21 March 2024
EMA/170439/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fabhalta

International non-proprietary name: iptacopan

Procedure No. EMEA/H/C/005764/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AA	Aplastic anaemia
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ARC	Absolute reticulocyte count
ARR	Annualised rate ratio
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUCtau	AUC from time zero to the end of the dosing interval tau
Bas	Baseline
Bb	Fragment Bb of Factor B
BCC	Basal cell carcinoma
b.i.d.	Bis in die/twice a day
BMD	Bone marrow disorder
BMF	Bone marrow failure
BTH	Breakthrough haemolysis
C3	Complement component 3
C3G	C3 glomerulopathy
C5	Complement component 5
CD55	Complement decay-accelerating factor
CD59	MAC-inhibitory protein
CI	Confidence interval
C_{max}	Observed maximum plasma (or serum or blood) concentration following drug administration
COVID-19	Coronavirus disease 2019
CSF	Clinical Service Form
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Plasma (or serum or blood) concentration at the beginning or end of a dosing interval
DSC	differential scanning calorimetry
EBMT	European Group for Bone Marrow Transplantation
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
EVH	Extravascular haemolysis
FAS	Full analysis set
FDA	Food and Drug Administration
FMI	Final Market Image
GPI	Glycosylphosphatidylinositol
Hb	Haemoglobin
HLT	MedDRA high level term
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem-cell transplantation
IgAN	IgA nephropathy
IgG	Immunoglobulin G
ITP	Immune thrombocytopenia
IVH	Intravascular haemolysis
LDH	Lactate dehydrogenase
LPLV	Last patient last visit
MAC	Membrane attack complex
MAVE	Major adverse vascular event

MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model of Repeated Measures
MoA	Mechanism of action
NEC	Not elsewhere classifiable
NO	Nitric oxide
NORD	National Organization for Rare Disorders
PD	Pharmacodynamics
PGIS	Patient Global Impression of Severity of fatigue
PIG-A	Phosphatidylinositol glycan class A
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
p.o.	Per os
Pop-PK	Population pharmacokinetics
Pop-PKPD	Population pharmacokinetics/pharmacodynamics
PRO	Patient Reported Outcome
QoL	Quality of life
QTcF	QTc derived from Fridericia's formula
RBC	Red blood cell
REP	Rollover extension programme
SAAWP	Severe Aplastic Anaemia Working Party
RTP	Randomised treatment period
SAE	Serious adverse event
SBP	Summary of Biopharmaceutic Studies and Associated Analytical Methods
sC5b-9	Soluble sC5b-9
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedure
TGA	Thermogravimetric analysis
T_{max}	The time to reach the maximum concentration after drug administration
ULN	Upper limit of normal
USPI	United States Prescribing Information
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 21 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Fabhalta, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 September 2020.

Fabhalta, was designated as an orphan medicinal product EU/3/20/2281 on 04 June 2020 in the following condition: treatment of paroxysmal nocturnal haemoglobinuria.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Fabhalta as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Fabhalta.

The applicant applied for the following indication:

Iptacopan Novartis is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):

- *who have haemolysis with clinical symptom(s), or*
- *who are anaemic after treatment with a complement inhibitor.*

The approved indication is:
Fabhalta is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0322/2021 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance iptacopan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5.2. Accelerated assessment

The applicant submitted a request for accelerated assessment which was consequently withdrawn before the final CHMP decision.

1.6. PRIME

Fabhalta was granted eligibility to PRIME on 20 September 2020 in the following indication: Treatment of C3 glomerulopathy.

Upon granting of eligibility to PRIME, Martina Weise was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 09 February 2021. The objective of the meeting was to discuss the development programme in C3 glomerulopathy and broader regulatory strategy for the product.

1.7. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
12 December 2019	EMEA/H/SA/3968/3/2019/III	*Prof. Fernando de Andrés Trelles and Dr Hrefna Gudmundsdottir*

The scientific advice pertained to the following *non-clinical, and clinical* aspects:

- *The adequacy of the nonclinical safety studies to support initiation of the Phase 3 study and potential registration.*
- *The adequacy of the clinical pharmacology program to support initiation of the Phase 3 study and potential registration; the design and key elements of said study and its adequacy to establish benefit/risk and support registration; the adequacy of the safety measures in the clinical development and of the safety data package to support registration; the adequacy of the proposed PNH clinical development program to support an indication in the treatment of adult patients with haemolytic PNH (with or without prior treatment with anti-C5 antibody).*

The applicant has also received scientific advice / protocol assistance in other indications, which are mentioned below in the interest of completeness: treatment of IgA nephropathy EMEA/H/SA/3968/2/2018/II (clinical questions), EMEA/H/SA/3968/4/2020/I (non-clinical questions,

including adequacy of reproductive, juvenile toxicity and carcinogenicity studies), EMEA/H/SA/3968/2/FU/1/2020/II (clinical); treatment of C3 glomerulopathy EMEA/H/SA/3968/1/2018/III (clinical and non-clinical development including juvenile toxicity program), EMEA/H/SA/3968/1/FU/1/2020/PA/PR/II (clinical); treatment of atypical haemolytic uremic syndrome (aHUS) EMEA/H/SA/3968/5/2020/III (clinical and quality questions, including adequacy of manufacturing control and release measures); lupus nephritis EMA/SA/0000064131 (clinical); generalised myasthenia gravis EMA/SA/0000129434 (clinical)

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Kristina Dunder

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Lina Seibokiene

The application was received by the EMA on	21 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 August 2023
The CHMP Co-Rapporteur's Assessment was circulated to all CHMP and PRAC members on	21 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 February 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	08 February 2024
The CHMP agreed on the consolidated List of Outstanding issues to be sent to the applicant during the meeting on	22 February 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	27 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	07 March 2024

to all CHMP and PRAC members on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 March 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fabhalta on	21 March 2024
The CHMP adopted a report on similarity of iptacopan Novartis with Aspaveli and Voydeya on (see Appendix on similarity)	21 March 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	21 March 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired, chronic, life-threatening blood disorder associated with anaemia due to haemolysis. It is most frequently caused by a somatic mutation in the PIGA gene of haematopoietic stem cells. Haemolysis can result in a range of debilitating consequences such as severe fatigue, chest pain, and transfusion dependence, all of which contribute to a reduced quality of life. If left untreated, PNH can cause severe and potentially fatal complications for patients. Thrombotic events are the main cause of severe complications and death in PNH. PNH requires life-long treatment. Therapy is aimed at controlling complement-mediated haemolysis and thus counteracting anaemia.

2.1.2. Epidemiology

PNH has an annual incidence of 1-10 new cases per 1 million individuals. The median age of diagnosis is in the early thirties; it affects men and women in equal proportions and has no clear ethnic or geographic preferences (Stern and Connell Ther Adv Hematol. 2019). In Europe or the United Kingdom (UK), the annual incidence of PNH has been reported as 1.3 to 2.98 per 1,000 000 (Korkama et al. Presented at EHA 2018; Hill et al. Nat Rev Dis Primers 2017).

As of July 2017, according to the International PNH Registry population, the European population is well represented (3012/4439 patients from more than 30 countries located in Europe) and median age at disease onset for PNH was 35.5 years (Schrezenmeier et al. Ann Hematol. 2020).

