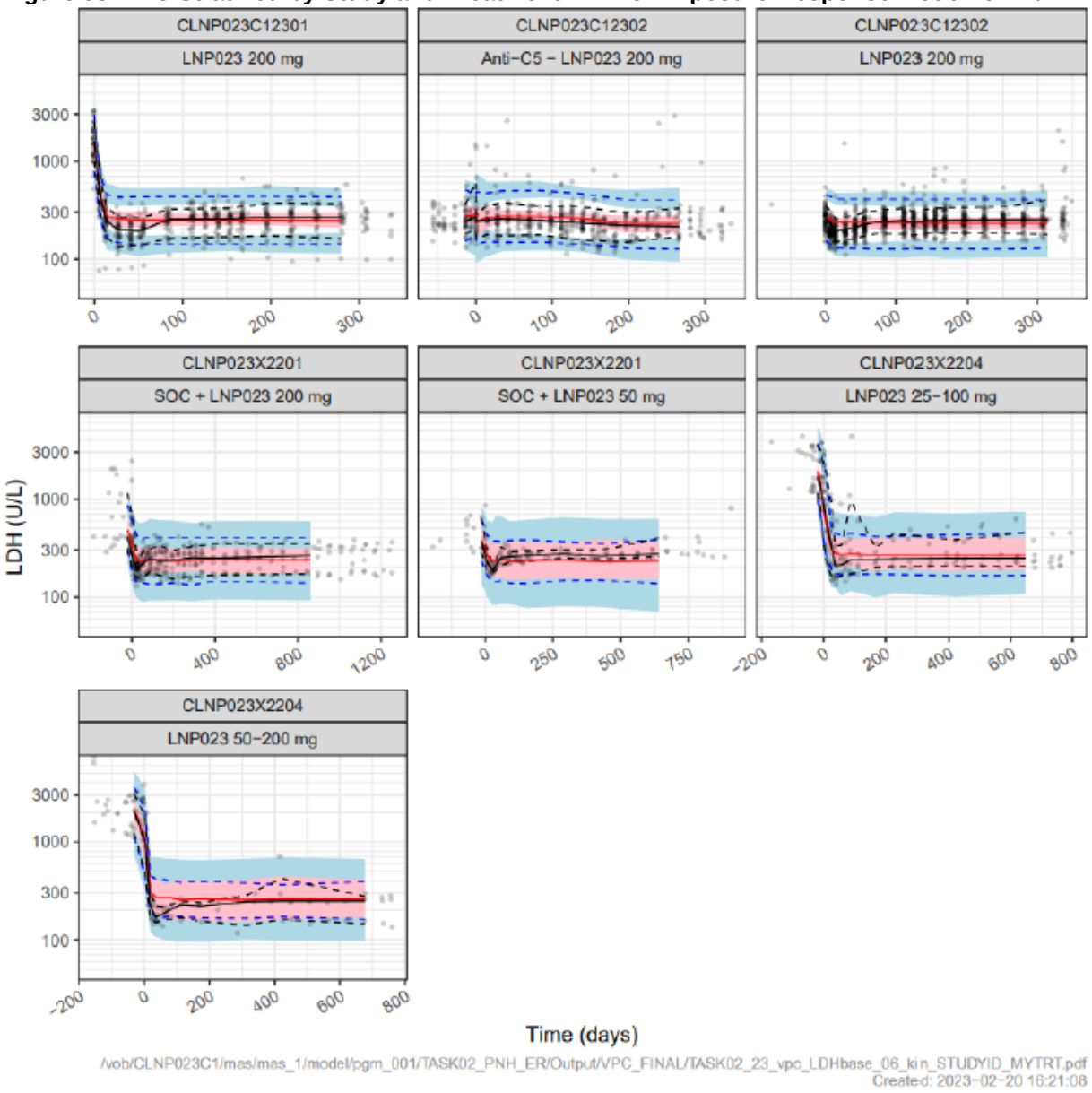
Source: Lnp023-modeling-report-exposure, Figure 7-11
Black points: non-censored data. Red line: loess smooth. Horizontal dashed line: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: IPRED, individual prediction; IWRES, individual weighted residuals; LDH, lactate dehydrogenase

Figure 52. Observed Data Versus Population and Individual Predictions for Exposure-Response Model for LDH



Source: Lnp023-modeling-report-exposure, Figure 7-11
Black points: non-censored data. Red line: loess smooth. Solid black line: y=x.
Abbreviations: LDH, lactate dehydrogenase

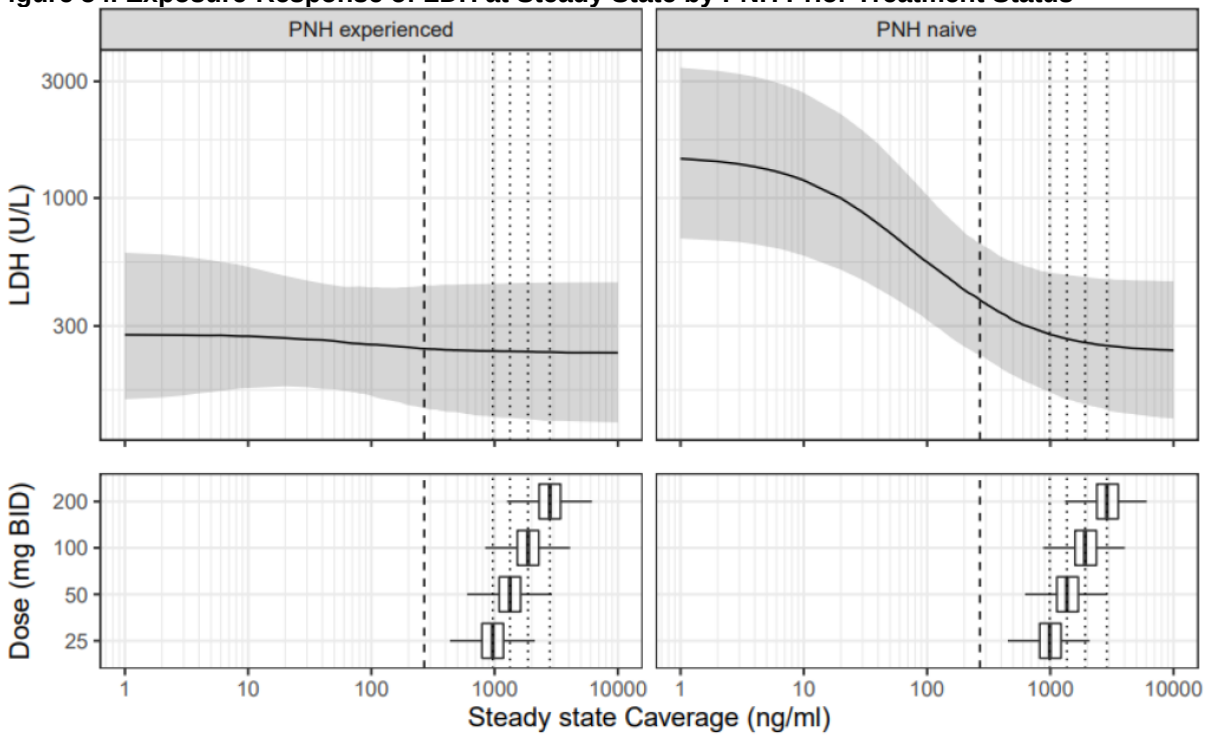
Figure 53. VPC Stratified by Study and Treatment Arm for Exposure-Response Model for Hb



Source: Lnp023-modeling-report-exposure, Figure 7-14
Solid and dashed lines: quantiles (solid black line: 50%, dashed black lines: 5% and 95%) of the observed data within bin. Red solid line: median model prediction. Dashed blue lines: 5th and 95th quantiles of model prediction. Shaded areas represent 95% confidence intervals for the percentiles. Dots are observations. Percentiles are plotted at the median time point in the bins.
Abbreviations: Hb, hemoglobin; LDH, lactate dehydrogenase; LNP023, iptacopan; SOC, standard of care; VPC, visual predictive check

The exposure-response correlation for LDH is shown in Figure 54. Subjects who were anti-C5 naïve had a steep LDH exposure response, whereas subjects who were treatment naïve had a shallower LDH exposure response, which was driven by the different baseline values considering the same parameter estimates for EC_{50} and YTRT (response at steady state). The estimated EC_{90} [90% confidence interval] was ~270 ng/mL [238, 302]. As this value was low, 100% of subjects were expected to reach this average concentration ($C_{average}$) already at the lowest dose of 25 mg BID iptacopan (Table 171).

Figure 54. Exposure-Response of LDH at Steady State by PNH Prior Treatment Status



Source: Lnp023-modeling-report-exposure, Figure 7-18
Solid line: median ER prediction. Grey area: 90% of population. Vertical dashed line: EC90 of LDH.
Vertical dotted lines: median steady state Caverage per dose level.
Abbreviations: BID, twice daily; $C_{average}$, average concentration; EC_{90}, 90% maximal effective concentration; ER, exposure-response; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria

Table 171. Proportion of PNH Subjects Expected to Reach $C_{average}$ Exposure Greater or Equal to EC_{90} of LDH With Different Iptacopan Doses

Popula-tion	Dose	N	Median Cave (ng/ml)	Q05 Cave (ng/ml)	Q95 Cave (ng/ml)	Nb. ≥EC90 (270 ng/ml)	% ≥EC90 (270 ng/ml)
PNH	25	3200	975.35	599.83	1583.69	3200	100
	50	3200	1344.75	827.01	2183.50	3200	100
	100	3200	1887.50	1160.80	3064.77	3200	100
	200	3200	2835.86	1744.03	4604.64	3200	100

Source: Lnp023-modeling-report-exposure, Table 7-13
Abbreviations: C_{ave}, average concentration; EC_{90}, 90% maximal effective concentration; LDH, lactate dehydrogenase; Nb., number of simulated subjects; PNH, paroxysmal nocturnal hemoglobinuria; Q05, 5th quantiles of the simulated population; Q95, 95th quantiles of the simulated population

Hb

The parameter estimates for the final model is listed in Table 172. The estimated EC_{50} value [90% CI] was 218.7 ng/mL [184.5, 259.2], and consequently, the EC_{90} value was 1968.3 ng/ml [1660.6, 2332.9]. The population value of the maximal Hb level achieved on iptacopan treatment was estimated to be 127 g/L (RSE=1.33%), which was above the lower limit of normal of 120 g/L for Hb. Differences in baseline Hb levels by prior treatment status (anti-C5 naïve versus

experienced) were captured via the covariate effect of Hb on Y_{Base}. In addition, sex and PNH prior treatment status were identified as covariates for k_{in} and Y_{TRT}.

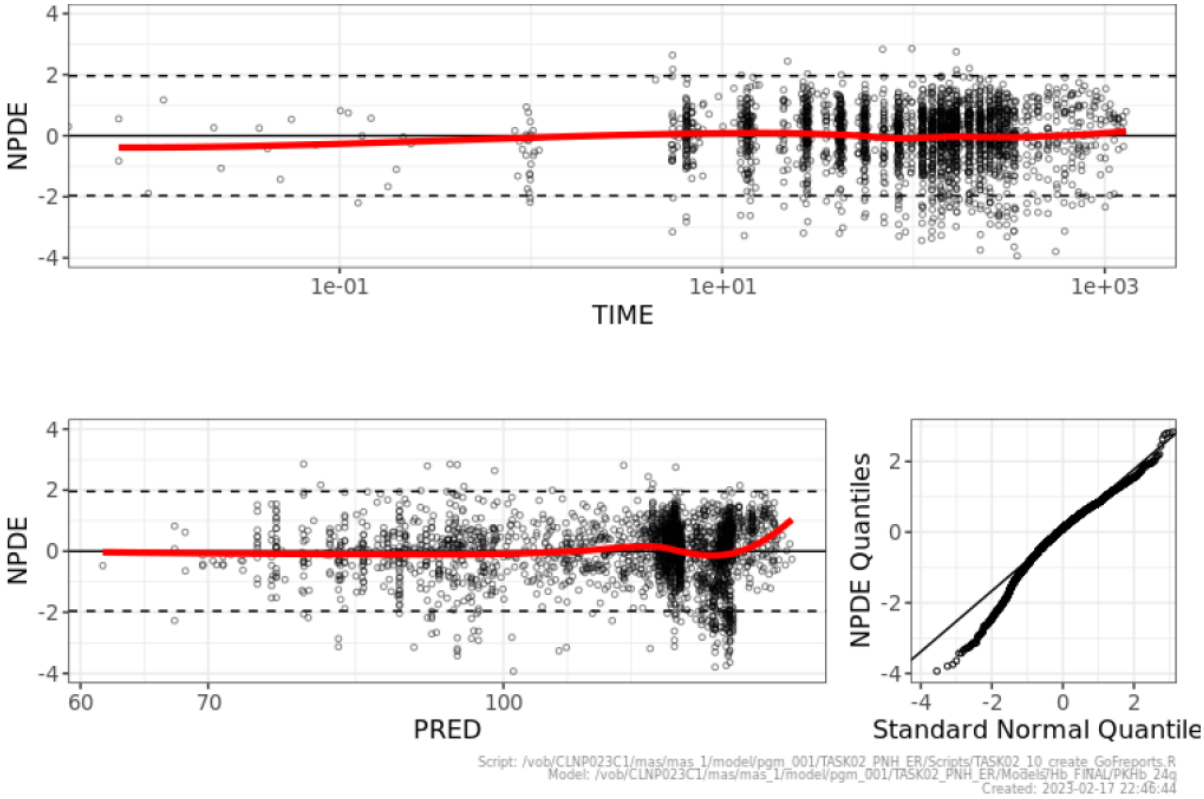
Table 172. Parameter Estimates of Final Hb Model

Parameter	Value	RSE* (%)	Shrinkage (%)	p-value
Structural (population) parameters (units)				
Hb level at baseline (Y_{Base}, g/L)	87.50	0.51		
EC50 (ng/ml)	219.00	10.42		
Hb level on iptacopan treatment (Y_{TRT}, g/L)	127.00	1.33		
Hb production rate (k_{in}, g/L/day)	18.20	12.09		
Inter-individual variability, IIV**				
IIV Y_{Base} (omega_Base)	0.03	14.16	72	
IIV Y_{TRT} (omega_YTRT)	0.11	6.58	10	
IIV kin (omega_kin)	0.87	8.75	32	
Covariate effects				
beta_Base_logtHBB	0.84	4.95		<2.2e-16
beta_YTRT_MYPOPTYPE2_PNH_naive	0.07	30.71		0.0011
beta_YTRT_SEX_M	0.07	26.71		0.00018
beta_kin_MYPOPTYPE2_PNH_naive	-1.69	10.70		<2.2e-16
beta_kin_SEX_M	-0.55	31.60		0.0016
Residual variability				
Constant residual error (a2, g/L)	6.73	1.51		

Source: Lnp023-modeling-report-exposure, Table 7-14
*IIV is provided as standard deviation.
Abbreviations: EC_{50}, half-maximal effective concentration; Hb, hemoglobin; IIV, inter-individual variability; K_{in},: production rate; M, male; PNH, paroxysmal nocturnal hemoglobinuria; RSE, relative standard error; Y_{Base}, baseline response prior to iptacopan treatment; Y_{TRT}, response to iptacopan treatment