2.1.3. Aetiology and pathogenesis

Paroxysmal nocturnal haemoglobinuria (PNH) is characterised by chronic complement-mediated haemolysis caused by a somatic mutation in the PIGA (phosphatidylinositol glycan anchor biosynthesis class A) gene of haematopoietic stem cells leading to impaired biosynthesis of the

glycosylphosphatidylinositol anchor, with subsequent loss of phosphatidylinositol bound cell surface proteins, including the complement regulatory proteins (CD55 & CD59) on all progeny cells including red blood cells (RBCs). The deficient PNH cells will eventually expand over normal haematopoiesis, the clonal expansion being the prerequisite for disease manifestation. The lack of complement inhibitory proteins on the surface of PNH RBCs leads to increased C3b and C3d deposition on these cells (due to absence of CD55) followed by membrane attack complex (C5b-9 or MAC) formation (due to absence of CD59) and erythrocyte lysis leading to intravascular haemolysis (Schrezenmeier *et al.* Ann Hematol. 2020, Brodsky Blood 2014). Inhibition of intravascular haemolysis by anti-C5 therapies increases survival time of PNH RBCs in the blood stream leading to an accumulation of C3b and C3d PNH RBCs. These opsonised PNH RBCs become target for extravascular haemolysis via the reticuloendothelial system.

2.1.4. Clinical presentation, diagnosis

The clinical spectrum of PNH varies and signs and symptoms include anaemia, thrombosis, smooth muscle dystonia, fatigue, haemoglobinuria, chronic kidney disease and pulmonary hypertension. The clinical presentation is driven by uncontrolled complement activation on CD55 and CD59 deficient PNH type RBCs culminating with haemolysis and the release of free haemoglobin, and platelet activation (Hill *et al.* Blood 2013). Haemolysis results in release of intracellular haemoglobin and lactate hydrogenase (LDH) into the circulation. Irreversible binding to and inactivation of nitric oxide (NO) by haemoglobin and inhibition of NO synthesis with consequent vasoconstriction and tissues ischemia, result in abdominal pain, dysphagia, erectile dysfunction, platelet activation and a prothrombotic status (Brodsky, Blood 2014; Hill *et al.* Blood 2013). The occurrence of extravascular haemolysis in the context of anti C5 therapies can lead to substantial residual anaemia. Furthermore, beyond complement-mediated haemolysis leading to anaemia, PNH is clinically characterised by severe thrombophilia and bone marrow failure (BMF) (Risitano *et al.*, Immunobiology .2012). Thromboembolism is the leading cause of morbidity and mortality in patients with PNH and can occur at any site; although venous is more common (80–85%), it can also be arterial (15–20%) (Hillmen *et al.* Blood 2007).

2.1.5. Management

To most effectively manage PNH, both intravascular (IVH) and extravascular haemolysis (EVH) need to be controlled. This is reflected in improvements across the following key markers of disease activity: haemoglobin level, LDH level, ARC, bilirubin level, transfusion requirements, and FACIT-Fatigue score. The C5 inhibitors eculizumab (Soliris) and ravulizumab (Ultomiris) have shown increased survival and improved outcomes in PNH by controlling IVH, reflected in LDH improvements; however, C5 inhibitors do not control EVH. In many patients treated with C5 inhibitors, although LDH is largely controlled, ARC and bilirubin levels remain elevated, indicative of ongoing haemolysis. Despite the availability of eculizumab over the past 13 years, some patients remain symptomatically limited by their disease and still require PRBC transfusion because not all key markers of disease activity are meaningfully improved. Danicopan (Voydeya), a reversible inhibitor of complement factor D, was recently approved as an add-on to ravulizumab or eculizumab for the treatment of adult patients with PNH who have residual haemolytic anaemia.

Pegcetacoplan (Aspaveli), targeting C3 in the proximal complement system, was approved in 2021 for patients who are anaemic after treatment with a C5 inhibitor for at least 3 months. It is administered twice weekly by subcutaneous infusion (1080 mg/20 mL) via a pump. In the phase III PEGASUS study in adult patients with a haemoglobin level <10.5 g/dL despite eculizumab therapy, pegcetacoplan was superior to eculizumab in improving haemoglobin levels. Pegcetacoplan also improved other clinical

and haematological parameters of haemolysis, as well as quality of life (QOL) outcomes (Hillmen *et al.* N Engl J Med.2021).

Pegcetacoplan was recently approved in the EU as monotherapy for the treatment of adult patients with PNH who have haemolytic anaemia.

2.2. About the product

LNP023 (iptacopan) is a novel, oral, small molecule compound that inhibits factor B (FB). Factor B is a key protease of the complement alternative pathway (AP).

The complement system is a major arm of innate immunity and comprises a cascade of sequentially activated proteases directed at the elimination of pathogens. There are three pathways of complement activation: immune complexes activate the classical complement pathway (CP), whereas carbohydrate-binding proteins attaching to pathogen surfaces activate the lectin pathway (LP). The AP is continuously active mediating ~ 80% of complement activation. All three pathways result in the formation of the C3 convertase – a heterozygous protease complex that catalyses the proteolytic cleavage of C3 into C3a and C3b. Iptacopan inhibits the activity of Factor B by binding to the active site of Bb thereby blocking cleavage of C3 by the C3 convertase of the alternative pathway (figure below).

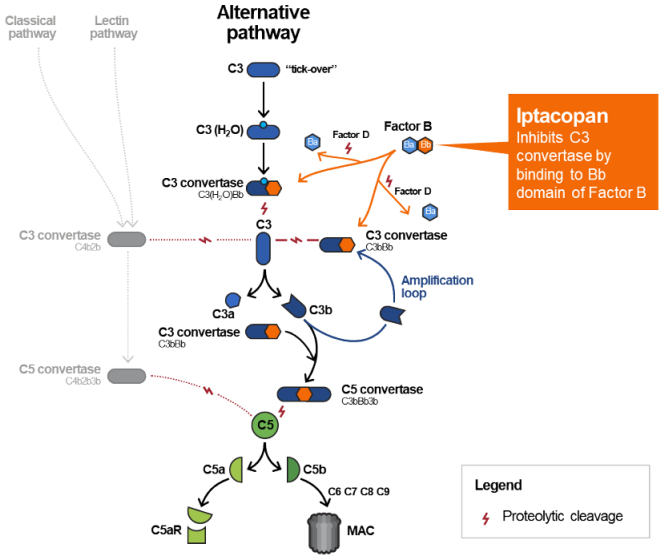


Figure 1: Iptacopan is a proximal complement inhibitor that specifically binds to FB to inhibit the activation of the AP and amplification loop. AP, alternative pathway; FB, Factor B; MAC, membrane attack complex. (Rizk et al. 2023)

2.3. Type of application and aspects on development

The iptacopan PNH development program included a total of 170 PNH patients. The primary efficacy and safety data supporting the PNH indication was provided by:

1. Pivotal Phase III study CLNP023C12302 (APPLY-PNH), a randomised, active-controlled study, comparing 200 mg twice daily iptacopan monotherapy to anti-C5 treatment in 97 PNH patients with residual anaemia despite prior anti-C5 therapy.