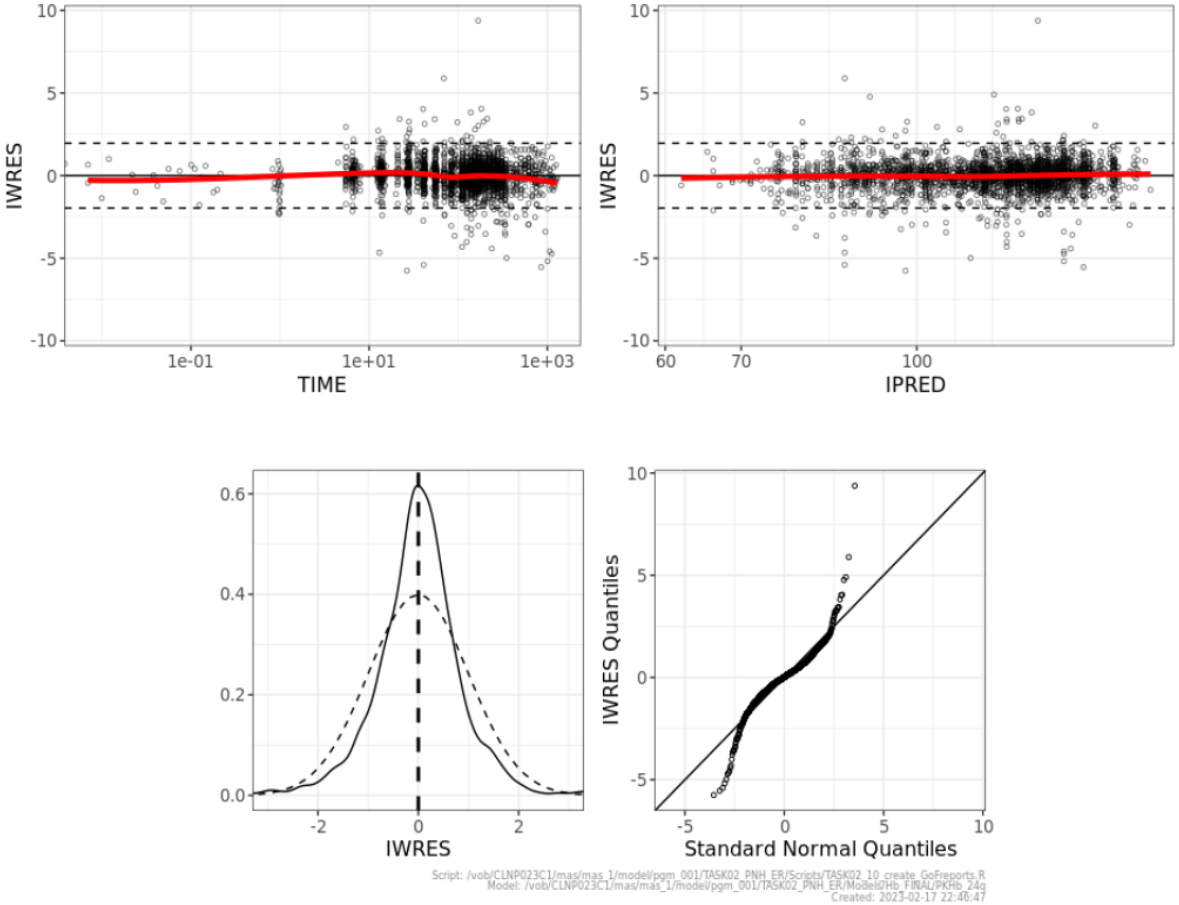
Goodness-of-fit plots showed that the final Hb model appeared to be able to describe the data. There were no major trends observed when considering unstratified NPDE versus time since first dose and versus prediction (Figure 55). Individual weighted residuals versus time and versus individual predictions (Figure 56) and plots of observed data versus population and individual predictions (Figure 57) also did not show major trends. Visual predictive checks showed that the model appeared to be able to capture the Hb time course, the steady state level on treatment, as well as interindividual variability structure (Figure 58).

Figure 55. NPDE Panel (NPDE Versus Time, NPDE Versus PRED) for Exposure-Response Model for Hb



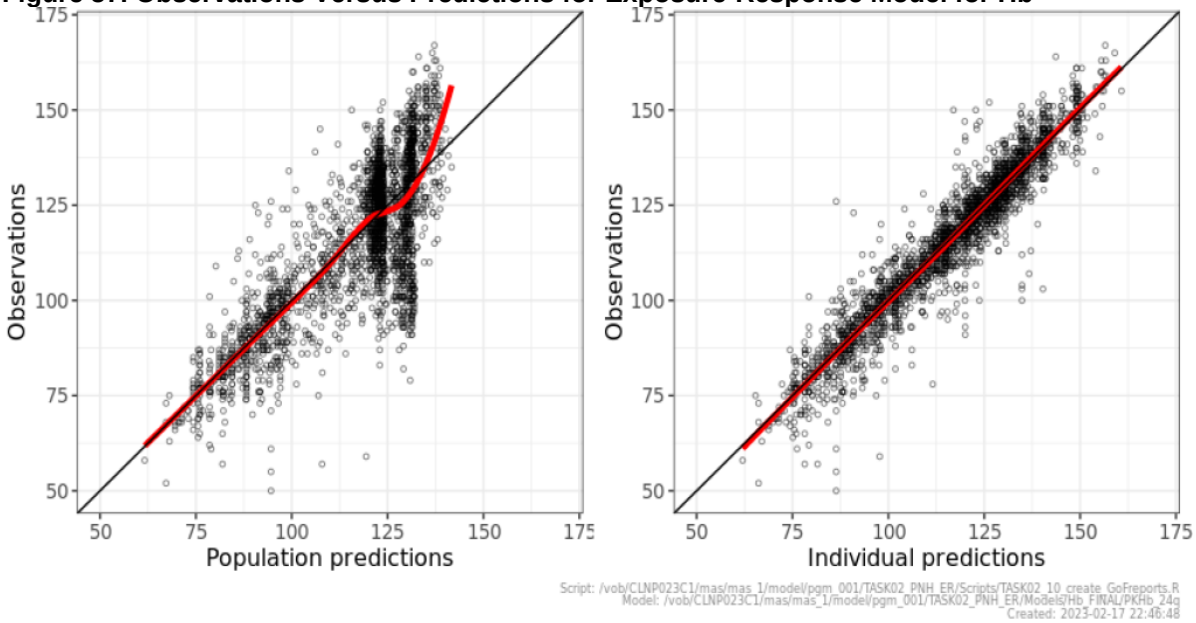
Source: Lnp023-modeling-report-exposure, Figure 7-19
Black points: noncensored data. Red line: loess smooth on all data. Horizontal dashed line: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: Hb, hemoglobin; NPDE, normalized prediction distribution errors; PRED, prediction

Figure 56. IWRES Panel (IWRES Versus Time, IWRES Versus IPRED) for Exposure-Response Model for Hb



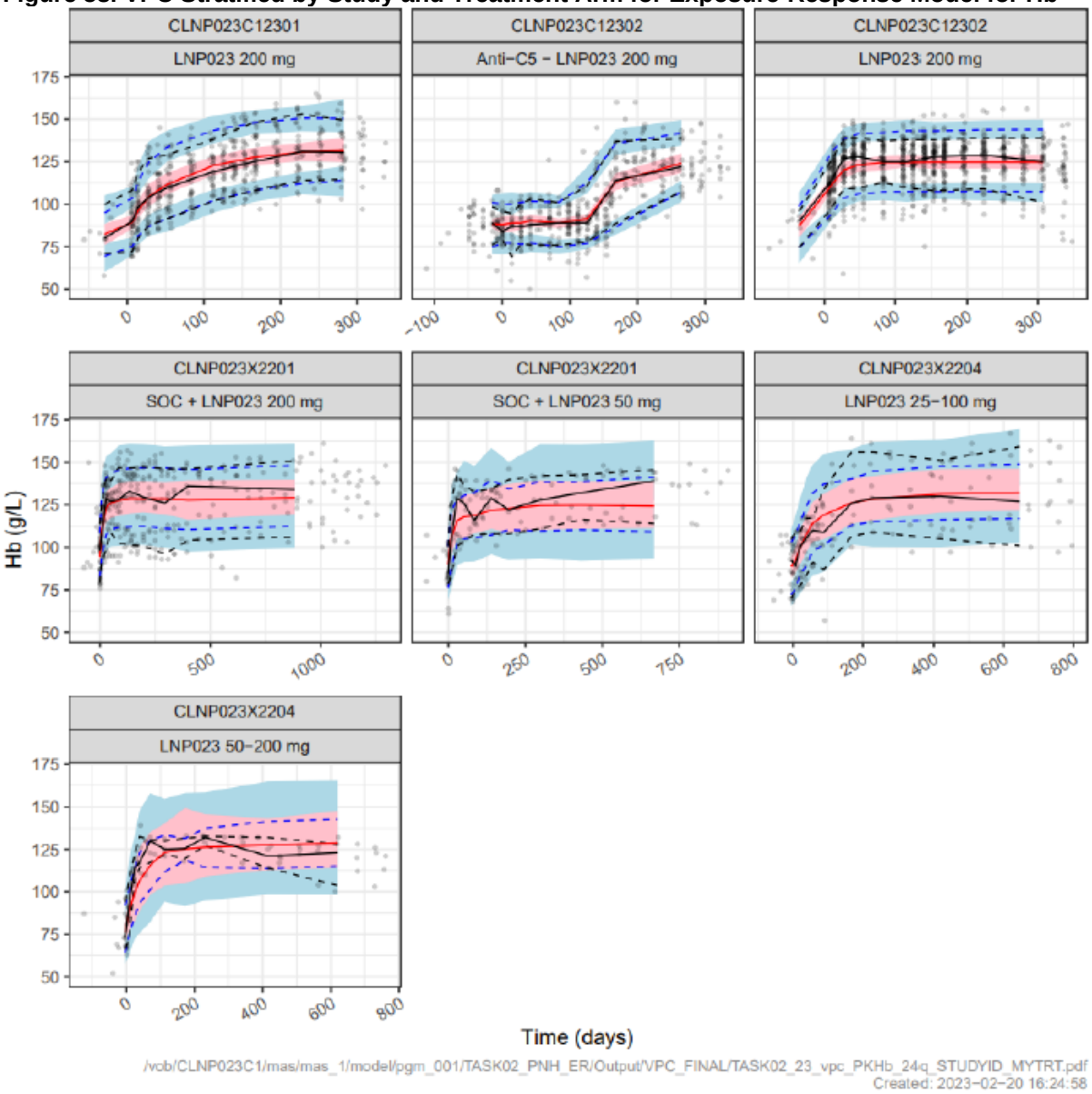
Source: Lnp023-modeling-report-exposure, Figure 7-22
Black points are noncensored data. Red line: loess smooth to highlight trend (if any). Horizontal dashed line: ±2 Standardized Residuals. Solid black line: y=x.
Abbreviations: Hb, hemoglobin; IPRED, individual prediction; IWRES, individual weighted residuals

Figure 57. Observations Versus Predictions for Exposure-Response Model for Hb



Source: Lnp023-modeling-report-exposure, Figure 7-23
Black points are noncensored data. Red line: loess smooth to highlight trend (if any). Solid black line: y=x.
Abbreviations: Hb, hemoglobin

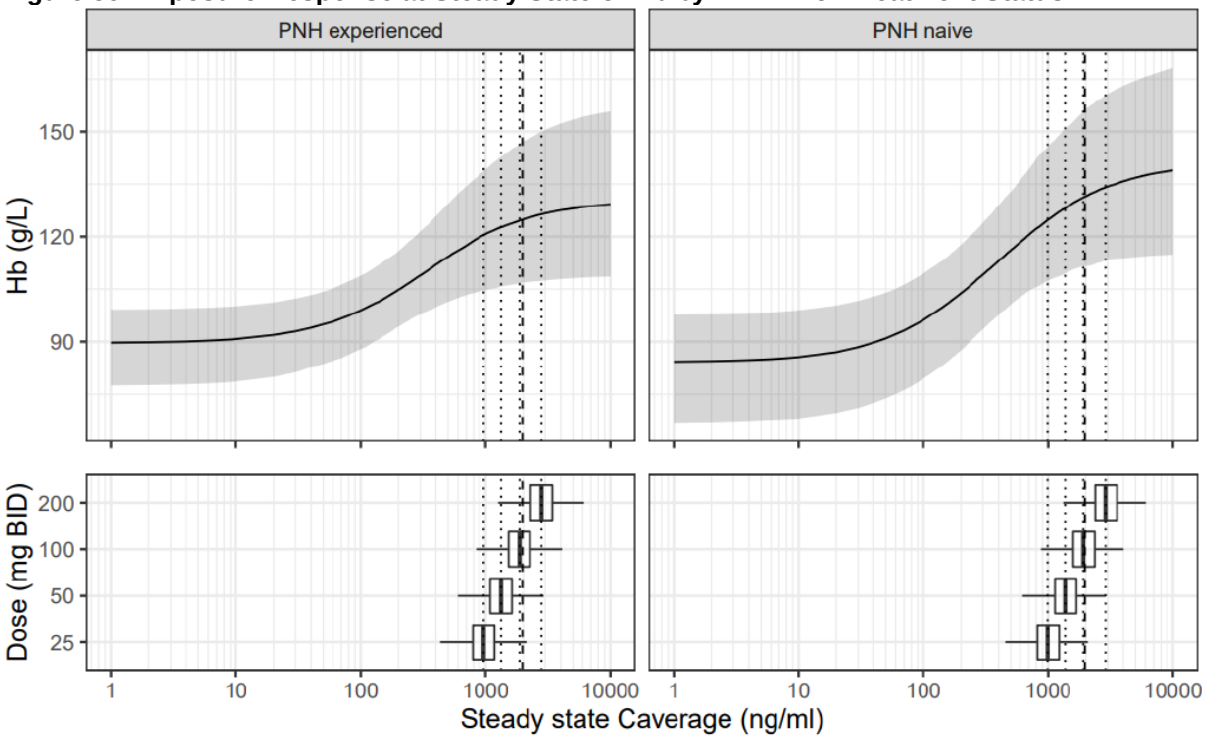
Figure 58. VPC Stratified by Study and Treatment Arm for Exposure-Response Model for Hb



Source: Lnp023-modeling-report-exposure, Figure 7-25
Solid and dashed lines: quantiles (solid black line: 50%, dashed black lines: 5% and 95%) of the observed data within bin. Red solid line: median model prediction. Dashed blue lines: 5th and 95th quantiles of model prediction. Shaded areas represent 95% confidence intervals for the percentiles. Dots are observations. Percentiles are plotted at the median time point in the bins.
Abbreviations: Hb, hemoglobin; LNP023, iptacopan; VPC, visual predictive check

The exposure-response correlation for Hb is shown in Figure 59. In both subjects who were anti-C5 naïve and experienced, Hb levels increased with iptacopan exposure, with a slightly greater magnitude of response observed for subjects who were anti-C5 naïve than for subjects who were experienced. The estimated EC_{90} [90% CI] of Hb was ~1970 ng/ml [1661, 2333], with ~89% of subjects expected to reach this $C_{average}$ exposure with the 200 mg BID dose (Table 173).