2. Supportive Phase III study CLNP023C12301 (APPOINT-PNH), a single arm, open-label, study, evaluating 200 mg twice daily iptacopan monotherapy in 40 PNH patients who were naïve to complement inhibitor treatment.

Supportive studies:

- Two open-label Phase II PNH studies in 29 PNH patients (CLNP023X2201 in anti-C5 experienced patients and CLNP023X2204 in complement inhibitor-naïve patients) providing a minimum of 2 years of long-term efficacy and safety data with 200 mg b.i.d. iptacopan monotherapy.

Up to 4 years of safety data are available from patients who rolled over to the PNH roll-over extension programme (CLNP023C12001B).

CHMP Scientific Advice

The applicant received CHMP Scientific Advice on the non-clinical pharmacology and the clinical program. Overall, the proposed clinical development program was found acceptable (CHMP advice letter, procedure EMEA/H/SA/3968/3/2019/III). However, the SAWP recommended to blind the study given the proposed single pivotal study and since the main variable involves a subjective decision (i.e. the need for transfusions). Patient-reported outcomes may also be affected by the knowledge of treatment allocation. This advice was not followed. The APPLY study was conducted as an open-label study, thus avoiding the operational challenges with a double dummy design (oral versus infusion). The recommendation to use a treatment policy strategy as the primary estimand was accepted by the applicant. In the advice, the SAWP also expressed some concerns on the interpretability of the APPOINT-study based of the single-arm design.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a hard capsule containing 200 mg of iptacopan (as hydrochloride monohydrate) as active substance.

Other ingredients are:

capsule shell: gelatine, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172); *printing ink:* black iron oxide (E172), concentrated ammonia solution (E527), potassium hydroxide (E525), propylene glycol (E1520), shellac (E904).

The product is available in PVC/PE/PVDC blisters with aluminium foil as described in section 6.5 of the SmPC.

2.4.2. Active substance

General information

The chemical name of iptacopan hydrochloride monohydrate is (2S,4S)-2-(4-Carboxyphenyl)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-1-ium chloride-water (1/1) corresponding to the molecular formula $C_{25}H_{30}N_2O_4.HCl.H_2O$ (salt on solvate (hydrate) form). It has a relative molecular mass of 477.00 and the following structure:

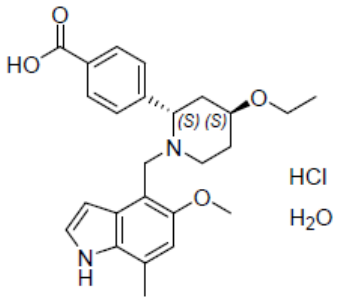


Figure 2: active substance structure

The chemical structure of the active substance was elucidated by a combination of UV-VIS, elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and mass spectrometry. The solid state properties of the active substance were measured by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and XPRD.

Iptacopan hydrochloride monohydrate is a white or almost white to pale purplish-pink powder. Different polymorphic forms exhibit different solubilities; hydrate H_B, the proposed polymorphic form of this application, shows high solubility in aqueous buffer media, simulated intestinal fluids and water, as discussed below.

Iptacopan hydrochloride monohydrate exhibits stereoisomerism due to the presence of two chiral centres. Single crystal structure analysis provided absolute configuration of the two chiral centres, which are both S. Enantiomeric purity is ensured during the synthesis is controlled routinely by chiral HPLC/specific optical rotation.

Polymorphism has been observed for iptacopan. Iptacopan hydrochloride monohydrate (hydrate H_B)was found to be obtained as the only form by the proposed manufacturing process. The identity of the crystalline form is controlled by an X-ray powder diffraction method.

Manufacture, characterisation and process controls

Two active substance manufacturers are proposed. Iptacopan hydrochloride monohydrate is manufactured following a convergent synthesis. Each step has been described in detail, including process parameters and in-process controls.

The active substance is synthesised using well defined starting materials with acceptable specification. The starting materials comply with the principles outlined in the ICH Q11 guideline and ICH Q11 Q&A. The selection of the starting materials is considered acceptable. An extensive discussion on potential organic and mutagenic impurities was provided. Potential mutagenic impurities were classified according to ICH M7, purge data and toxicity results. Spike and purge experiments were presented for each specified impurity, and it was satisfactorily demonstrated that the impurities concerned are purged to the level where they pose no risk to the resulting active substance. Purge and fate of unreacted reagents have also been evaluated.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. During early phase development, the active substance was obtained as anhydrous form A. For the late phase development, the active substance was isolated as the monohydrate form H_B, which is the thermodynamically more stable form. Changes introduced during both phases of development have been presented in sufficient detail and have been justified. The quality of the active substance used in the late phase development is considered to be comparable with that produced by the proposed commercial process.

The manufacturer applies a structured risk assessment approach to identify criticality of each process parameter (critical and non-critical) and their impact on the quality of the active substance. Narrative description of manufacturing process includes the quantities (PAR: proven acceptance ranges) of materials used (e.g., starting materials, intermediates, reagents, solvents, catalysts, etc.), process parameters (e.g., temperature, pH, etc.), IPCs indicated, and expected yield ranges for each manufacturing stage. Set points, target values and/or proven acceptable ranges (PARs) for all process parameters defined are based on process development. The PARs are established experimentally and/or based on scientific understanding and/or ensure that specifications of relevant intermediates/active substance are met.

Robustness of the manufacturing process to changes of reaction scale and equipment was demonstrated throughout development and confirmed by dedicated scientific investigations. Based on these scientific investigations, the manufacturing process includes scale ranges, which are expected to deliver the desired active substance quality.

The active substance is stored in a low-density polyethylene (LDPE) bag, which complies with relevant Commission regulation and Ph. Eur., placed in a quadruple laminated foil bag and sealed.

Specification

The active substance specification includes tests for appearance (visual examination), particle size (laser light diffraction), identity (IR Spectroscopy, X-Ray diffraction pattern), related substances (HPLC), residual solvents (headspace GC), water (Coulometer with oven, Ph. Eur.), sulphated ash (incineration), assay (HPLC and by titration), microbiology (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on commercial scale batches of active substance from one of the two manufacturer for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Stability data on commercial scale batches manufactured at the second proposed manufacturing site for up to 6 months under long term conditions (25 ºC / 60% RH) and accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release with the exception of particle size (not tested) and clarity and colour of the solution (tested only during stability). The analytical methods used were the same as for release and were stability with the exception of the visual method for clarity and colour of the solution.

The polymorphic form H_B was also monitored during active substance stability studies: no formation of other crystalline polymorphs has been detected under stress studies, long-term and accelerated storage conditions in the packaging material intended for the drug substance storage. Thus, the polymorphic form of hydrate H_B was shown to be stable during long-term storage in the intended packaging configuration.

All tested parameters were within the specifications, no trend was observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. The active substance is photostable.