Figure 59. Exposure-Response at Steady State of Hb by PNH Prior Treatment Status



Source: Lnp023-modeling-report-exposure, Figure 7-30
Solid line: median ER prediction. Grey area: 90% of population. Vertical dashed line: EC90 of LDH. Vertical dotted lines: median steady state Caverage per dose level.
Abbreviations: BID, twice daily; C_{ave}, $C_{average}$; EC_{90}, 90% maximal effective concentration; ER, exposure-response; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria

Table 173. Proportion of Subjects With PNH Expected to Reach Caverage Greater or Equal to EC_{90} of Hb With Different Iptacopan Doses

Dose (mg bid)	N	Median Cave (ng/ml)	Q05 Cave (ng/ml)	Q95 Cave (ng/ml)	Nb. ≥EC90 (1970 ng/ml)	% ≥EC90 (1970 ng/ml)
25	3200	975.35	599.83	1583.69	31	0.97%
50	3200	1344.75	827.01	2183.50	350	10.94%
100	3200	1887.50	1160.80	3064.77	1428	44.62%
200	3200	2835.86	1744.03	4604.64	2862	89.44%

Source: Lnp023-modeling-report-exposure, Table 7-20
Abbreviations: BID, twice daily; C_{ave}, average concentration; EC_{90}, 90% maximal effective concentration; Hb, hemoglobin; Lnp023, iptacopan; Nb., number of simulated subjects; PNH, paroxysmal nocturnal hemoglobinuria; Q05, 5th quantiles of the simulated population; Q95, 95th quantiles of the simulated population

Reviewer Comment:

The proposed exposure analyses for LDH and Hb appeared to be acceptable. The model-estimated EC_{90} (for both subjects who were previously treated and those who were treatment naïve) were 270 and 1970 ng/mL for LDH and Hb, respectively. Based on the population PK analysis, the steady-state average concentration for 200 mg BID was approximately 2949 ng/mL, which was higher than the estimated EC_{90} for both efficacy endpoints and located in the plateau phase of the exposure-response relationship for the two endpoints.

Exposure-Response Analysis for Safety

Data from the following studies were used:

- CLNP023X2201 (subjects with anemia and hemolysis despite standard of care treatment with anti-C5; iptacopan as add-on to eculizumab)
- CLNP023X2204 (subjects who were complement inhibitor naïve)
- CLNP023C12301 (subjects who were complement inhibitor naïve)
- CLNP023C12302 (subjects with residual anemia despite treatment with anti-C5).

Subjects from this pool of data were treated with iptacopan at doses of 25 mg BID (study X2204), 50 mg BID (studies X2201 and X2204), 100 mg BID (study X2204), and 200 mg BID (studies X2201, X2204, C12301, C12302) covering a broad range of exposure. Additionally, subjects from study C12302 randomized to anti-C5 treatment provided data at zero iptacopan exposure. A total of 166 subjects with exposure ≥0 was included in the analysis. Given the different follow-up duration between the studies and in order to have a consistent amount of data across all subjects, only data up to 6 months of treatment were included in the analysis.

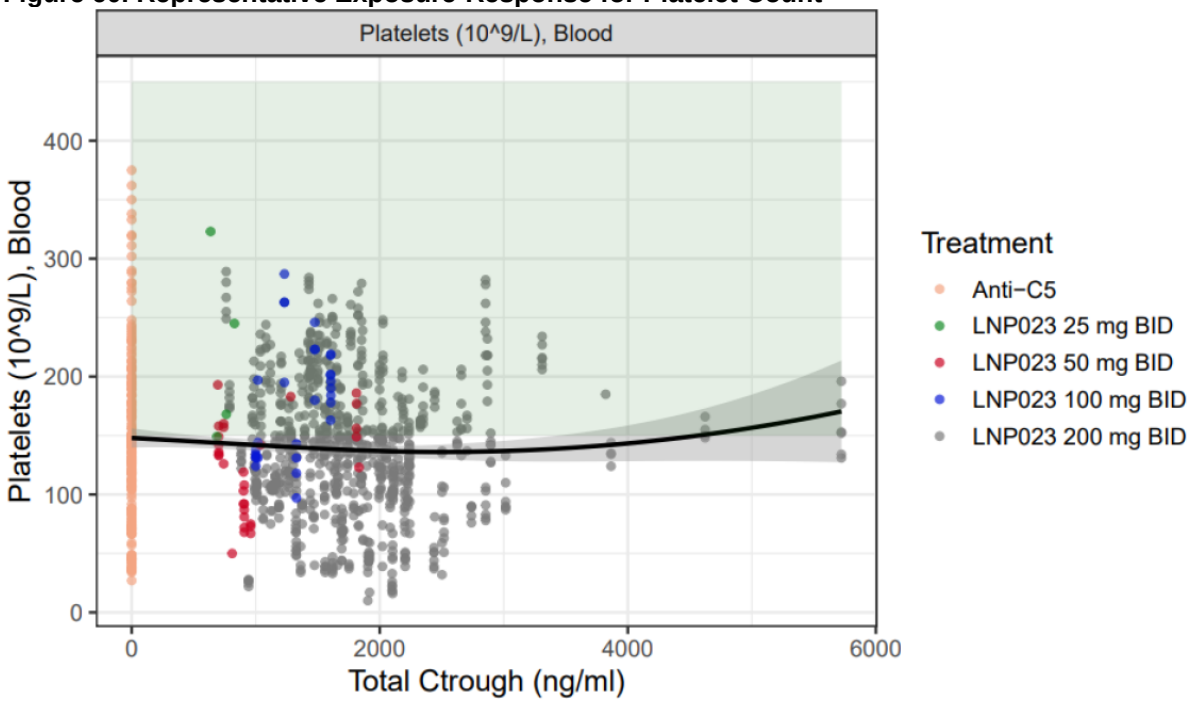
A mixed model for repeated measures was used to assess the relationship between PK exposure and changes from baseline for the safety outcomes, including cholesterol, platelet count, triiodothyronine (T3), dihydrotestosterone, follicle-stimulating hormone (FSH), thyrotropin, and thyroxine. The PK metrics tested included bound and unbound steady-state maximum ($C_{max,ss}$), trough ($C_{trough,ss}$), and average concentration ($C_{avg,ss}$). The six metrics showed strong correlations. The fraction of unbound was estimated based on Equation 4, where the E_0=0.006 represented free fraction at low concentrations, E_{max}=0.19 was the fraction unbound once most of the on-target binding was saturated, EC_{50}=1316.56 ng/mL was the concentration at which the fraction unbound is 50% from E_{max}, and n=3.1 was the hill function coefficient. Parameters were estimated using data from healthy subjects from study CLNP023A2105.

Equation 4. Fraction of Unbound Iptacopan

$$f_u = E_0 + \frac{E_{max} \cdot C_{tot}^n}{(EC_{50}^n + C_{tot}^n)}$$

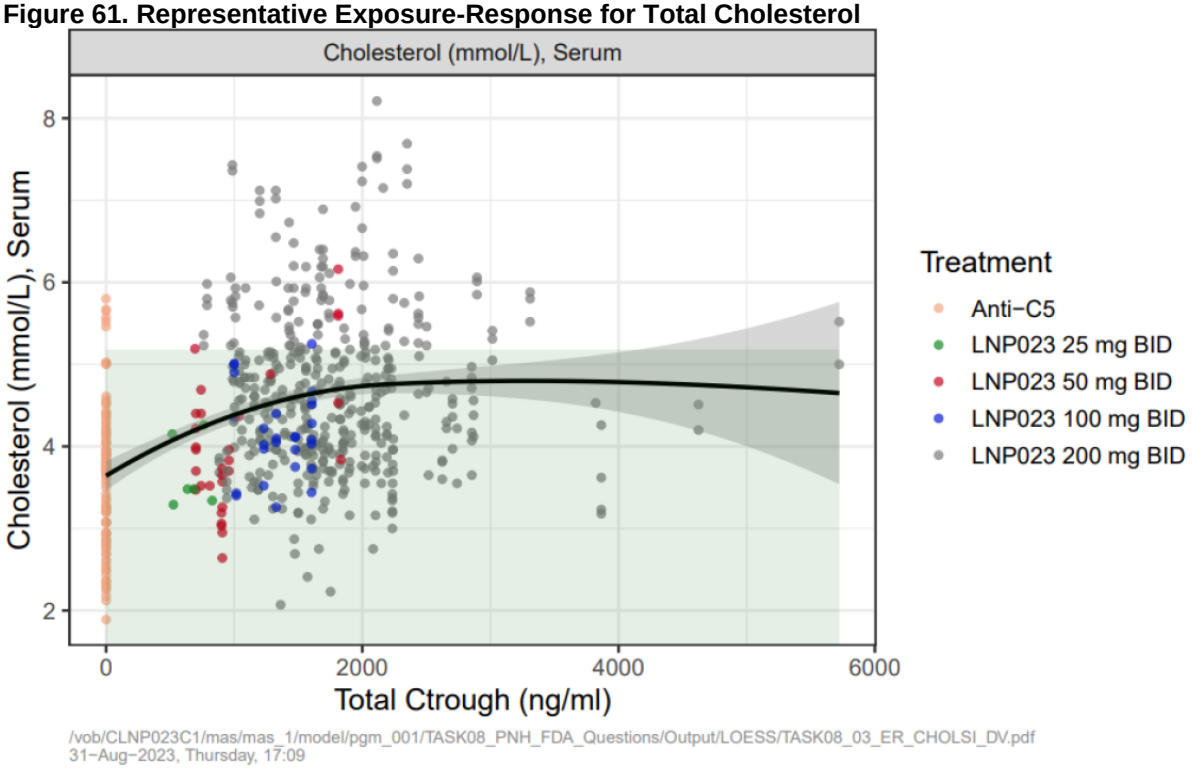
The first model including data with zero iptacopan exposure was fitted for all parameters and the six metrics of exposure. Nominal statistical significance was reported for changes from baseline in platelet count (Figure 60), total cholesterol (Figure 61), and triiodothyronine (Figure 62). Nominal statistical significance was observed for all six exposure metrics, which was expected given the strong correlation between the various exposure metrics. No statistical correlations were identified for the rest safety outcomes. The second model including only non-zero exposure to iptacopan was fitted for all parameters and the six metrics of exposure. There was no nominally statistically significant relationship between exposure and any parameter at alpha level of 0.01.

Figure 60. Representative Exposure-Response for Platelet Count



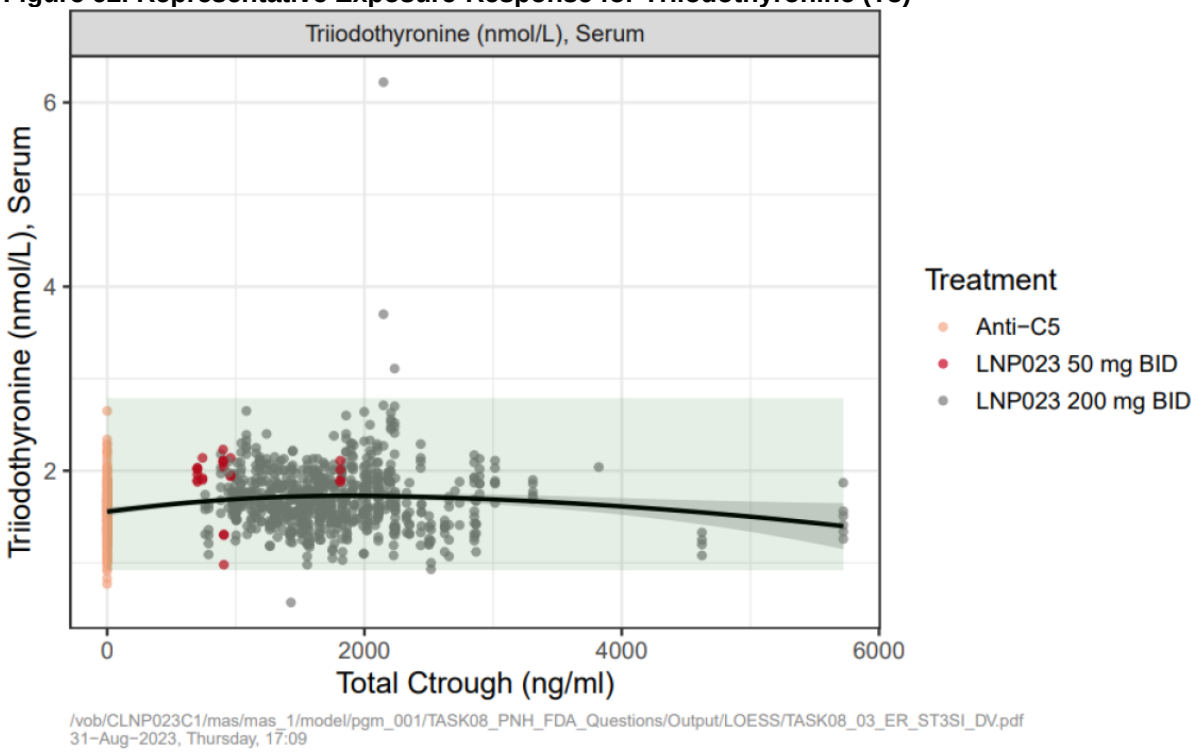
Source: Response to FDA Information Request e-mail dated August 9, 2023, Figure 2-3
Points represent individual exposure-response data at various times (months 1-6) colored by the corresponding dose level. Black line and grey area: loess smooth (span=1) and 95% confidence interval on the scale of the y axes. Green area delimits the range between lower limit and upper limit of normal.
Abbreviations: BID, twice daily; C_{trough}, trough concentration; FDA, Food and Drug Administration; LNP023, iptacopan

Figure 61. Representative Exposure-Response for Total Cholesterol



Source: Response to FDA Information Request e-mail dated August 9, 2023, Figure 2-3
Points represent individual exposure-response data at various times (months 1-6) colored by the corresponding dose level. Black line and grey area: loess smooth (span=1) and 95% confidence interval on the scale of the y axes. Green area delimits the range between lower limit and upper limit of normal.
Abbreviations: BID, twice daily; C_{trough}, trough concentration; FDA, Food and Drug Administration; LNP023, iptacopan

Figure 62. Representative Exposure-Response for Triiodothyronine (T3)



Source: Response to FDA Information Request e-mail dated August 9, 2023, Figure 2-5
Points represent individual exposure-response data at various times (months 1-6) colored by the corresponding dose level. Black line and grey area: loess smooth (span=1) and 95% confidence interval on the scale of the y axes. Green area delimits the range between lower limit and upper limit of normal. In study X2204, free T3 was measured instead of total T3, hence data doses 25 and 100 mg bid is missing in this graph.
Abbreviations: BID, twice daily; C_{trough}, trough concentration; FDA, Food and Drug Administration; LNP023, iptacopan; T3, triiodothyronine

Reviewer Comment:

The proposed exposure analyses for the selected safety parameters appeared to be acceptable. Based on the exposure-response analysis for safety, iptacopan treatment decreased the platelet counts and increased total cholesterol and T3 compared to anti-C5 treatment. However, the effects of iptacopan were independent of PK exposures. See Section 7 for a description of thrombocytopenia, thyroid abnormalities, and lipid abnormalities observed in clinical trials and the clinical significance. In summary, based on the PK/PD and exposure-response analyses for efficacy and safety, the proposed dosage of 200 mg BID appears to be acceptable for the general patient population.

14.6. Pharmacogenetics

1. Background

A. Submission Description

Iptacopan is a first-in-class factor B inhibitor and, through this mechanism, acts as a proximal inhibitor of the alternative complement pathway to control intravascular and extravascular hemolysis. The Applicant is seeking approval for the treatment of adults with PNH.

There are no dose adjustments related to pharmacogenetics (PGx) in the proposed labeling.

B. Specific Issues/Questions

The Applicant investigated effects of variants in PK-related genes on iptacopan PK by combining data from the first-in-human and Japanese ethnic sensitivity studies. The Applicant reported associations of *CYP2C8*3* and *SLCO1B1*1B* with reduced exposure and found that no Japanese participants were carriers of *CYP2C8*3*. The reviewer verified the Applicant's analyses and correlated PGx findings with observed minor PK differences between Japanese and non-Japanese participants.

2. Assessment

A. Materials Reviewed

Data Sources

Reports and datasets submitted by the Applicant that contain PGx information are listed in Table 174.

Table 174. Reports and Datasets for PGx Analyses of Iptacopan

Report Name	Datasets
Response to FDA information request e-mail dated May 18, 2023	LNP023X2101_PKPG.xpt LNP023X1102_PKPG.xpt
Impact of genetic factors on LNP023 pharmacokinetics in pooled studies CLNP023X2101, CLNP023X1102	
Addendum 2 to clinical study report CLNP023X1102 (exploratory PK-PG analysis)	

Source: Reviewer generated
Abbreviations: FDA, Food and Drug Administration, LNP023, iptacopan; PGx, pharmacogenomics, PK, pharmacokinetics

A description of studies that investigated PGx associations with iptacopan PK are listed in Table 175.

Table 175. Description of Studies Included in the PK-PGx Study Report

Study	Description	Number of Participants in PK-PGx Study
CLNP023X2101	Phase 1, first-in-human, randomized, subject blinded, placebo-controlled single and multiple ascending dose and food effect study conducted in Germany	72
CLNP023X1102	Phase 1, randomized, subject-blinded, placebo-controlled single ascending dose study conducted in Japan as a Japanese ethnic sensitivity study	24

Source: Reviewer generated
Abbreviations: PGx, pharmacogenomics; PK, pharmacokinetic

Analysis Methods

Genotyping was performed by the Illumina Global Screening Array microarray (v GSAMD-24v2-0 with "Multi Disease" content). Per the Applicant, the following variants and alleles of interest were investigated: *CYP2C8*2*, *3* (rs11572080 and rs10509681), *4*, *5*, *6*, *7*, *8*, *11*, *12*, *14*, rs66501115; *SLCO1B3* rs11045585; *SLCO1B1*1B* (rs2306283), *5*, *17*; *UGT1A1*6*, *28*, *60*, *93*; *UGT1A3*3*; and *UGT1A8*3*. The Applicant focused on rs11572080 to define

*CYP2C8*3* and rs2306283 to define *SLCO1B1*1B* (now *SLCO1B1*37*). The Applicant developed a combination score for genotypes at *CYP2C8* rs11572080 and *SLCO1B1* rs2306283 where each genotype was scored as 1 if an alternative allele was present, otherwise 0, and values summed for a possible combination score of 0, 1, or 2.

A description of significant variants is provided in Table 176.

Table 176. Description of Variants Associated With Iptacopan PK

Variant	Functional Consequence	MAF††
*CYP2C8*3* (defined by rs11572080 and rs10509681)†	Substrate-dependent; increased, decreased, or no change in function†	rs11572080 Europeans: 10% South Asians: 4% African Americans: 2% East Asians: 0%
*SLCO1B1*37* (formerly *SLCO1B1*1B*, defined by rs2306283 when present alone)‡	Uncertain; normal and increased function‡ *SLCO1B1*37* is considered a normal function allele‡	African Americans: 76% East Asians: 74% South Asians: 45% Europeans: 41%

Source: Reviewer generated
†Reviewed in PMID: 23962911
‡Reviewed in PMID: 35797228
††https://www.ncbi.nlm.nih.gov/snp/
Abbreviations: CYP, cytochrome P450; MAF, macrophage-activating factor; PK, pharmacokinetic; PMID, PubMed identifier; SLCO, solute carrier organic anion-transporter

The Applicant tested associations using analysis of covariance models with the raw and natural log-transformed PK parameters as dependent variables and genotype, dose, age, race, sex, and weight (included per information request) as independent variables. In addition, the Applicant performed the Wald test and Benjamini-Hochberg procedure for multiple test comparison.

B. Evidence Analysis

Question 1. Do *CYP2C8* and *SLCO1B1* Variants Correlate with Observed PK Differences Between Japanese and Non-Japanese Subjects?

Clinical PK

The reviewer noted that mean AUC_{inf} after a single 400 mg dose of iptacopan in non-Japanese participants was ~20% lower compared to Japanese participants.

A combined total of 96 participants had genotype and PK data available from studies X2101 and X1102. Pharmacokinetic parameters assessed included predicted total body CL, predicted AUC_{inf}, predicted dose-adjusted AUC_{inf} (AUC_{IFDP}), C_{max}, dose-adjusted C_{max}, and time to maximum concentration. Pharmacokinetic parameters were not combined across doses studied (5 mg to 400 mg) due to under-proportional PK with increasing doses, but PK parameters at the same dose in X2101 and X1102 were combined for analysis.

Compared to the *CYP2C8* rs11572080 C/C genotype, the C/T and T/T genotypes were significantly associated with higher predicted CL and lower AUC_{IFDP} in at least one of the models (raw or transformed). Findings were similar for *CYP2C8* rs10509681. Compared to the *SLCO1B1* rs2306283 A/A genotype, the A/G and G/G genotypes were significantly associated with lower AUC_{IFDP} in at least one of the models (raw or transformed). Compared to the *SLCO1B1* rs2306283 A/A genotype, the A/G genotype was significantly associated with higher

CL in the transformed model only. Combination scores of 1 or 2 compared to 0 were significantly associated with higher CL and lower AUC_{IFDP} in at least one of the models (raw or transformed). Results for variants with significant findings are shown in Table 177. No Japanese participants were carriers of CYP2C8*3.

Table 177. Summary of Results for Additive Linear Models to Test for PGx Associations With Iptacopan PK Parameters for Pooled Studies X2101 and X1102

PK Param	GT Counts			PK ~ GT + Dose + Age + Sex + Race + Weight						log2(PK) ~ GT + Dose + Age + Sex + Race + Weight					
CYP2C8 rs11572080															
	CC	CT	TT	β for CT	β for TT	p-Val for CT	p-Val for TT	Wald p-Val	Adj Wald p-Val	β for CT	β for TT	p-Val for CT	p-Val for TT	Wald p-Val	Adj Wald p-Val
CLRFP	63	5	1	2044.859	1079.444	**	-	**	.	0.543	0.854	*	*	**	.
C_{MAXD}	82	10	1	-1.963	-14.87	-	.	-	-	-0.175	-0.278	-	-	-	-
C_{MAX}	82	10	1	-320.018	-298.852	-	-	-	-	-0.175	-0.278	-	-	-	-
T_{MAX}	82	10	1	0.524	0.183	*	-	.	-	0.486	0.295	*	-	-	-
AUC_{IFPD}	63	5	1	-69.421	-493.775	-	***	***	**	-0.543	-0.854	*	*	**	.
AUC_{IFP}	63	5	1	-13779.257	-7734.83	**	-	*	-	-0.543	-0.854	*	*	**	.
SLCO1B1 rs2306283															
	AA	AG	GG	β for AG	β for GG	p-Val for AG	p-Val for GG	Wald p-Val	Adj Wald p-Val	β for AG	β for GG	p-Val for AG	p-Val for GG	Wald p-Val	Adj Wald p-Val
CLRFP	19	32	18	488.068	238.762	-	-	-	-	0.275	0.242	*	-	.	-
C_{MAXD}	29	44	21	-3.368	-4.919	.	*	.	-	-0.216	-0.224	*	*	*	-
C_{MAX}	29	44	21	-410.492	-557.118	*	*	.	-	-0.216	-0.224	*	*	*	-
T_{MAX}	29	44	21	0.281	-0.107	.	-	.	-	0.243	-0.045	-	-	-	-
AUC_{IFPD}	19	32	18	-102.465	-109.622	**	*	**	.	-0.275	-0.242	*	-	.	-
AUC_{IFP}	19	32	18	-5151.971	-3643.619	.	-	-	-	-0.275	-0.242	*	-	.	-
Combination score															
	0	1	2	β for 1	β for 2	p-Val for 1	p-Val for 2	Wald p-Val	Adj Wald p-Val	β for 1	β for 2	p-Val for 1	p-Val for 2	Wald p-Val	Adj Wald p-Val
CLRFP	17	46	5	502.808	1763.811	-	**	*	-	0.294	0.695	*	**	**	*
C_{MAXD}	25	58	9	-3.867	-5.395	*	.	.	-	-0.224	-0.308	*	*	*	-
C_{MAX}	25	58	9	-508.814	-554.605	*	.	*	-	-0.224	-0.308	*	*	*	-
T_{MAX}	25	58	9	0.007	0.601	-	*	.	-	0.01	0.546	-	*	.	-
AUC_{IFPD}	17	46	5	-109.561	-212.902	**	***	***	**	-0.294	-0.695	*	**	**	*
AUC_{IFP}	17	46	5	-5343.525	-13725.494	.	*	*	-	-0.294	-0.695	*	**	**	*

Source: Reviewer's analysis
Significance codes: 0.001 '***'; 0.01 '**'; 0.05 '*'; 0.1 '.'; 1 '-'
Abbreviations: AUC_{IFPD}, predicted dose-adjusted area under concentration-time curve to infinity; AUC_{IFP}, predicted area under concentration-time curve to infinity; CLRFP, predicted total body clearance; C_{MAXD}, dose-adjusted maximum concentration; C_{MAX}, maximum plasma concentration; GT, genotype; param, parameter; param, parameter; PGx, pharmacogenomics; PK, pharmacokinetic; T_{MAX}, time to maximum concentration; SLCO, solute carrier organic anion-transporter

3. Recommendations

A. Summary

*CYP2C8*3* (rs11572080 and rs10509681) and *SLCO1B1*37* (formerly *SLCO1B1*1B*, rs2306283) were associated with lower iptacopan exposure. Genotyping covered an adequate breadth of genes and variants pertinent to iptacopan's PK pathways. The observed lack of *CYP2C8*3* carriers in Japanese participants is consistent with allele frequencies. *CYP2C8*3* may have contributed to the observed 20% lower mean AUC_{inf} after a single 400 mg dose of iptacopan in non-Japanese participants compared to Japanese participants. Overall, the Applicant reported similar PK and PD effects in Japanese and non-Japanese participants.

No dose adjustment is recommended at this time. Of note, dose adjustments would be complicated by the nonproportional PK of iptacopan. Overall, PK-PGx findings were exploratory with only minor PK differences noted and were not linked to potential impact on safety or efficacy, and there were no CYP2C8 or OATP1B1 drug-drug interactions with similar magnitude of exposure differences that have proposed dose adjustments.

B. Labeling

There are no recommendations for labeling.

C. Postmarketing Studies

There are no postmarketing studies recommended.

14.7. Physiologically-Based Pharmacokinetic Analysis

Executive Summary

The aim of this review is verifying the adequacy of the Applicant's PBPK analysis related to the DDI liability of iptacopan:

- With rifampin as a victim of CYP2C8, UGT1A1 and OATP1B1/3 modulation
- With gemfibrozil as a victim of CYP2C8 and OATP1B1/3 inhibition
- With repaglinide as a perpetrator of CYP2C8 inhibition

The Division of Pharmacometrics has reviewed the PBPK submission (report DMPK R2270401, modeling files) and response to FDA's request for information (dated July 20, 2023) to conclude the following:

- The PBPK analysis was inadequate to predict the DDI effect of CYP2C8 and OATP1B1/3 modulators on iptacopan PK and the DDI risk of iptacopan on a CYP2C8 substrate, mainly due to uncertainty related to the contribution of hepatic OATP1B1/3 uptake to iptacopan disposition.

1. Background

Iptacopan was proposed to be cleared by CYP2C8, UGT1A1, renal elimination, and biliary secretion.

In vitro, iptacopan was determined to be a substrate for the hepatic uptake transporters, organic anion transporting protein (OATP) 1B1 and OATP1B3, and the efflux transporters P-glycoprotein (P-gp), multidrug resistance associated protein (MRP) 2, and breast cancer resistance protein (BCRP) (reports DMPK R1500516, DMPK R1600579, DMPK R1600140, DMPK R1500730, and DMPK R1800300).

Iptacopan exhibited less than dose proportional increase in exposure (i.e., C_{max} and AUC) in the dose range of 5 to 200 mg after a single dose and 25 to 200 mg after twice daily (BID) dosing [study CLNP023X2101]. The nonlinearity was assumed to be due to iptacopan's target-mediated drug disposition (TMDD) by irreversibly binding to factor B (FB) in human plasma. The PK of iptacopan approaches dose proportionality at steady-state doses of 100 mg BID and 200 mg BID (Summary Clinical Pharmacology Report). Steady state was achieved after approximately 5 to 7 days of twice daily dosing. Iptacopan showed concentration-dependent plasma protein binding due to binding to the target FB.

2. Applicant's PBPK Modeling Effort

2.1 Methods

2.1.1 Model Development and Verification

The PBPK analyses were performed using the population-based PBPK software Simcyp® (V21.1, Simcyp Ltd., a Certara Company, Sheffield, United Kingdom).

(b) (4)

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4. Conclusions

The PBPK analysis was inadequate to predict the DDI effect of CYP2C8 and OATP1B1/3 modulators on iptacopan PK and the DDI risk of iptacopan on a CYP2C8 substrate, mainly due to uncertainty related to contribution of hepatic OATP1B1/3 uptake to iptacopan disposition.

15. Study/Trial Design

15.1. Protocol Synopsis – APPLY-PNH

Table 182. Protocol Summary

Protocol number	CLNP023C12302
Full Title	A randomized, multicenter, active-comparator controlled, open label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult patients with PNH and residual anemia, despite treatment with an intravenous anti-C5 antibody
Brief Title	Study of efficacy and safety of twice daily oral LNP023 in adult PNH patients with residual anemia despite anti-C5 antibody treatment
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this Phase 3 study is to determine whether LNP023 is efficacious and safe for the treatment in PNH through demonstration of superiority of LNP023 compared to anti-C5 antibody treatment in adult PNH patients presenting with residual anemia despite treatment with anti-C5 antibody therapy
Primary Objective(s)	The primary objectives are to: • Demonstrate superiority of LNP023 compared to anti-C5 antibody treatment in the proportion of participants achieving a sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions. • Demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in the proportion of participants achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions. The primary clinical questions of interest are: What is the treatment effect of LNP023 at a dose of 200 mg b.i.d. versus anti-C5 antibody treatment in PNH patients with residual anemia, regardless of discontinuation of study medication and occurrence of breakthrough hemolysis or Major Adverse Vascular Events (MAVEs), on the odds of being a responder, with the endpoints defined as a composite of • An increase in Hb levels from baseline ≥ 2 g/dL • Hb levels ≥ 12 g/dL both assessed between Day 126 and Day 168 and of not requiring RBC transfusions between Day 14 and Day 168.
Secondary Objectives	• To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment in transfusion avoidance as the proportion of participants who remain free from transfusions by assessing the proportion of participants not receiving any packed red blood cell transfusions per protocol established criteria between Day 14 and Day 168 • To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in average change in hemoglobin by assessing the change from baseline in hemoglobin (g/dL) as mean of visits between Day 126 and Day 168 • To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in improving fatigue, using the FACIT-Fatigue questionnaire by assessing the change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168 • To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in average change in reticulocyte counts by assessing the change from baseline in reticulocyte count (109/L) as mean of visits between Day 126 and Day 168 • To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in average percent change in LDH by assessing the percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168 • To demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in the rate of breakthrough hemolysis (BTH) of participants with breakthrough hemolysis reported between Day 1 and Day 168

	• To assess rates of MAVEs (incl. thrombosis) of LNP023, compared to anti-C5 antibody treatment occurring between Day 1 and Day 168 • The assessment of safety and tolerability of LNP023 compared to anti-C5 antibody treatment
Study design	This study is a multi-center, randomized, open-label, active comparator-controlled, parallel group study, which is comprised of a screening period, a 24-week, active controlled, parallel group treatment period and a 24-week LNP023 treatment extension period.
Study population	Approximately ninety one (91) patients diagnosed with PNH, who are treated with a stable regimen of anti-C5 antibody (Standard of Care (SoC); either eculizumab or ravulizumab) for at least 6 months prior to Randomization, but still presenting with residual anemia (i.e., Hb < 10 g/dL) will be enrolled.