Data from stress testing have been also presented. No degradation was observed in the solid samples in different conditions (1 month at 50 °C and 60 °C with < 30% RH and 75% RH and for 1 month at 80 °C in atmosphere of nitrogen and oxygen). The active substance is also stable when exposed to freeze-thaw cycle for 28 days. The active substance shows significant degradation in solution when stressed under acidic, alkaline, hydrolytic and oxidative conditions. Hygroscopicity study showed that drug substance is found to be slightly hygroscopic.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container, with no special storage conditions.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as a hard capsule containing 200 mg of iptacopan as hydrochloride monohydrate. The finished product is described as a size 0 hard capsule with pale yellow opaque cap and body with black imprint "LNP200" on body and "NVR" on cap, containing white or almost white to pale purplish-pink powder.

No overage is included in the finished product. The QTPP for iptacopan hard capsule was to develop a standard, immediate release, solid oral dosage form, capable to maintain the in vivo performance of the early clinical formulation, while ensuring a robust manufacturing process. As the finished product consists of pure active substance filled into capsules, the components of the hard gelatine capsule shell are the only excipients used in the manufacture of the finished product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report. Compatibility and stability studies support the compatibility of the active substance with the capsule. Iptacopan is manufactured by using standard operations commonly used in the manufacturing of solid oral dosage forms, e.g., sieving and encapsulation.

Iptacopan hydrochloride monohydrate is classified as a Biopharmaceutics classification system (BCS) class III compound based on high solubility and low permeability. As already mentioned in the active substance section, polymorphism has been observed for iptacopan. Iptacopan hydrochloride

monohydrate was found to be the thermodynamically stable form and was therefore selected for further development. There were minor differences between early clinical, late-phase clinical and commercial formulations, consisting of: active substance form, dosage strength, capsule sizes, capsule colour and imprint.

No bioequivalence study was performed between the early clinical formulation and the proposed commercial formulation. This is accepted as comparison of dissolution profiles between formulations is presented and were found acceptable.

The discriminatory power of the QC dissolution method has not been demonstrated, due to the very rapid dissolution of API. This is accepted since iptacopan hydrochloride monohydrate belongs to BCS class III.

The primary packaging is PVC/PE/PVDC blisters with aluminium foil. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: sieving of the active substance, followed by encapsulation into empty hard gelatine capsules, primary and secondary packaging. The process is considered to be a standard manufacturing process.

The manufacturing of bulk iptacopan capsules and the primary packaging are performed in different countries. This is acceptable and supported by a transport study.

Description of manufacturing process includes details about the process parameters. The manufacture of the finished product is controlled by IPCs performed during encapsulation and packaging.

The proposed holding time for the bulk product of 12 months in laminated aluminium foil bag under conditions "Do not store above 30 °C. Protect from light" is supported by long-term and accelerated stability data.

Full process validation on three full commercial scale batches was carried out. Based on validation data and adequacy of in-process controls, the manufacturing process is considered sufficiently robust to consistently manufacture finished product of the expected quality, complying with the designated specification.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of content and of shell (visual examination), identity (UV), water (coulometric with oven), specific impurity (LC-MS), dissolution (UV, Ph. Eur.), uniformity of dosage units (HPLC -Ph. Eur.), identity, assay and degradation products (HPLC), microbiology (Ph. Eur.).

The proposed finished product specification is in line with ICH Q6A and it is considered acceptable for this type of dosage form. The specification parameters, analytical methods and acceptance criteria were satisfactorily described and justified. The limits for specified impurities and for specific impurity are toxicologically justified.

The proposed specification is supported by batch results that were provided for clinical, verification, registration stability and process validation batches. Results for all batches are in line with specification/test method valid at the time of analysis.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed, and updated, as requested, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided on full scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for water, specific impurity, dissolution, assay and degradation products, microbiology. In addition, content of enantiomer and identity by XRPD were tested. All tested parameters under all conditions remained within the acceptance criteria. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photostable.

In addition, an open dish study and freeze and thaw cycle study was performed on one batch of the finished product. There was no change with respect to all stability attributes (appearance, assay, related substances, water content, and dissolution).

Based on available stability data, the proposed shelf-life of 2 years without special storage conditions, as stated in the SmPC (section 6.3 and 6.4), are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Minor concerns have been addressed satisfactorily during the procedure. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The pharmacodynamic activity and selectivity of iptacopan was characterised in a number of *in vitro* and *in vivo* pharmacological studies. In addition, safety pharmacology studies were conducted with iptacopan to assess effects on the cardiovascular, respiratory, and central nervous systems. The pivotal safety pharmacology studies were conducted in accordance with good laboratory practice (GLP) and ICH Guidelines S7A and S7B.

The pharmacologic target of iptacopan, Factor-B (FB), is evolutionarily conserved across mammalian species, and iptacopan has been demonstrated *in vitro* to inhibit FB from different species, including rodents, dogs, rabbits, monkeys and humans. This allowed evaluation of potential on-target toxicities in nonclinical *in vivo* studies.

The program of nonclinical pharmacokinetics for iptacopan included absorption, distribution, metabolism, and excretion (ADME) studies in the same strains and species that were used for chronic toxicity or carcinogenicity testing (mouse, rat and dog). Both oral and intravenous dosing routes were evaluated in all species to estimate absorption and oral bioavailability. Additional information obtained from the ADME studies includes pharmacokinetic parameters and 14C-iptacopan-derived radioactivity tissue distribution, routes and rates of excretion, and metabolic pathways. *In vitro* blood/plasma distribution, protein binding and metabolism studies were performed to support the *in vivo* studies.

A complete toxicology program (subchronic, chronic, genotoxicity, carcinogenicity, reproductive and developmental toxicology, phototoxicity and other mechanistic studies) was conducted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The applicant conducted an *in vitro* study to determine the binding affinity of iptacopan (here referred to as LNP023) to the catalytically active domain of human FB. Moreover, *in vitro* studies were performed to show inhibition of the alternative complement activation pathway (AP) using serum from various species (human, cynomolgus monkey, rat, mouse, dog, pig), or whole blood (human). Additionally, the applicant studied the effect of LNP023 on the classical complement pathway in human serum. Finally, several translational studies were performed to show the effect of LNP023 on AP activation: a PNH surrogate assay using blocking antibodies against CD55 and CD59, a sheep red blood cell lysis assay using serum from patients with complement-driven diseases (aHUS, C3GN, DDD, MPGN) and a binding and inhibition analysis comparing wildtype and human mutations of FB, which are present in aHUS. *In vivo* studies focused on the effect of LNP023 on LPS-induced complement pathway activation in mice and on prophylactic as well as therapeutic effects of LNP023 treatment in a rat model of membranous nephropathy. Moreover, pharmacokinetic analyses were performed *ex vivo* using rat and dog serum after chronic treatment (26 – 52 weeks) with LNP023.