Key Inclusion criteria	• Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with RBCs and WBCs granulocyte/monocyte clone size ≥ 10%
	• Stable regimen (dose and intervals) of anti-C5 antibody treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization
	• Mean hemoglobin level <10 g/dL
	  • Over a minimum of 4 months before screening visit
	  • Confirmed by central laboratory assessment during screening
	• Vaccination against Neisseria meningitidis infection is required prior to the start of treatment. If the patient has not been previously vaccinated, or if a booster is required, vaccine should be given according to local regulations, at least 2 weeks prior to first dosing.
	• If not received previously, vaccination against Streptococcus pneumoniae and Haemophilus influenzae infections should be given, if available and according to local regulations. The vaccines should be given at least 2 weeks prior to first dosing.

Key Exclusion criteria	• Participants on a stable eculizumab dose but with a dosing interval of 11 days or less or participants on stable ravulizumab dose but with a dosing interval of less than 8 weeks. • Known or suspected hereditary complement deficiency at screening • History of hematopoietic stem cell transplantation • Patients with laboratory evidence of bone marrow failure (reticulocytes <100x109/L; platelets <30x109/L; neutrophils <500x106/L). • Active systemic bacterial, viral (incl. COVID-19) or fungal infection within 14 days prior to study drug administration • A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus. • Major concurrent comorbidities including but not limited to severe kidney disease (e.g., eGFR < 30 mL/min/1.73 m^2,dialysis) , advanced cardiac disease (e.g., NYHA class IV), severe pulmonary disease (e.g., severe pulmonary) hypertension (WHO class IV), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.
Study treatment	LNP023 Anti-C5 antibodies (either eculizumab or ravulizumab)
Treatment of interest	The randomized treatment (the investigational treatment LNP023 200 mg b.i.d. or stable regimen of anti-C5 antibody therapy (SoC)) regardless of whether patient discontinues treatment (treatment policy).
Efficacy assessments	• Hemoglobin, reticulocytes, LDH and other PNH-related laboratory parameters • Red blood cell transfusions • Breakthrough hemolysis

	• Patient Reported Outcomes (PRO)–FACIT-Fatigue • Major Adverse Vascular Events (MAVEs) incl. thrombosis
Key safety assessments	• Laboratory evaluations in blood and urine • Adverse event monitoring • ECG • Coagulation panel/thrombosis • Reproductive and thyroid hormones monitoring
Other assessments	An assessment of patient-reported outcomes is planned in this trial using European Organization For The Research And Treatment Of Cancer Quality Of Life Questionnaire (EORTC QLQ-C30), EuroQol - 5 Dimensions- 5 Level (EQ-5D-5L), and Patient Global Impression of Severity of fatigue (PGIS). Exploration of the meaningfulness of the change demonstrated in patient report outcomes will be performed with an optional Patient Interview.
Data analysis	All efficacy analyses will use the full analysis set (FAS) that includes all patients randomized into the study. Primary efficacy estimands represented by the following endpoints: • Proportions of participants achieving a sustained increase in hemoglobin levels from baseline ≥ 2 g/dL between Day 126 and Day 168 in the absence of transfusions between Day 14 and Day 168 • Proportions of participants achieving sustained hemoglobin levels ≥ 12 g/dL between Day 126 and Day 168 in the absence of transfusions between Day 14 and Day 168 Superiority of LNP023 compared to anti-C5 antibody treatment will be determined using an odds ratio and tested by a simultaneous weighted permutation test derived from a conditional logistic model accounting for the stratification factors used at randomization and with adjustment for baseline hemoglobin levels and sex, used in the analysis of the two endpoints. Besides the odds ratio a marginal logistic model adjusting for stratification factors and covariates will be used to compare the proportions of both treatments using standardization. Secondary efficacy estimands represented by the following endpoints: • Proportions of participants who are transfusion free by protocol specified criteria between Day 14 and Day 168 • Differences in average change from baseline in hemoglobin levels between Day 126 and Day 168 estimated under the hypothetical condition of being free from transfusion between Day 14 and Day 168 • Differences in average score changes from baseline evaluated between Day 126 and Day 168 of FACIT-Fatigue • Differences in average changes from baseline in reticulocyte counts evaluated between Day 126 and Day 168 • Differences in average percent change from baseline in LDH evaluated between Day 126 and Day 168 • Rates of breakthrough hemolysis between Day 1 and Day 168 • Rates of MAVEs between Day 1 and Day 168 Following successful rejection of the hypotheses associated with the primary estimands, the secondary estimand hypotheses will be tested applying weighted Simes' tests with pre-defined weights allocated to the different levels of secondary hypotheses. The testing procedure applies alpha propagation rules according to the principles of graphical procedures for multiplicity adjustment. The estimands of interest as well as methods for obtaining comparisons are described in detail in the corresponding sections.

Source: Applicant's Protocol for APPLY-PNH
Abbreviations: BID, twice daily; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EORTC, European Organization For The Research And Treatment Of Cancer Quality Of Life Questionnaire; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy- Fatigue; FAS, full analysis set; Hb, hemoglobin; LDH, lactate dehydrogenase; LNP023, iptacopan; MAVE, major adverse vascular events; NYHA, New York Heart Association; PGIS, Patient Global Impression of Severity of Fatigue; PNH, paroxysmal nocturnal hemoglobinuria; PRO, patient reported outcomes; RBC, red blood cell; WBC, white blood cell; WHO, World Health Organization

15.2. Protocol Synopsis- APPOINT-PNH

2 Synopsis

Name of product: Iptacopan/LNP023

Protocol identification number: CLNP023C12301, EudraCT no. 2020-003172-41

Title of study: A multicenter, single-arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who are naive to complement inhibitor therapy

Investigators:

Régis Peffault De Latour, MD, Saint-Louis Hospital, France (Principal Investigator and Steering Committee Chair).

Antonio Maria Risitano, MD, Phd, AORN San Giuseppe Moscati-Avellino, Italy (Principal Investigator and Steering Committee Co-Chair).

Study centers: 16 centers across 10 countries enrolled subjects. The country and respective number of centers are as follows: China (3), Czech Republic (1), France (1), Germany (3), Italy (1), Japan (1), Malaysia (2), Republic of Korea (1), Singapore (2), United Kingdom (1).

Publication (reference): None

Study period:

Study initiation date: 19-Jul-2021 (first patient first visit)

Data cut-off date: 02-Nov-2022 (Primary endpoint completion date)

Phase of development (phase of this clinical study): III

Objectives:

The registration clinical study report synopsis presents the primary, all secondary efficacy, safety and exploratory results and analyses for the 24-week core treatment period (all patients that completed the Day 168 visit) as well as the safety data from the on-going extension treatment period until the data cut-off date (02-Nov-2022). A final clinical study report is planned when all patients have completed the extension treatment period.

Primary objective and endpoint

The primary objective was to assess the effect of iptacopan on proportion of patients treated with iptacopan achieving a sustained increase from baseline in hemoglobin levels of ≥ 2 g/dL in the absence of RBC transfusion.

- Primary endpoint: Increase from baseline Hb levels ≥ 2 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.

For simplicity in this document the efficacy estimands are divided into 3 main categories:

- Treatment policy estimand: To assess the efficacy benefit regardless of the occurrence of intercurrent events such as treatment discontinuation, breakthrough hemolysis events and MAVEs. All data are included in the analysis.
- Direct efficacy estimand: To assess the direct efficacy benefit of iptacopan not including any efficacy benefit derived from RBC transfusion use. Impact of transfusion use is factored out through the analysis approach.
- Including transfusion estimand: To assess the benefit of iptacopan treatment in conjunction with RBC transfusion use as part of a treatment strategy. All data are included in the analysis.

Primary endpoint estimated label and endpoint definitions are provided in Table 183.

Table 183. Primary Estimand and Endpoint

Estimand label	Endpoint definition
Primary: treatment policy estimand	Patient achieved a sustained hematological response, defined as increase from baseline Hb levels ≥ 2 g/dL for 3 out of 4 assessments between Day 126 and Day 168. Patient did not receive a transfusion nor met one of the following pre-defined criteria for transfusion: 1. Hb between >7 and ≤ 9g/dL (>6 and ≤8 g/dL for Chinese population) with signs/symptoms of sufficient severity to warrant a transfusion or 2. Hb ≤7g/dL (≤6g/dL for patients in China), regardless of presence of clinical signs and/or symptoms

Source: APPOINT-PNH CSR
Abbreviations: CSR, clinical study report; Hb, hemoglobin; PNH, paroxysmal nocturnal hemoglobinuria

Secondary objectives, endpoints and estimands are provided in Table 184.

Table 184. Secondary Objectives, Endpoints and Estimands

Secondary Objective(s)	Endpoint(s)	Estimand label
To assess the effect of iptacopan on the proportion of patients achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions	Response defined as having Hb levels ≥ 12 g/dL between Day 126 and Day 168 in absence of red blood cell transfusion between Day 14 and Day 168	treatment policy estimand
To assess the effect of iptacopan on transfusion avoidance (TA) defined as the proportion of patients who remain free from transfusions	Absence of administration of packed-red blood cell transfusions between Day 14 and Day 168	treatment policy estimand
To assess the effect of iptacopan on average change in hemoglobin	Change from baseline in hemoglobin (g/dL) as mean of visits between Day 126 and Day 168	direct efficacy estimand
To assess the effect of iptacopan on average percent change in Lactate Dehydrogenase (LDH)	Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168	including-transfusion estimand
To assess the effect of iptacopan on the rate of breakthrough hemolysis (BTH)	Occurrences of breakthrough hemolysis reported between Day 1 and Day 168	including-transfusion estimand
To assess the effect of iptacopan on average change in reticulocyte counts	Change from baseline in reticulocyte counts (10^9/L) as mean of visits between Day 126 and Day 168	including-transfusion estimand
To assess the effect of iptacopan on improving fatigue, using the FACIT-Fatigue questionnaire	Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168	including-transfusion estimand
To assess the rates of Major Adverse Vascular Events (MAVEs incl. thrombosis)	Occurrences of MAVEs occurring between Day 1 and Day 168	including-transfusion estimand
To assess safety and tolerability of iptacopan*	Safety assessments (including adverse events/serious adverse events, safety laboratory parameters, vital signs etc.) between Day 1 and Day 168	-

*The assessment of safety and tolerability is not included among the secondary estimands

Source: APPOINT-PNH CSR
Abbreviations: BTH, breakthrough hemolysis; CSR, clinical study report; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy- Fatigue; incl., including; LDH, lactate dehydrogenase; MAVE, major adverse vascular events; PNH, paroxysmal nocturnal hemoglobinuria; TA, transfusion avoidance

Study design and methodology:

Study CLNP023C12301 was a multicenter, single-arm, open-label trial which is comprised of 8 weeks screening period, 24-week core treatment period and 24-week extension treatment period.

Eligible PNH patients with hemolysis (LDH > 1.5 ULN) and anemia (hemoglobin <10 g/dL), who were naive to complement inhibitor therapy, including anti-C5 antibody treatment, patients received iptacopan monotherapy at a dose 200 mg orally b.i.d

Number of patients planned: A total of 40 patients were planned. All patients provided written informed consent prior to the start of any study-related activities.

Number of patients analyzed: A total of 40 patients were enrolled and started study treatment in the trial.

A treatment duration of 24 weeks is considered appropriate to assess the effect of iptacopan on the primary and secondary efficacy endpoints, as well as on safety and tolerability.

Diagnosis and main criteria for inclusion and exclusion:

The study population consisted of PNH patients with hemolysis (LDH > 1.5 ULN) and anemia (hemoglobin <10 g/dL), who were naive to complement inhibitor therapy.

Key inclusion criteria included:

- Male and female patients ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with RBCs and WBCs (granulocyte/monocyte) clone size ≥ 10%.
- Mean hemoglobin level <10 g/dL confirmed by central laboratory assessment during Screening and prior to starting study treatment:
  - By two hemoglobin measurements (mean < 10 g/dL), 2 to 8 weeks apart, for patients not receiving a RBC transfusion during Screening.
  - By one hemoglobin measurement (<10 g/dL) carried at the first Screening visit for patients receiving a RBC transfusion after which he/she will be eligible.
- LDH > 1.5 x Upper Limit of Normal (ULN) for at least 2 central laboratory measurements 2 to 8 weeks apart during the screening period.

- Vaccination against *Neisseria meningitidis* infection was required prior to initiation of iptacopan treatment. If iptacopan treatment was started less than 2 weeks post-vaccination or before a specific vaccination was given, prophylactic antibiotic was to be given to the patient at the start of iptacopan and for at least 2 weeks after vaccination.
- If not received previously, vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* should be given (if available and according to local/national regulations), and are recommended at least 2 weeks prior to initiation of iptacopan treatment. However, administration of these vaccines less than 2 weeks prior to start of iptacopan treatment or up to 2 weeks (up to Day 14) after iptacopan initiation, was at the discretion of the investigator. If iptacopan treatment was started less than 2 weeks post-vaccination or before a specific vaccination was given, patient had to be given prophylactic antibiotic at the start of iptacopan and for at least 2 weeks after vaccination.

Key exclusion criteria included:

- Prior treatment with a complement inhibitor, including anti-C5 antibody.
- Known or suspected hereditary complement deficiency.
- History of hematopoietic stem cell transplantation.
- Patients with laboratory evidence of bone marrow failure (reticulocytes $<100x10^9$/L; platelets $<30x10^9$/L; neutrophils $<0.5x10^9$/L).
- Active systemic bacterial, viral (including COVID-19) or fungal infection within 14 days prior to study drug administration.
- A history of recurrent invasive infections caused by encapsulated organisms, e.g., meningococcus or pneumococcus.
- Major concurrent comorbidities including but not limited to severe kidney disease, advanced cardiac disease, severe pulmonary disease, or hepatic disease that in the opinion of the investigator precluded patient's participation in the study.
- Concomitant use of any of the following medications is prohibited if not on a stable regimen for the time period indicated below prior to Screening:
  - Erythropoiesis-stimulating agents (ESAs) for at least 8 weeks.
  - Any immunosuppressants for at least 8 weeks.
  - Systemic corticosteroids given for hematological conditions (less than 0.25 mg/kg/d) for at least 4 weeks.
  - Vitamin K antagonists (e.g., warfarin) with a stable international normalized ratio (INR) for at least 4 weeks.
  - Low-molecular-weight heparin, and the direct oral anticoagulants rivaroxaban, apixaban and edoxaban, for at least 4 weeks.
  - Iron supplements, vitamin B12, or folic acid for at least 4 weeks.
  - Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) such as roxadustat for at least 8 weeks.
  - Androgens for at least 4 weeks.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of investigational drug and for 1 week after stopping of investigational drug.