Table 1: Overview of non-clinical individual primary pharmacodynamic studies

Study	Assay	Report number
In vitro		
Binding affinity of LNP023 to catalytic domain of human FB.	TR-FRET and dose titration of LNP023 from 0.0003 µM to 100 µM	RD-2015-00230
AP inhibition in serum (human, monkey, mouse, rat, dog, pig)	Zymosan assay with dose-titration of LNP023	RD-2015-00152 RD-2017-00357 RD-2017-00003 RD-2014-00521 RD-2014-00605 RD-2015-00228
AP inhibition in human whole blood	Zymosan assay with dose-titration of LNP023	RD-2015-00153
CP inhibition	Wieslab Complement System assay with dose titration of LNP023.	RD-2022-00256
PNH surrogate assay for AP inhibition	LNP023 dose-titration in PNH-like human erythrocytes	RD-2015-00232
AP inhibition in serum from patients with complement-driven diseases	Sheep red blood lysis assay using two doses of LNP023 in serum from patients with aHUS, C3GN, DDD, MPGN	RD-2020-00407
Binding and functional inhibition of FB mutants identified in patients with aHUS	Fluorescence polarisation assay; C3 convertase assay; Zymosan assay	RD-2022-00012
In vivo		
LPS model in mice (PK/PD)	C57Bl/6 mice injected with LPS prior to LNP023 treatment	RD-2015-00210
Passive Heymann nephritis model for membranous nephropathy in rats – prophylactic LNP023 treatment	Sprague Dawley rats injected with LNP023 prior to anti-Fx1A-induced kidney injury	DIS R1720571
Passive Heymann nephritis model for membranous nephropathy in rats – therapeutic LNP023 treatment	Sprague Dawley rats injected with anti-Fx1A serum prior to LNP023 treatment	DIS R1820106a
Ex vivo PD rat	Serum samples after 26-week daily treatment of rats	RD-2019-00023
Ex vivo PD dog	Serum samples after 39-week and 52-week daily treatment of dogs (beagle)	RD-2018-00505 RD-2020-00544

The most relevant studies listed in the table above are presented in more detail below.

***In vitro* studies**

Binding affinity assay (RD-2015-00230)

The binding affinity of LNP023 to the catalytic domain of FB was analysed using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. FRET involves two fluorophores, a donor and an acceptor. LNP023 inhibited binding of the active site reporter ligand to human Factor B concentration-dependently. The binding affinity (IC50) was calculated as 0.0096 +/- 0.0027 µM (n=6; calculated from linear regression analysis).

The figure below shows the binding curve (inhibition of binding between donor and acceptor) with increasing doses of LNP023.

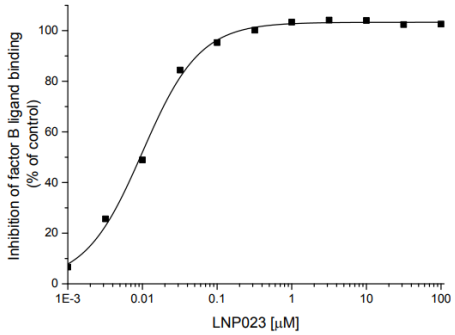


Figure 3: Concentration-dependent inhibition of human factor B reporter ligand binding by LNP023

Further analysis using surface plasmon resonance assay revealed a binding affinity of K_d = 0.0079 +/- 0.0019 µM (Schubart *et al.* 2019).

Alternative pathway inhibition by LNP023 in serum of various species (RD-2015-00152, RD-2017-00357, RD-2017-3, RD-2014-00521, RD-2014-00605, RD 2015-00228)

To test the inhibition of the alternative complement pathway by LNP023, the applicant performed Zymosan assays using serum of various species. Zymosan is a polysaccharide complexed with proteins found in the cell wall of fungi (e.g. *Saccharomyces cerevisiae*), which is known to activate the alternative complement pathway. In parallel, the classical and lectin pathways of complement activation were blocked using $MgCl_2$ and EGTA.

LNP023 blocked AP activation by zymosan in serum- or blood-based (only human) assays, which contain all soluble components of the complement system across various species (human, cynomolgus monkey, mouse, rat, rabbit, dog, pig). LNP023 inhibited C3b deposition on zymosan with an IC50 value of 110 nM in 50% mouse serum. In all other species MAC deposition (i.e. C9) was used as a readout. The IC50 value for inhibition of MAC formation was 560 nM in 50% rat serum, 110 nM in 50% rabbit serum, 410 nM in 50% dog serum and between 80 nM and 400 nM in 50% cynomolgus monkey serum.

The figures below show a % inhibition for each LNP023 concentration relative to the baseline/negative control (EDTA-treated serum) and the maximum response (normal serum) from human, cynomolgus monkey, and mouse serum. IC50 values were calculated with Prism using log(inhibitor) vs. response equation (variable slope). Maximum and minimum were constrained to 100 and 0, respectively.

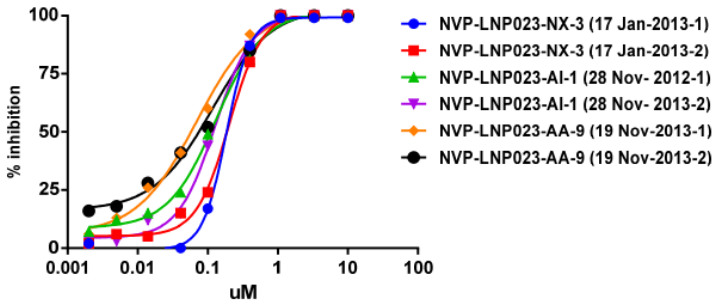


Figure 4: 50% Human serum assay

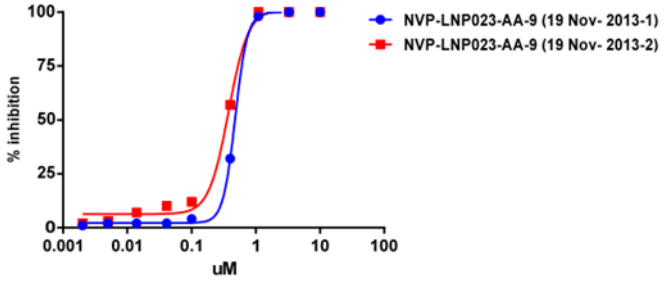


Figure 5: 50% Cynomolgus serum assay

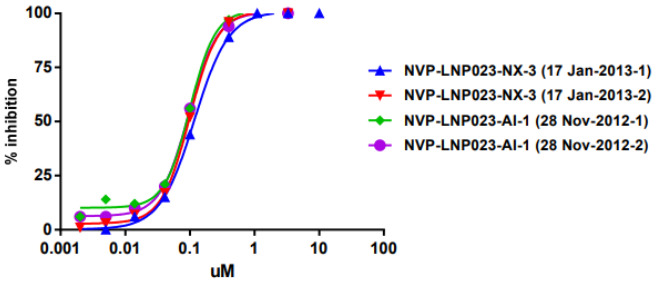


Figure 6: 50% Mouse serum assay

In vitro assay for classical complement pathway inhibition (RD-2022-00256)

The aim of this study was to test if LNP023 inhibits the classical complement pathway. Therefore, the commercial Wieslab Complement System Classical Pathway assay (SVAR Life Science) was performed according to manufacturer's instructions. It is a semi-quantitative immunoassay, which uses specific activators of the classical pathway coated on an assay plate and measures the generation of C5b-9 with a specific antibody conjugated to alkaline phosphatase after addition of serum.