16. Efficacy

16.1. APPLY-PNH: Exploratory Efficacy Endpoint Results

The efficacy results described below were reported by the Applicant. These results are exploratory and do not support any labeling claims.

Erythrocytes

At baseline, the mean (SD) erythrocyte count was comparable and below the lower limit of normal (normal reference range: 4.1 to 5.9×10^{12}/L for males; 3.8 to 5.9×10^{12}/L for females) for both the iptacopan group (2.50×10^{12}/L (0.34)) and the anti-C5 group (2.43×10^{12}/L (0.41)). In the iptacopan group, an increase in the mean (SD) erythrocyte count was seen between day 7 (3.03 (0.35)×10^{12}/L) and day 42 (3.75 (0.45)×10^{12}/L). From day 56 until day 168 (3.72 (0.50)×10^{12}/L), the mean (SD) erythrocyte count was stable. In the anti-C5 group, no trend was seen, and the mean erythrocyte count remained consistently low through day 168.

Erythrocyte Distribution Width

At baseline, the mean (SD) erythrocyte distribution width was comparable and above the upper limit of normal ([ULN]; normal reference range: 11.6 to 14.8%) for both the iptacopan group (19.36% (4.63)) and anti-C5 group (20.36% (5.55)). In the iptacopan group, a reduction in mean (SD) erythrocyte distribution width was observed at day 28 (15.94% (3.39)). Thereafter, mean erythrocyte distribution width was stable until day 168 (15.18% (1.82)). In the anti-C5 group, the mean erythrocyte distribution width remained consistently high through day 168.

Haptoglobin

Mean (SD) haptoglobin at baseline was comparable and below the lower limit of normal (normal reference range: 0.3 to 2 g/L) for both the iptacopan group (0.12 g/L (0.09)) and the anti-C5 group (0.11 g/L (0.05)). The lower limit of quantification for haptoglobin is <0.2 g/L (central laboratory). In the iptacopan group, an increase in haptoglobin was seen on day 28, with a mean (SD) haptoglobin of 0.34 g/L (0.28). From day 56 onwards, mean haptoglobin was below the lower limit of normal until day 168, at which point the mean (SD) haptoglobin was 0.15 g/L (0.240) and below the lower limit of quantification. In the anti-C5 group, mean haptoglobin remained consistently low through day 168.

Indirect Bilirubin

Mean (SD) indirect bilirubin at baseline was comparable and above the ULN (normal reference range: 2 to 17 µmol/L) for both the iptacopan group (23.4 µmol/L (28.28)) and the anti-C5 group (22.6 µmol/L (19.92)). The median (range) indirect bilirubin was comparable between the iptacopan group (15.0 µmol/L (3 to 152)) and the anti-C5 group (16.0 µmol/L (2 to 99)). In the iptacopan group, a reduction in the mean and median indirect bilirubin values was observed as early as day 7. Thereafter, mean and median indirect bilirubin were stable until day 168, at which point the mean (SD) indirect bilirubin was 7.6 µmol/L (7.65) and median (range) indirect bilirubin was 5.0 mmol/L (0 to 46). In the iptacopan group, the mean and median total bilirubin

values were within normal range from day 7 through the end of the randomized treatment period. In the anti-C5 group, mean (SD) indirect bilirubin between baseline (22.6 µmol/L (19.92)) and postbaseline until day 168 (18.8 µmol/L (13.58)) remained consistently high.

Number and Units of RBC Transfusions

Five subjects (8.1%) in the iptacopan group and 19 (54.3%) in the anti-C5 group received at least one transfusion. Among the subjects who received transfusions, the mean (SD) number of transfusions per subject was 1.4 (0.89) in the iptacopan group and 4.9 (3.97) in the anti-C5 group. Among the subjects who were transfused, the mean (SD) number of units of red blood cell (RBC) transfused per subject was 2.2 (1.64) in the iptacopan group and 8.2 (6.73) in the anti-C5 group. Among the subjects who were transfused, the median (range) number of units of RBC transfused per subject was 2.0 (1 to 5) units in the iptacopan group and 7.0 (1 to 28) units in the anti-C5 group.

PNH Signs and Symptoms

Overall, 39/62 (62.9%) subjects in the iptacopan group and 24/35 (68.6%) subjects in the anti-C5 group reported PNH signs and symptoms at baseline. At the end of the randomized treatment period, 15/62 (24.2%) subjects in the iptacopan group and 20/35 (57.1%) in the anti-C5 group reported at least one PNH-related sign and symptom.

Feeling weak or tired was the most frequently reported event. At baseline, 48.4% of subjects in the iptacopan group reported none, while 29%, 19.4%, and 3.2% reported mild, moderate, and severe events, respectively. In the anti-C5 group, 31.4% of subjects reported none, and 34.3%, 25.7%, and 5.7% reported mild, moderate, and severe weakness and fatigue at baseline, respectively. On day 168, 80.6% of subjects in the iptacopan group reported none, 14.5% reported mild, 4.8% reported moderate, and 0 reported severe weakness or fatigue, while 45.7% of subjects reported none, 31.4% reported mild, 17.1% reported moderate, and 5.7% reported severe weakness or fatigue in the anti-C5 group.

At baseline, hemoglobinuria was reported for 83.9% of subjects as none, 11.3% as mild, and 4.8% as moderate in the iptacopan group, whereas hemoglobinuria was reported in 85.7% of subjects as none, 8.6% as moderate, and 2.9% as severe in the anti-C5 group. On day 168, this changed to 100% reported as none in the iptacopan group versus 85.7% reported as none, 8.6% as mild, and 5.7% as moderate in the anti-C5 group.

At baseline, shortness of breath was reported for 71% of subjects as none, 14.5% as mild, 12.9% as moderate, and 1.6% as severe in the iptacopan group, whereas shortness of breath was reported as none for 62.9% of subjects, as mild for 20%, as moderate for 11.4%, and as severe for 2.9% in the anti-C5 group. On day 168, shortness of breath was reported for 93.5% of subjects as none, 4.8% as mild, and 1.6% as moderate in the iptacopan group whereas it was reported for 71.4% of subjects as none, 5.7% as mild, 17.1% as moderate, and 5.7% as severe in the anti-C5 group.

PNH Clone Size

Mean (SD) total PNH RBC clone size at baseline was slightly higher in the iptacopan group (64.65% (27.45)) than that in the anti-C5 group (57.39% (29.73)). In the iptacopan group, an increase in mean (SD) total PNH RBC clone size was observed from day 28 (83.48% (16.47)) to

day 112 (93.39% (9.82)), with the mean (SD) thereafter stable until day 168 (93.17% (10.72)). In the anti-C5 group, mean (SD) of total PNH RBC clone size was stable from baseline (57.39% (29.73)) until day 168 (59.68% (26.71)).

Clinical Reviewer Comment:

Overall, markers of hemolysis (except for haptoglobin) and transfusion burden improved with iptacopan therapy. The findings on PNH signs and symptoms are difficult to interpret in an open-label trial.

16.2. APPOINT-PNH: Secondary Efficacy Endpoint Results

The efficacy results described below were reported by the Applicant. These results were exploratory and do not support any labeling claims.

Hemoglobin Levels ≥12 g/dL in Absence of Red Blood Cell Transfusion

The proportion of subjects who achieved hemoglobin (Hb) levels of ≥12 g/dL in the absence of RBC transfusions was 19/33 (62.8%) between day 14 and day 168. The total number of subjects in the study was 40; however, only 33 subjects had nonmissing data.

Absence of Administration of Packed Red Blood Cell Transfusions

Between day 14 and day 168, 40/40 subjects (97.6%) avoided transfusion. Twenty-eight subjects (70.0%) received at least one transfusion in the 6 months prior to start of study treatment.

Change From Baseline in Hb

Mean (SD) Hb at baseline was 8.16 (1.09) g/dL and median (range) Hb at baseline was 8.05 g/dL (5.80 to 10.00). The adjusted mean change from baseline in Hb between day 126 and day 168 was +4.28 g/dL (95% CI: 3.87, 4.70). In subjects treated with iptacopan, the increases in Hb levels were seen early in the core treatment period, with an adjusted mean change from baseline (95% CI) in Hb of 0.74 g/dL (0.31, 1.17) on day 7. A further increase in Hb was observed on day 14, with an adjusted mean change from baseline (95% CI) in Hb of 1.51 g/dL (1.06, 1.96). At each visit from day 28 until day 168, the adjusted mean change from baseline in Hb level was >2 g/dL.

Percent Change From Baseline in LDH

Baseline mean (SD) LDH was 1698.8 (683.33) U/L and the median (range) LDH was 1581.5 U/L (522 to 3244 U/L). The ULN for LDH, for the Applicant, was 250 U/L. After treatment with iptacopan, there was an adjusted mean percent change from baseline in LDH levels between day 126 and day 168 of −83.55% (95% CI −84.90%, −82.08%). The adjusted mean percent change from baseline (95% CI) in LDH was −70.11% (−72.11, −67.97) on day 7 and greater than −83% (−84.55, −86.37) at any visit after day 7 in the core treatment period.

Occurrences of Breakthrough Hemolysis

In the treatment period, none of the subjects experienced clinical breakthrough hemolysis. One subject reported clinical breakthrough hemolysis in the extension period. The subject was hospitalized with coronavirus disease 2019 (COVID-19) at the time.

Change From Baseline in Reticulocyte Count

Baseline mean (SD) absolute reticulocyte count was 154.33 (63.66)×10^9/L, and the median (range) absolute reticulocyte count was 139.20 (59.4 to 324.8)×10^9/L. The ULN for absolute reticulocyte count is 123×10^9/L. The adjusted mean (95% CI) change from baseline in absolute reticulocyte count between day 126 and day 168 was −82.48×10^9/L (−89.33, −75.62). In subjects treated with iptacopan, decreases in absolute reticulocyte count were seen as early as day 7 in the core treatment period, with an adjusted mean (95% CI) change from baseline of −85.75×10^9/L (−93.16, −78.35). There was a further decrease in absolute reticulocyte count on day 14 with an adjusted mean change from baseline of −91.23×10^9/L (−96.94, −85.53). The maximum effect was on day 28, with an adjusted mean (95% CI) change from baseline of −93.04×10^9/L (−100.43, −85.65). At each visit from day 42 until day 168, the adjusted mean change from baseline in absolute reticulocyte count ranged between −78.99×10^9/L and < −87.46×10^9/L.

Change From Baseline in FACIT Fatigue Scores

Each of the 13 items of the FACIT-Fatigue scale ranges from 0 to 4; the range of possible scores is 0 to 52, with 0 being the worst possible score and 52 the best. The mean (SD) FACIT-Fatigue score at baseline was 32.78 (10.17) points. The adjusted mean (95% CI) FACIT-Fatigue score change from baseline between day 126 and day 168 was +10.75 (8.66, 12.84) points. On day 168, the mean (SD) FACIT-Fatigue score reached 43.9 (6.24) points. There was an increase in the adjusted mean change from baseline in FACIT-Fatigue scores from day 7 (+3.26 points) until day 84 (+10.30 points). At each visit from day 126 until day 168, the adjusted mean change from baseline in FACIT-Fatigue score was ≥9.91 points.

Occurrences of Major Adverse Vascular Events

In the core treatment period and extension treatment period until the cutoff date, none of the subjects experienced major adverse vascular events.

17. Clinical Safety

17.1. APPLY-PNH: Adverse Events by System Organ Class

Table 185. Subjects With Adverse Events by System Organ Class, Safety Population, Trial APPOINT-PNH Randomized Treatment Period

System Organ Class	Iptacopan N=62 n (%)	Anti-C5 N=35 n (%)	Iptacopan Versus Anti-C5 Risk Difference (%) (95% CI)
Nervous system disorders	16 (25.8)	1 (2.9)	22.9 (10.7, 35.2)*
Gastrointestinal disorders	20 (32.3)	7 (20.0)	12.3 (-5.4, 29.9)
Renal and urinary disorders	7 (11.3)	1 (2.9)	8.4 (-1.2, 18.1)
Psychiatric disorders	5 (8.1)	0	8.1 (1.3, 14.8)*
Investigations	13 (21.0)	5 (14.3)	6.7 (-8.7, 22.1)
Eye disorders	4 (6.5)	0	6.5 (0.3, 12.6)*
Reproductive system and breast disorders	4 (6.5)	0	6.5 (0.3, 12.6)*
Respiratory, thoracic and mediastinal disorders	7 (11.3)	2 (5.7)	5.6 (-5.4, 16.6)
Vascular disorders	5 (8.1)	1 (2.9)	5.2 (-3.5, 13.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (4.8)	0	4.8 (-0.5, 10.2)
Injury, poisoning and procedural complications	6 (9.7)	2 (5.7)	4.0 (-6.7, 14.6)
Cardiac disorders	4 (6.5)	1 (2.9)	3.6 (-4.6, 11.8)
Musculoskeletal and connective tissue disorders	11 (17.7)	5 (14.3)	3.5 (-11.5, 18.5)
Ear and labyrinth disorders	2 (3.2)	0	3.2 (-1.2, 7.6)
General disorders and administration site conditions	9 (14.5)	4 (11.4)	3.1 (-10.6, 16.8)
Skin and subcutaneous tissue disorders	3 (4.8)	1 (2.9)	2.0 (-5.7, 9.7)
Endocrine disorders	1 (1.6)	0	1.6 (-1.5, 4.7)
Metabolism and nutrition disorders	4 (6.5)	2 (5.7)	0.7 (-9.1, 10.6)
Hepatobiliary disorders	3 (4.8)	2 (5.7)	-0.9 (-10.2, 8.5)
Immune system disorders	1 (1.6)	2 (5.7)	-4.1 (-12.4, 4.2)
Infections and infestations	24 (38.7)	17 (48.6)	-9.9 (-30.4, 10.7)
Blood and lymphatic system disorders	8 (12.9)	8 (22.9)	-10.0 (-26.2, 6.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier. The on-treatment period for Anti-C5 is from the fist dose date until one day before the next planned dose or the analysis cut-off date, whichever is earlier.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria

17.2. APPOINT-PNH: Adverse Events by System Organ Class

Table 186. Subjects With Adverse Events by System Organ Class, Safety Population, Trial APPOINT-PNH

System Organ Class	Iptacopan Core Period N=40 n (%)	Iptacopan Core + Ext. Period N=40 n (%)
Infections and infestations	16 (40.0)	19 (47.5)
Gastrointestinal disorders	11 (27.5)	15 (37.5)
Investigations	12 (30.0)	14 (35.0)
Nervous system disorders	13 (32.5)	14 (35.0)
General disorders and administration site conditions	7 (17.5)	10 (25.0)
Metabolism and nutrition disorders	7 (17.5)	9 (22.5)
Skin and subcutaneous tissue disorders	7 (17.5)	9 (22.5)
Respiratory, thoracic and mediastinal disorders	6 (15.0)	8 (20.0)
Renal and urinary disorders	5 (12.5)	7 (17.5)
Injury, poisoning and procedural complications	3 (7.5)	6 (15.0)
Eye disorders	3 (7.5)	4 (10.0)
Musculoskeletal and connective tissue disorders	4 (10.0)	4 (10.0)
Blood and lymphatic system disorders	1 (2.5)	2 (5.0)
Cardiac disorders	2 (5.0)	2 (5.0)
Psychiatric disorders	2 (5.0)	2 (5.0)
Reproductive system and breast disorders	1 (2.5)	2 (5.0)
Hepatobiliary disorders	1 (2.5)	1 (2.5)
Vascular disorders	0	1 (2.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as events that started during the on-treatment period. The on-treatment period for iptacopan is from the first dose date until 7 days after the date of the last dose administered or the analysis cut-off date, whichever is earlier.
Duration of the Core period is 24 weeks. Duration of the Ext. period is 24 weeks. Duration of the Core + Ext. period is 48 weeks.
Abbreviations: Ext., extension; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria

17.3. PNH Pool Safety Results

The PNH pool included 170 subjects with PNH treated with iptacopan (154 received iptacopan as monotherapy and 15 received iptacopan as add-on therapy) from studies C12302 (APPLY-PNH), C12301 (APPOINT-PNH), C12001B (PNH REP), X2201, X2204, and treatment period 4 of LFG316X2201 study. Note, regarding the PNH pool, the add-on study group only contained events from while the patients were on add-on therapy. These subjects could have also received monotherapy at some point which would be represented in the pooled study arm, because that included both add-on and monotherapy. Therefore, the pooled study group can have more events than the monotherapy and add-on therapy study arms.