Three independent experiments were performed to test the effect of LNP023 on classical complement pathway activation. Complement activation was quantified by detection of the terminal complement complex. LNP023 did not inhibit the classical pathway up to a concentration of 100 µM in 1% human serum (figure below, black lines). As a positive control for the assay, the C5-specific antibody eculizumab inhibited C5b-9 generation in 1% serum with an IC50 of 27 pM ± 5 pM (figure below, gray lines).

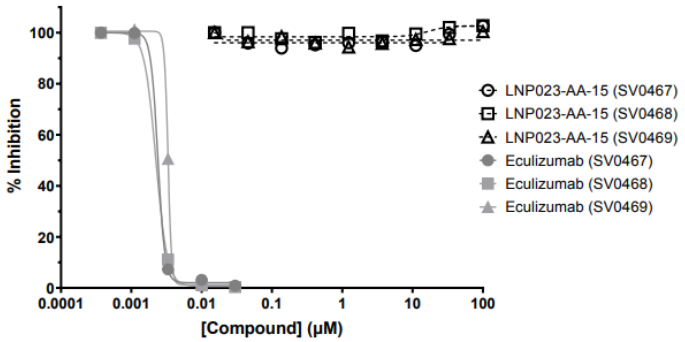


Figure 7: LNP023 does not inhibit classical pathway activity in the Wieslab assay

In vivo studies

Lipopolysaccharide injection of mice (RD-2015-00210)

To assess the effect of LNP023 *in vivo*, the applicant applied a Lipopolysaccharide (LPS) injection model in C57Bl/6 mice, which causes a dose- and time-dependent activation of the AP. Complement activation in serum was assessed by a semi-quantitative Immunoblot measurement of C3d and iC3b, which are cleavage fragments of C3b.

LPS-induced C3d+iC3b generation in plasma was effectively and dose-dependently inhibited by the oral administration of LNP023. Moreover, percentage inhibition of complement activation correlated with the plasma concentration of LNP023. Combined *in vivo* EC50 (IC50) value for iptacopan from both experiments was 560 nM (240 ng/mL); the corresponding EC90 (IC90) value was 1,120 nM (470 ng/mL).

Passive Heymann nephritis model for membranous nephropathy in rats (DIS R1720571)

While conventional global knockout mouse models of the PNH-causing PIGA gene show high embryonic lethality, conditional knockouts often have no or a very mild haemolysis phenotype with no observable effect on the alternative pathway. On the other side, nephropathies are often linked to deregulated (alternative) complement pathway activations. Therefore, the applicant analysed the effect of LNP023 by using a well-described disease model, the Passive Heymann nephritis (PHN) model for membranous nephropathy. The PHN model is characterised by the development of immune complexes in the subepithelial space on the outer surface of the glomerular basement membrane following administration of heterologous antibody to rat proximal tubular brush border (anti-Fx1A) targeting megalin and receptor associated protein (RAP). The applicant performed prophylactic and therapeutic LNP023 treatments.

Prophylactic treatment with LNP023 (20 and 60mg/kg p.o.; b.i.d.) starting at the time of disease induction prevented proteinuria. Therapeutic dosing of iptacopan after onset of proteinuria (day 6) immediately halted further disease progression. Histologic analysis at the end of the study showed that prophylactic or therapeutic administration of iptacopan attenuated glomerulopathy as characterised by enlarged glomeruli, basal membrane and Bowman's capsule thickening, and enlarged/rounded podocytes, prevented tubular degeneration and reduced transcription of the kidney injury marker KIM-1. In addition, near-complete inhibition of complement activation, i.e. absence of glomerular C3 deposition in most animals, was seen after therapeutic compound treatment.

2.5.2.2. Secondary pharmacodynamic studies

The secondary PD studies showed that some off-target inhibition of oestrogen receptor alpha (ERa), the kinase mTOR and mono amino oxidase A (MAO-A) by iptacopan at therapeutically relevant concentrations cannot be excluded.

Table 2: Overview of the non-clinical secondary pharmacodynamic studies

Type of study	Test system or protocol	Method of administration	Report number	Salient findings
> *In vitro* pharmacology				
LNP023 inhibition of human cathepsin proteases	LNP023 was tested at 1, 3, 10, 30, 100 µM on a panel of 12 human cathepsin proteases	*In vitro*	DIS R1720165	No relevant findings
LNP023 inhibition of human G-protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors, and enzymes (off-target panel)	Dose-titration of LNP023 from 0.003 µM to 30 µM (or up to 100 µM) to determine IC_{50} in a panel of radioligand binding and functional assays on 122 GPCRs, ion channels, nuclear receptors, transporters, and enzymes.	*In vitro*	RD-2015-00689	Up to 45% inhibition of the human oestrogen receptor (ER) α; up to 20% inhibition of MAO-A
LNP023 inhibition of human nuclear receptors	LNP023 was tested up to 100 µM in in cellular and nuclear receptor functional assays (prostaglandin receptors EP1, EP3, FP and TP)	*In vitro*	RD-2020-00450	No relevant findings
LNP023 inhibition of human kinases	LNP023 was tested from 0.003 µM to 10 µM against the activity of 31 protein kinases	*In vitro*	RD-2019-00018	Inhibition of ATP-binding MTOR [ATP-binding site of mTOR]; IC50 = 9.9 µM
> *In vivo* pharmacology				
DNP-KLH immunisation of mice to determine effects on T cell dependent antibody responses (PK/PD)	C57BL/6J mice were immunised with DNP-KLH/alum i.p. and treated with 30 mg/kg or 100 mg/kg LNP023 or vehicle p.o. b.i.d., starting 2 h prior to immunisation. The primary antibody response was analysed on Day 8, and the secondary antibody response on Day 19 following a second immunisation (boost) on Day 9. Readouts: Blood PK, anti-DNP antibody titres (IgG and IgM, ELISA), germinal centre response in the spleen (flow cytometry), cell proliferation in the spleen (Ki67 immunohistochemistry) and AP inhibition (Western Blot).	*In vivo,* oral	RD-2018-00517	Iptacopan at 100 mg/kg b.i.d. had no meaningful impact on the B cell response to DNP-KLH in mice.
Sheep red blood cell immunisation of rats to determine effects on T cell dependent antibody responses (PK/PD)	Wistar rats were injected with $1x10^8$ SRBCs i.v. and treated with 6, 20, 60 or 120 mg/kg LNP023 or vehicle b.i.d. p.o starting 2 h prior to immunisation and continued throughout the study. Blood was sampled on day 4 (2 h post dosing) and day 7 (about 12 h post dosing) to determine SRBC-specific IgM (ELISA), AP inhibition (Western Blot) and blood PK.	*In vivo,* oral gavage	RD-2018-00519	Iptacopan at 20 mg/kg b.i.d. or above had no meaningful impact on the B cell response to SRBCs in rats.

2.5.2.3. Safety pharmacology programme

Cardiac ion channel studies

In vitro effect of iptacopan on the hERG (human ether-à-go-go-related gene) channel current (responsible for the rapid delayed rectifier current (IKr) that regulates repolarisation of the cardiac action potential) was tested in early non GLP studies followed by a definitive GLP study in voltage-clamped human embryonic kidney (HEK293) cells, that stably express the hERG gene.