Overview of Adverse Events

The majority of subjects had mild or moderate treatment-emergent adverse events.

Table 187. Overview of Adverse Events, Safety Population, ISS Pooled PNH Trials

Event Category	Pooled Monotherapy Studies LNP023 N=154 n (%)	Pooled Add-on Study LNP023 N=15 n (%)	All Pooled Studies* LNP023 N=170 n (%)
SAE	22 (14.3)	3 (20.0)	29 (17.1)
SAEs with fatal outcome	0	1 (6.7)	2 (1.2)
Life-threatening SAEs	2 (1.3)	1 (6.7)	4 (2.4)
AE leading to permanent discontinuation of study drug	0	1 (6.7)	1 (0.6)
AE leading to dose modification of study drug	1 (0.6)	0	2 (1.2)
AE leading to interruption of study drug	1 (0.6)	0	2 (1.2)
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
Other	2 (1.3)	1 (6.7)	4 (2.4)
Any AE	128 (83.1)	13 (86.7)	144 (84.7)
Severe and worse	11 (7.1)	3 (20.0)	19 (11.2)
Moderate	50 (32.5)	4 (26.7)	56 (32.9)
Mild	67 (43.5)	6 (40.0)	69 (40.6)

Source: adae.xpt; Software R
* The add-on study group only contained events from while the patients were on add-on therapy. These subjects could have also received monotherapy at some point which would be represented in the pooled study arm, because that included both add-on and monotherapy. Therefore, the pooled study group can have more events than the monotherapy and add-on therapy study arms.Treatment-emergent adverse events defined as events that started during the on-treatment period, which is defined as the first dose of LNP023 200 mg BID up to the earlier date between data cutoff date and the last dose + 7 days.
Duration is 48 weeks for C12302 (APPLY-PNH) and C12301 (APPOINT-PNH). Duration is 13 weeks plus up to 3 years for CLNP023X2201. Duration is 12 weeks plus up to 2 years for CLNP023X2204. Duration is up to 21 weeks for CLFG316X2201. Duration is up to 36 months for CLNP023C12001B PNH REP.
Pooled Monotherapy Studies includes all treatment-emergent adverse events from C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, and CLNP023C12001B PNH REP.
Pooled Add-on Study includes only treatment-emergent adverse events with a start date while the subject received add-on therapy in CLNP023X2201.
All Pooled Studies includes all treatment-emergent adverse events from C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, CLNP023C12001B PNH REP, and CLNP023X2201.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; BID, twice daily; ISS, integrated summary of safety; LNP023, iptacopan; N, number of subjects in treatment arm; n, number of subjects with at least one event; PNH, paroxysmal nocturnal hemoglobinuria; REP, roll-over extension program; SAE, serious adverse event

Serious Adverse Events

In the PNH pool, 29 (17.1%) subjects experienced a serious adverse event. The most common serious adverse events were due to infections.

Table 188. Subjects With Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Occurring in at Least 2% of Subjects in Any Arm, Safety Population, ISS Pooled PNH Trials

System Organ Class FMQ (Narrow) Preferred Term	Pooled Monotherapy Studies LNP023 N=154 n (%)	Pooled Add-on Study LNP023 N=15 n (%)	All Pooled Studies LNP023 N=170 n (%)
Infections and infestations (SOC)	9 (5.8)	0 (0)	11 (6.5)
Bacterial Infection (FMQ)	3 (1.9)	0 (0)	5 (2.9)*
Viral Infection (FMQ)	4 (2.6)	0 (0)	4 (2.4)
COVID-19	4 (2.6)	0 (0)	4 (2.4)

System Organ Class FMQ (Narrow) Preferred Term	Pooled Monotherapy Studies LNP023 N=154 n (%)	Pooled Add-on Study LNP023 N=15 n (%)	All Pooled Studies LNP023 N=170 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy (FMQ)	2 (1.3)	1 (6.7)	5 (2.9)
Squamous cell carcinoma of the tongue	0	1 (6.7)	1 (0.6)
Vascular disorders (SOC)			
Hemorrhage (FMQ)	0	1 (6.7)	1 (0.6)
Hemorrhage intracranial	0	1 (6.7)	1 (0.6)

Source: adae.xpt; Software R
* This table has a 2% cutoff applied. The rows with PTs will only show up if at least one study arm meets the 2% cutoff.
Treatment-emergent adverse events defined as events that started during the on-treatment period, which is defined as the first dose of LNP023 200 mg BID. up to the earlier date between data cutoff date and the last dose + 7 days.
Pooled Monotherapy Studies includes all treatment-emergent adverse events from C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, and CLNP023C12001B PNH REP.
Pooled Add-on Study includes only treatment-emergent adverse events with a start date while the subject received add-on therapy in CLNP023X2201.
All Pooled Studies includes all treatment-emergent adverse events from C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, CLNP023C12001B PNH REP, and CLNP023X2201.
Serious adverse events defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 48 weeks for C12302 (APPLY-PNH) and C12301 (APPOINT-PNH). Duration is 13 weeks plus up to 3 years for CLNP023X2201. Duration is 12 weeks plus up to 2 years for CLNP023X2204. Duration is up to 21 weeks for CLFG316X2201. Duration is up to 36 months for CLNP023C12001B PNH REP.
Bronchitis bacterial replaces: Bronchitis bacterial
Klebsiella infection replaces: Bronchitis bacterial
Abbreviations: BID, twice daily; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; FMQ, FDA medical query; ISS, integrated summary of safety; LNP023, iptacopan; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; PT, preferred term; REP, roll-over extension program; SOC, system organ class

Common Treatment-Emergent Adverse Events

Table 189. Subjects With Adverse Events by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Occurring in at Least 2% of Subjects in Any Arm, Safety Population, ISS Pooled PNH Trials

System Organ Class FMQ (Narrow) Preferred Term	Pooled Monotherapy Studies LNP023 N=154 n (%)	Pooled Add-on Study LNP023 N=15 n (%)	All Pooled Studies LNP023 N=170 n (%)
Blood and lymphatic system disorders (SOC)			
Thrombocytopenia (FMQ)	10 (6.5)	1 (6.7)	13 (7.6)*
Thrombocytopenia	6 (3.9)	1 (6.7)	9 (5.3)
Platelet count decreased	4 (2.6)	0	4 (2.4)
Anemia (FMQ)	2 (1.3)	0	5 (2.9)
Anaemia	1 (0.6)	0	4 (2.4)
Cardiac disorders (SOC)			
Systemic Hypertension (FMQ)	8 (5.2)	0	9 (5.3)
Hypertension	7 (4.5)	0	8 (4.7)
Arrhythmia (FMQ)	5 (3.2)	0	5 (2.9)
Palpitations (FMQ)	3 (1.9)	1 (6.7)	4 (2.4)
Palpitations	3 (1.9)	1 (6.7)	4 (2.4)

System Organ Class FMQ (Narrow) Preferred Term	Pooled Monotherapy Studies LNP023 N=154 n (%)	Pooled Add-on Study LNP023 N=15 n (%)	All Pooled Studies LNP023 N=170 n (%)
Ear and labyrinth disorders (SOC)			
Vertigo (FMQ)	2 (1.3)	1 (6.7)	3 (1.8)
Vertigo	2 (1.3)	1 (6.7)	3 (1.8)
Endocrine disorders (SOC)			
Hyperglycemia (FMQ)	4 (2.6)	0	4 (2.4)
Gastrointestinal disorders (SOC)			
Diarrhea (FMQ)	16 (10.4)	0	19 (11.2)
Diarrhea	16 (10.4)	0	19 (11.2)
Abdominal Pain (FMQ)	16 (10.4)	1 (6.7)	18 (10.6)
Abdominal pain	8 (5.2)	1 (6.7)	10 (5.9)
Abdominal pain upper	4 (2.6)	1 (6.7)	5 (2.9)
Nausea (FMQ)	11 (7.1)	0	12 (7.1)
Nausea	11 (7.1)	0	12 (7.1)
Vomiting (FMQ)	10 (6.5)	0	11 (6.5)
Vomiting	9 (5.8)	0	10 (5.9)
Dyspepsia (FMQ)	5 (3.2)	1 (6.7)	6 (3.5)
Abdominal pain upper	4 (2.6)	1 (6.7)	5 (2.9)
General disorders and administration site conditions (SOC)			
Pyrexia (FMQ)	8 (5.2)	2 (13.3)	12 (7.1)
Pyrexia	7 (4.5)	2 (13.3)	11 (6.5)
Dizziness (FMQ)	8 (5.2)	1 (6.7)	10 (5.9)
Dizziness	5 (3.2)	0	6 (3.5)
Vertigo	2 (1.3)	1 (6.7)	3 (1.8)
Fatigue (FMQ)	7 (4.5)	2 (13.3)	9 (5.3)
Asthenia	4 (2.6)	2 (13.3)	6 (3.5)
Peripheral Edema (FMQ)	4 (2.6)	0	5 (2.9)
Oedema peripheral	3 (1.9)	0	4 (2.4)
Local Administration Reaction (FMQ)	2 (1.3)	1 (6.7)	3 (1.8)
Medical device site pain	0	1 (6.7)	1 (0.6)
Hepatobiliary disorders (SOC)			
Hepatic Injury (FMQ)	6 (3.9)	0	6 (3.5)
Alanine aminotransferase increased	4 (2.6)	0	4 (2.4)
Infections and infestations (SOC)			
Viral Infection (FMQ)	40 (26.0)	3 (20.0)	45 (26.5)
COVID-19	38 (24.7)	0	40 (23.5)
Influenza	1 (0.6)	2 (13.3)	3 (1.8)
Herpes zoster	1 (0.6)	1 (6.7)	2 (1.2)
Oral herpes	0	1 (6.7)	1 (0.6)
Nasopharyngitis (FMQ)	23 (14.9)	3 (20.0)	28 (16.5)
Nasopharyngitis	13 (8.4)	1 (6.7)	15 (8.8)
Upper respiratory tract infection	8 (5.2)	0	8 (4.7)
Rhinitis	1 (0.6)	2 (13.3)	3 (1.8)
Bacterial Infection (FMQ)	21 (13.6)	1 (6.7)	26 (15.3)
Urinary tract infection	6 (3.9)	0	7 (4.1)
Periodontitis	0	1 (6.7)	1 (0.6)
Pneumonia (FMQ)	6 (3.9)	0	7 (4.1)
Pneumonia	4 (2.6)	0	4 (2.4)
Fungal Infection (FMQ)	3 (1.9)	1 (6.7)	4 (2.4)
Fungal foot infection	0	1 (6.7)	1 (0.6)

System Organ Class FMQ (Narrow) Preferred Term	Pooled Monotherapy Studies LNP023 N=154 n (%)	Pooled Add-on Study LNP023 N=15 n (%)	All Pooled Studies LNP023 N=170 n (%)
Metabolism and nutrition disorders (SOC)			
Lipid Disorder (FMQ)	9 (5.8)	1 (6.7)	11 (6.5)
Hypertriglyceridaemia	1 (0.6)	1 (6.7)	3 (1.8)
Musculoskeletal and connective tissue disorders (SOC)			
Arthralgia (FMQ)	9 (5.8)	0	10 (5.9)
Arthralgia	9 (5.8)	0	10 (5.9)
Back Pain (FMQ)	4 (2.6)	1 (6.7)	6 (3.5)
Back pain	4 (2.6)	1 (6.7)	6 (3.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy (FMQ)	2 (1.3)	1 (6.7)	5 (2.9)
Squamous cell carcinoma of the tongue	0	1 (6.7)	1 (0.6)
Nervous system disorders (SOC)			
Headache (FMQ)	27 (17.5)	2 (13.3)	30 (17.6)
Headache	26 (16.9)	2 (13.3)	29 (17.1)
Migraine	1 (0.6)	1 (6.7)	2 (1.2)
Psychiatric disorders (SOC)			
Insomnia (FMQ)	6 (3.9)	3 (20.0)	9 (5.3)
Insomnia	6 (3.9)	2 (13.3)	8 (4.7)
Poor quality sleep	0	1 (6.7)	1 (0.6)
Parasomnia (FMQ)	0	1 (6.7)	1 (0.6)
Nightmare	0	1 (6.7)	1 (0.6)
Renal and urinary disorders (SOC)			
Renal & Urinary Tract Infection (FMQ)	7 (4.5)	0	9 (5.3)
Urinary tract infection	6 (3.9)	0	7 (4.1)
Reproductive system and breast disorders (SOC)			
Abnormal Uterine Bleeding (FMQ)	4 (2.6)	0	4 (2.4)
Sexual Dysfunction (FMQ)	1 (0.6)	1 (6.7)	2 (1.2)
Vulvovaginal dryness	1 (0.6)	1 (6.7)	2 (1.2)
Respiratory, thoracic and mediastinal disorders (SOC)			
Cough (FMQ)	5 (3.2)	0	7 (4.1)
Cough	4 (2.6)	0	6 (3.5)
Dyspnea (FMQ)	2 (1.3)	1 (6.7)	3 (1.8)
Dyspnoea exertional	1 (0.6)	1 (6.7)	2 (1.2)
Skin and subcutaneous tissue disorders (SOC)			
Rash (FMQ)	9 (5.8)	1 (6.7)	10 (5.9)
Dermatitis acneiform	1 (0.6)	1 (6.7)	2 (1.2)
Erythema (FMQ)	3 (1.9)	1 (6.7)	4 (2.4)
Flushing	0	1 (6.7)	1 (0.6)
Pruritus (FMQ)	2 (1.3)	2 (13.3)	4 (2.4)
Pruritus	2 (1.3)	2 (13.3)	4 (2.4)
Alopecia (FMQ)	1 (0.6)	1 (6.7)	2 (1.2)
Alopecia	1 (0.6)	1 (6.7)	2 (1.2)

System Organ Class FMQ (Narrow) Preferred Term	Pooled Monotherapy Studies LNP023 N=154 n (%)	Pooled Add-on Study LNP023 N=15 n (%)	All Pooled Studies LNP023 N=170 n (%)
Vascular disorders (SOC)			
Hemorrhage (FMQ)	10 (6.5)	2 (13.3)	15 (8.8)
Contusion	3 (1.9)	0	4 (2.4)
Haematuria	2 (1.3)	0	4 (2.4)
Petechiae	2 (1.3)	1 (6.7)	3 (1.8)
Ecchymosis	0	1 (6.7)	1 (0.6)
Haemorrhage intracranial	0	1 (6.7)	1 (0.6)

Source: adae.xpt; Software R
* This table has a 2% cutoff applied. The rows with PTs will only show up if at least one study arm meets the 2% cutoff. Treatment-emergent adverse events defined as events that started during the on-treatment period, which is defined as the first dose of LNP023 200 mg BID up to the earlier date between data cutoff date and the last dose + 7 days.
Pooled Monotherapy Studies includes all treatment-emergent adverse events from C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, and CLNP023C12001B PNH REP.
Pooled Add-on Study includes only treatment-emergent adverse events with a start date while the subject received add-on therapy in CLNP023X2201.
All Pooled Studies includes all treatment-emergent adverse events from C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, CLNP023C12001B PNH REP, and CLNP023X2201.
Duration is 48 weeks for C12302 (APPLY-PNH) and C12301 (APPOINT-PNH). Duration is 13 weeks plus up to 3 years for CLNP023X2201. Duration is 12 weeks plus up to 2 years for CLNP023X2204. Duration is up to 21 weeks for CLFG316X2201. Duration is up to 36 months for CLNP023C12001B PNH REP.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: BID
, twice daily; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; FMQ, FDA medical query; ISS, integrated summary of safety; LNP023, iptacopan; N, number of subjects in treatment arm; n, number of subjects with adverse event; PNH, paroxysmal nocturnal hemoglobinuria; PT, preferred term; REP, roll-over extension program; SOC, system organ class

Drug Induced Liver Injury Assessment

The majority of liver laboratory abnormalities were related to hemolysis. Both cases of potential Hy's law were related to events of breakthrough hemolysis and not related to iptacopan. Two subjects (b) (6) and (b) (6) had concurrent adverse events of breakthrough hemolysis and LDH levels >1.5 times the ULN. For both subjects, aspartate transferase met the criteria of ≥3 times the ULN, but alanine transferase did not.