Iptacopan inhibited hERG current by 8.9 ± 0.5% at 100 µM (n = 3), 32.1 ± 1.2% at 300 µM (n = 3), 68.8 ± 3.0% at 600 µM (n = 3) and 86.3 ± 1.2% at 1000 µM (n = 3) versus 2.8 ± 0.7% (n = 3) in control samples. The IC50 for the inhibitory effect of iptacopan on hERG potassium current was 414.9 µM (equivalent to 175,303 ng/mL, ~ 230-fold above the human unbound C_{max} of 763 ng/mL); see figure below.

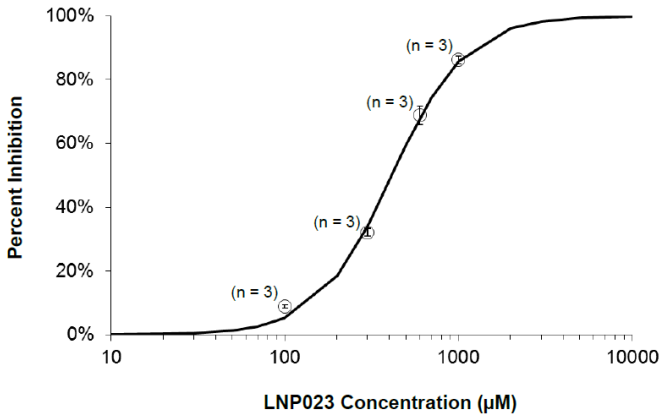


Figure 8: LNP023 Concentration-response relationship

Besides hERG, the following cardiac ion channels were also tested *in vitro* for inhibition by iptacopan:

- hKir2.1 (responsible for IK1, inwardly rectifying potassium current)
- hKvLQT1/hminK (responsible for IKs, slow delayed rectifier potassium current)
- hKv4.3 (responsible for Ito, transient outward potassium current)
- hCav1.2 (responsible for ICa,L current in the action potential and excitation-contraction coupling)
- Nav1.5 (responsible for action potential upstroke and conduction)

None of these channels was inhibited by more than 50% by the highest iptacopan concentration used (300 µM in most cases). Hence, IC50 could not be determined.

Mechanistic studies on hERG trafficking

Based on the finding of QTc prolongation in monkeys, the applicant investigated the potential effects of iptacopan on intracellular trafficking of hERG and thereby on the surface expression of the channel in HEK cells. No effect of iptacopan on surface expression was detected at concentrations up to 300 µM.

Studies in human primary cardiomyocytes

In vitro, non GLP, exploratory studies were conducted to further investigate potential mechanisms underlying the *in vivo* cardiovascular effects of iptacopan (increased heart rate and cardiac contractility) observed in juvenile when compared to adult dogs.

Cardiomyocytes from adult donors as well as from children were tested. Since the number of donors was low, no meaningful conclusions on differences between children and adults could be drawn. Therefore, only the effects of iptacopan on primary cardiac myocytes from adults (obtained from three donors) were described. Iptacopan's effect on contractility was compared to several control drug that either increase or decrease contractility. The controls revealed the expected effects, indicating that the primary cultured cardiomyocytes were in good state.

NVP-LNP023 slightly increased CA starting at concentration of 10 µM in Donor 1 (n = 11 cells), Donor 2 (n = 7 cells) and Donor 3 (n = 6 cells). Compared to 100% control, geometric means of NVPLNP023 effect on CA at 3 µM, 10 µM, 30 µM and 100 µM were 102%, 114%, 126% and 131%, respectively (figure below).

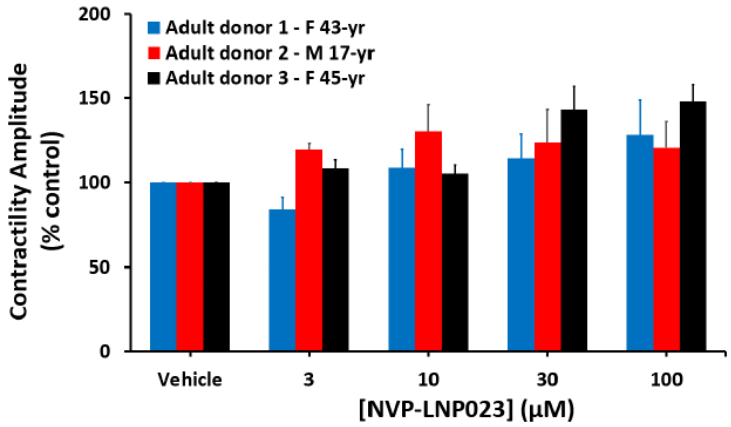


Figure 9: Percent Changes in Contractility Amplitude for NVP-LNP023 (= iptacopan) at 1Hz (3 donors)

<u>In vivo cardiovascular safety assessment</u>

Monkey

QTc prolongation was assessed in an ascending-dose study in cynomolgus monkeys. The animals (3 males) received ascending doses of iptacopan, 1 dose per dose level, from 10 mg/kg to 600 mg/kg. Jacketed telemetry was performed on all animals pretest and following each dose.

Dose-dependent QTc interval prolongation was observed at 300 and 600 mg/kg and the effects lasted from 9 to 17 hours post the 300 mg/kg dose and from 9 to 20 hours post the 600 mg/kg dose (figure below). QTc interval prolongation was observed in 2 of 3 animals at 300 mg/kg and in all three animals at 600 mg/kg. There were no test article-related effects on other ECG intervals or arrhythmias.