Table 190. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, ISS Pooled PNH Trials

Quadrant	All Pooled Studies LNP023 N=170 n/N_w (%)
Potential Hy's law (right upper)	2/169 (1.2)
Cholestasis (left upper)	10/169 (5.9)
Temple's corollary (right lower)	10/169 (5.9)
Total	22/169 (13)

Source: ad b.xpt; Software R
One subject (b) (6) only had baseline liver laboratory data and therefore is not included in this analysis.
All Pooled Studies includes C12302 (APPLY-PNH), C12301 (APPOINT-PNH), CLNP023X2204, CLFG316X2201, CLNP023C12001B PNH REP, and CLNP023X2201.
This analysis includes local and central laboratory data regardless of on-treatment status. The Applicant applied the on-treatment flag in their laboratory analysis.
Abbreviations: DILI, drug-induced liver injury; ISS, integrated summary of safety; LNP023, iptacopan; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PNH, paroxysmal nocturnal hemoglobinuria; REP, roll-over extension program

17.4. Deaths

In the entire development program, there were four deaths in the clinical trials. One subject (Subject (b) (6)) who died was diagnosed with lymphoproliferative disorder, which was related to iptacopan according to the Applicant. When queried regarding the relatedness of iptacopan to lymphoproliferative disorder, the Applicant replied that the relationship could not be excluded because iptacopan is a complement inhibitor and may have had a role due to its ability to inhibit the immune system. Therefore, a conservative stance was taken. Lymphoproliferative disorder can occur in the setting of a dysregulated immune system. The subject died 11 months after discontinuing iptacopan due to sepsis. The exact cause of the lymphoproliferative disorder is difficult to determine.

Table 191. Deaths on Iptacopan in Pooled PNH and Pooled Renal Studies, Safety Population

Patient details Study day of death	Cause of death (bold PT) Contributing event(s)	Comments
PNH patient (b) (6) 45 years old, female Day 699	**Septic shock,** **Lymphoproliferative disorder**	The patient had received eculizumab, prior to and during the study as standard of care at a dose of 1500 mg from Day -227 to Day 168 and 1200 mg from Day 196 to the last dose on Day 696. Lymphocytes at baseline were 0.22 $\times 10^9$/L (lymphopenia). The patient developed widespread lymphadenopathies and multiple extra-lymphatic nodules approximately 11 months after starting iptacopan 200 mg b.i.d. Subsequently, the patient was diagnosed with B-cell lymphoproliferative disorder, and iptacopan was discontinued (Day 356). The lymphoproliferative disorder was suspected to be related to iptacopan. Eleven months after discontinuation of iptacopan (Day 698), following a cycle of salvage chemotherapy, the patient developed febrile neutropenia, cholangitis and septic shock with fatal outcome.
PNH patient (b) (6) 78 years old, male Day 867	**General physical health deterioration,** Penetrating aortic ulcer, Escherichia bacteremia	The patient was diagnosed with basal cell carcinoma on Day 628 and recovered on Day 637. The patient had penetrating aortic ulcer on Day 765 and received interventions (surgery) – this event was reported as resolved with sequelae on Day 771. The patient received the last dose of iptacopan on Day 779. The patient had *Escherichia coli* bacteremia on Day 791 and recovered on Day 803 but had general physical health deterioration starting on Day 812 and recurrent *E. coli* bacteremia on Day 826. The patient was referred to palliative care on Day 841 and died on Day 867. The event was not suspected to be related to iptacopan.
PNH patient (b) (6) 52 years old, male Day 504	**Squamous cell carcinoma of the oral cavity,** **Squamous cell carcinoma of the tongue**	The patient had received eculizumab, prior to and during the study as standard of care at a dose of 900 mg until Day 325. The patient developed ulceration of a pre-existing tongue lesion on Day 44 which was histologically confirmed as squamous cell carcinoma (severe, grade 3) of the tongue on Day 100. The patient underwent surgeries on Day 112 and Day 353. The patient went into remission following hemiglossectomy. On Day 402, the patient was readmitted to the hospital due to severe odynophagia. A CT scan on Day 427 showed a new oral/neck lesion of 47x40 mm. Histology assessment on Day 441 confirmed the relapse of the known squamous cell carcinoma (described as human papillomavirus positive). The patient stopped iptacopan treatment on Day 452 and died on Day 504. The event was not suspected to be related to iptacopan.
Renal (C3G) patient (b) (6) 24 years old, female Day 501	**Cardiac arrhythmia**	The C3G patient had pre-existing conditions of anxiety, palpitations, hyperparathyroidism; concomitant medications of methylphenidate (ADRs of tachycardia and arrhythmia), venlafaxine (ADRs of tachycardia and arrhythmia), trazodone (warning for QT prolongation) and medical history of tobacco that are possible confounders for the event. The patient was found dead in her bathroom. The event was not suspected to be related to iptacopan. Autopsy results concluded cause of death was cardiac arrhythmia based on arterio-nephrosclerosis, clinical history of C3G and hypertension, focal myocardial scar, clinical history of hypocalcemia and history of having been found unresponsive in bathroom.

Source: Clinical Summary of Safety
Abbreviations: ADR, adverse drug reaction; b.i.d, twice daily; CT, computed tomography; C3G, C3 glomerulopathy; PNH, paroxysmal nocturnal hemoglobinuria; PT, preferred term; QT, QT interval

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Refer to Section 5 of the review for a description of the mechanism of action of iptacopan. There are no concerns for drug resistance with this class of medications for the proposed indication.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

A clinical inspection summary was completed by the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (OSI) with a final signature date of October 27, 2023. The Applicant and two foreign clinical investigators, Alexander Roeth, M.D., and Regis P. de Latour, M.D., were inspected for study CLNP023C12302.

OSI concluded that based on the inspection results, the study appears to have been conducted adequately and the study data derived from the above clinical investigator sites and Applicant are considered reliable. The data from study CLNP023C12302, submitted by the Applicant to the Agency for assessment, appear acceptable in support of the proposed indication.

23. Labeling: Key Changes and Considerations

This prescribing information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (Table 192). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

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(b) (4)

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- United States prescribing information
- Medication guide

24. Postmarketing Requirements and Commitments

Postmarketing Requirements

3. Participate in a registry to characterize the long-term safety of iptacopan in adults with paroxysmal nocturnal hemoglobinuria, with up to 5 years of follow-up. Submit yearly safety follow-up data and a summary of the major safety findings for all patients and all serious infections with encapsulated bacteria. The final study report should include an integrated safety dataset and patient-level data, including data on iptacopan dosing, meningococcal, pneumococcal, and *H. influenza* vaccination status, and concomitant medications.

   Draft Protocol: 04/2024
   Final Protocol: 08/2024

   Interim Report #1: 12/2025

   Interim Report #2: 12/2026

   Interim Report #3: 12/2027

   Interim Report #4: 12/2028

   Final Report Submission: 7/2030

4. Complete study APPLY-PNH (CLNP023C12302): “A randomized, multicenter, active-comparator controlled, open-label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult patients with PNH and residual anemia, despite treatment with an

intravenous anti-C5 antibody". Include an updated summary of safety and efficacy analyses and datasets at the time of final clinical study report submission.

Final Report Submission: 7/2024

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

   Final Report Submission: 7/2024

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

   Final Report Submission: 5/2029

25. Financial Disclosure

Table 193. Covered Clinical Studies: APPLY- PNH

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 217		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

Table 194. Covered Clinical Studies: APPOINT- PNH

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 73		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Literature

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27. Review Team

Table 195. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Courtney Hamilton, PharmD
Nonclinical reviewer	Bo Lee, PhD
Nonclinical team leader	Pedro DelValle, PhD
OCP reviewer(s)	Mohamad Kronfol, PhD; Yuan Ye, PhD; Karryn Crisamore, PhD
OCP team leader(s)	Sudharshan Hariharan, PhD; Jiang Liu PhD; Jeff Kraft, PhD
Clinical reviewer	Donna Whyte-Stewart, MD
Clinical team leader	Carrie Diamond, MD
Biometrics reviewer	Huan Wang, PhD
Biometrics team leader	Lola Luo, Phd
Cross-disciplinary team leader	Carrie Diamond, MD
Deputy Division director (pharm/tox)	Calvin (Lee) Elmore, PhD
Division director (OCP)	Doanh Tran, PhD
Division director (OB)	Yuan Li Shen, PhD
Division director (clinical)	Ann Farrell, MD
Office director (or designated signatory authority)	Hylton V. Joffe, MD, MMSc

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 196. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Theodore Carver, PhD
Microbiology	
OPDP	
OSI	Anthony Orencia
OSE/DEPI	Steve Bird
OSE/DMEPA	Selena Daniels, PharmD
OSE/DRISK	Lindsey Crist, PharmD, Jacqueline Sheppard, Anahita Tavakoli
Other	Barbara Bergquist

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

27.1. Reviewer Signatures

Table 27-197 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Courtney Hamilton ORO DROCHEN	Sections: 5 and 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Courtney Hamilton

Digitally signed by Courtney Hamilto

Date: 12/5/2023 2:01 PM EST
GUID: 20231251913

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Sudharshan Hariharan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Sudharshan Hariharan

Digitally signed by Sudharshan Harih

Date: 12/5/2023 2:01 PM EST
GUID: 202312519144

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Yeh Fong Chen OB DBIX	Sections: 6, 15, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Yeh Fong Chen**

Digitally signed by Yeh Fong Chen

Date: 12/5/2023 2:03 PM EST
GUID: 202312519311

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Donna Whyte-Stewart OCHEN DNH	Sections: 2, 3, 6, 7, 10, 11, 15, 16, 17, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Donna Whyte-Stewart**

Digitally signed by Donna Whyte-Ste

Date: 12/5/2023 2:03 PM EST
GUID: 202312519318

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Lola Luo OB DBIX	Sections: 6, 15, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Lola Luo

Digitally signed by Lola Luo

Date: 12/5/2023 2:03 PM EST
GUID: 202312519325

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Calvin Elmore OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Calvin Elmore

Digitally signed by Calvin Elmore

Date: 12/5/2023 2:03 PM EST
GUID: 202312519359

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Carrie Diamond OCHEN DNH	Sections: 1-4, 6-7, 15-17, 21-25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Carrie Diamond

Digitally signed by Carrie Diamond

Date: 12/5/2023 2:04 PM EST
GUID: 202312519427

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Bo Yeon Lee OCHEN DPTCHEN	Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Bo Yeon Lee

Digitally signed by Bo Yeon Lee

Date: 12/5/2023 2:05 PM EST
GUID: 202312519519

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Huan Wang OB DBIX	Sections: 6, 15, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Huan Wang

Digitally signed by Huan Wang

Date: 12/5/2023 2:05 PM EST
GUID: 202312519544

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Donna Whyte-Stewart OCHEN DNH	Sections: 2, 3, 6, 7, 14-17, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Donna Whyte-Stewart

Digitally signed by Donna Whyte-Ste

Date: 12/5/2023 2:06 PM EST
GUID: 202312519620

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Secondary Reviewer	Selena Daniels ODES DCOA	Sections: 4, 6.2.1.3, and 6.2.1.4.	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Selena Daniels

Digitally signed by Selena Daniels

Date: 12/5/2023 2:06 PM EST
GUID: 202312519642

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Mohamad Kronfol OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Mohamad Kronfol

Digitally signed by Mohamad Kronfo

Date: 12/5/2023 2:14 PM EST
GUID: 2023125191451

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Pedro Delvalle OCHEN DPTCHEN	Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Pedro Delvalle

Digitally signed by Pedro Delvalle

Date: 12/5/2023 2:18 PM EST
GUID: 2023125191838

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Sejal Kiani ORO DROCHEN	Sections: Section 12 Summary of Regulatory History	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Sejal Kiani

Digitally signed by Sejal Kiani

Date: 12/5/2023 2:20 PM EST
GUID: 2023125192019

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Virginia Kwitkowski**

Digitally signed by Virginia Kwitkows

Date: 12/5/2023 2:23 PM EST
GUID: 2023125192337

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Virginia Kwitkowski**

Digitally signed by Virginia Kwitkows

Date: 12/5/2023 2:24 PM EST
GUID: 202312519245

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Theodore Carver ONDP DNDPIII	Sections: 8	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Theodore Carver

Digitally signed by Theodore Carver

Date: 12/5/2023 2:28 PM EST
GUID: 202312519282

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Theodore Carver ONDP DNDPIII	Sections: 8	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Theodore Carver

Digitally signed by Theodore Carver

Date: 12/5/2023 2:28 PM EST
GUID: 2023125192854

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Tertiary Reviewer	David Reasner ODES DCOA	Sections: Sections 4, 6.2.1.3, and 6.2.1.4.	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: David Reasner

Digitally signed by David Reasner

Date: 12/5/2023 2:58 PM EST
GUID: 2023125195855

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Karryn Crisamore OCP DTPM	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Karryn Crisamore

Digitally signed by Karryn Crisamore

Date: 12/5/2023 3:21 PM EST
GUID: 2023125202121

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Manuela Grimstein OCP DPM	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Manuela Grimstein**

Digitally signed by Manuela Grimstei

Date: 12/5/2023 3:39 PM EST
GUID: 2023125203937

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Jayabharathi Vaidyanathan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Jayabharathi Vaidyanathan**

Digitally signed by Jayabharathi Vaid

Date: 12/5/2023 3:44 PM EST
GUID: 2023125204422

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE E DIAMOND
12/05/2023 02:04:55 PM

ANN T FARRELL
12/05/2023 02:10:54 PM

HYLTON V JOFFE
12/05/2023 04:13:55 PM