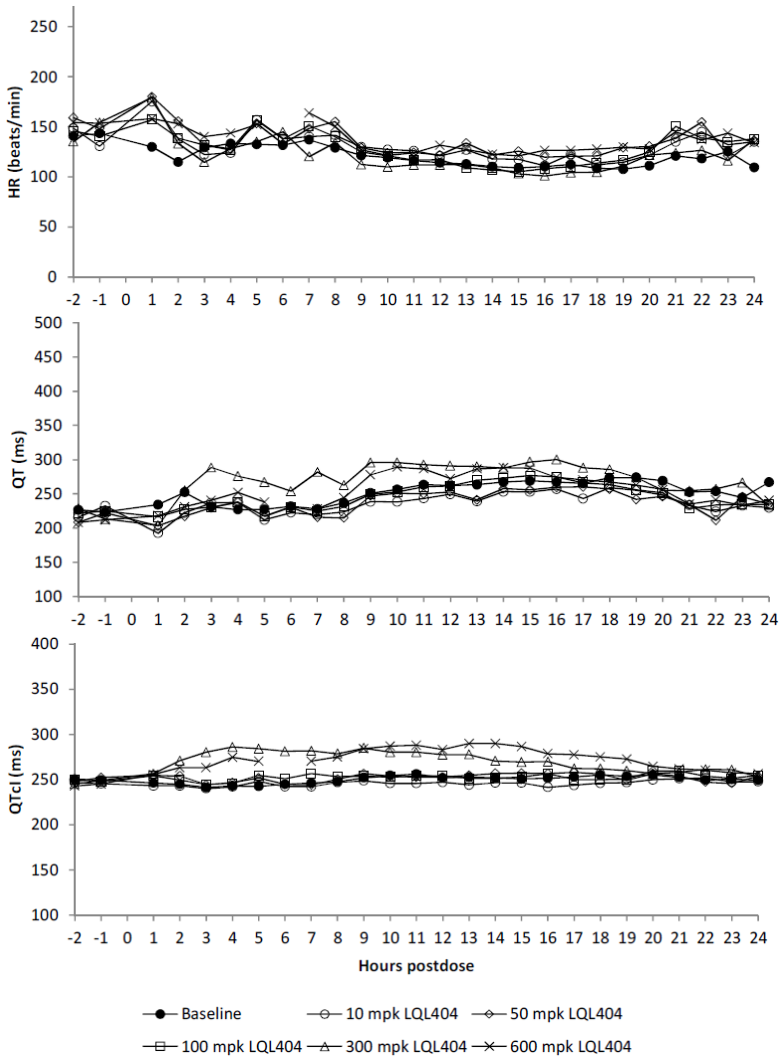


Figure 10: LNP023 changes in group mean HR, QT interval and QTc interval

Toxicokinetic data were also obtained in this study. With doses of 300 mg/kg and 600 mg/kg, where QTc prolongation was observed, C_{max} values of 88800 ng/mL and 138000 ng/mL, respectively, resulted. Human therapeutic C_{max} is 4120 ng/mL. This C_{max} is markedly lower than that reached with 50 mg/kg in monkeys. With the latter dose, there was clearly no QTc prolongation in monkeys.

Dog

Several telemetry studies were performed, in part within the frame of repeated-dose toxicity studies. Consistent findings were dose-dependent increase in HR, decrease in BP and decrease in PR interval. No changes in QTc were observed. Representative results are shown in the figures below.

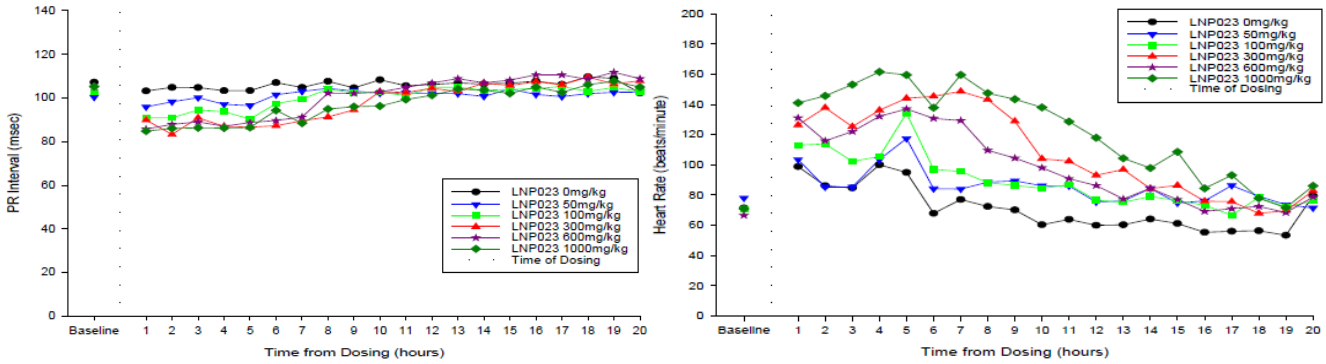


Figure 11: Absolute mean PR interval data (left) and absolute mean heart rate data (right) – Rising Dose Phase

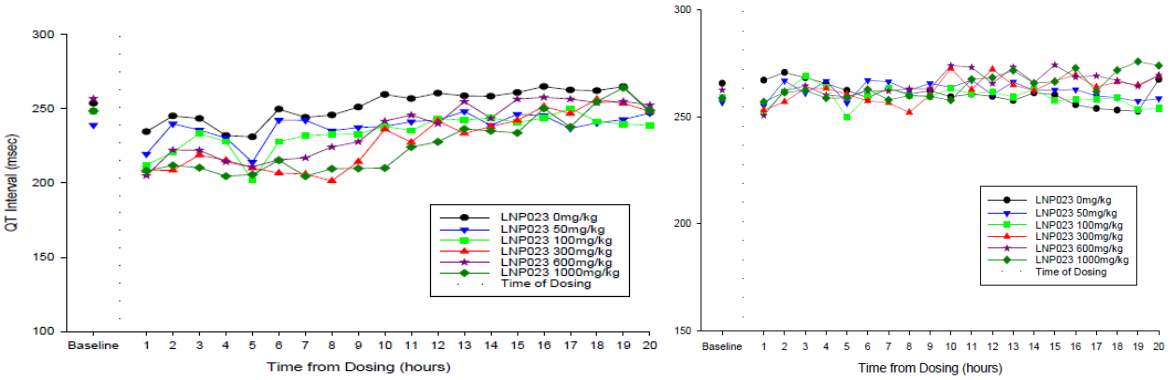


Figure 12: Absolute mean QT (left) and QTc (right) interval data – Rising dose phase

Rat

Iptacopan caused no changes in cardiovascular parameters in rats.

Respiratory and CNS safety

A safety pharmacology, GLP, study was conducted to determine the acute effects of iptacopan on the central nervous and respiratory systems in the rat. Iptacopan was administered orally (5 mL/kg) to groups of 6 male Wistar Han rats (approximately 9 to 12 weeks old) at doses of 100 and 1000 mg/kg for the respiratory function assessment. Comparisons were made with a respective vehicle control group. No test-item related biologically significant effects were observed at dose levels of 100 and 1000 mg/kg in the respiratory system of the male rat when compared to the vehicle treated group. For assessing CNS function, iptacopan was administered orally to groups of 6 male rats at doses of 112 and 770 mg/kg (doses adjusted based on formulation analysis results). Comparisons were made with a respective vehicle control group. At these doses, iptacopan did not produce behavioural or body temperature changes in the male rat when compared to the vehicle treated group.

2.5.2.4. Pharmacodynamic drug interactions

N/A

2.5.3. Pharmacokinetics

Analytical Methods

Iptacopan (free base) was quantified by high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) in plasma samples of rat, dog, mouse and rabbit. D5-iptacopan was used as the internal standard for LC-MS/MS quantification of iptacopan. Bioanalytical methods were validated for quantification of iptacopan in plasma of mouse, rat, dog, and rabbit under GLP conditions. The lower limit of quantification (LLOQ) in all species was 100 ng/mL using 10 µL plasma. Long-term stability of iptacopan at or below -60 °C was demonstrated for a period which covers the actual storage time of study samples.

Absorption

Following oral (po) dosing of non-radioactive iptacopan, T_{max} of iptacopan occurred between 0.6 and 1.51 h in mouse, rat, dog, and human. In all species, oral bioavailability was moderate with 46% in mouse, 40 to 68% in rat and 60% in dog. In rat, bioavailability was lower than absorption (81.8%, measured with radiolabelled iptacopan), indicating a low-to-moderate first-pass effect. Half-live was around 7h in mice, around 3h to 7h in rats and around 7h in dogs.

PK after repeated administration, dose proportionality and gender difference were derived from TK data. Data from the pivotal rat (26 wk) and dog (39 wk) study showed no consistent gender differences or deviations from dose-linearity. There was a slight increase of exposure after repeated dosing compared to the first dose.

Distribution

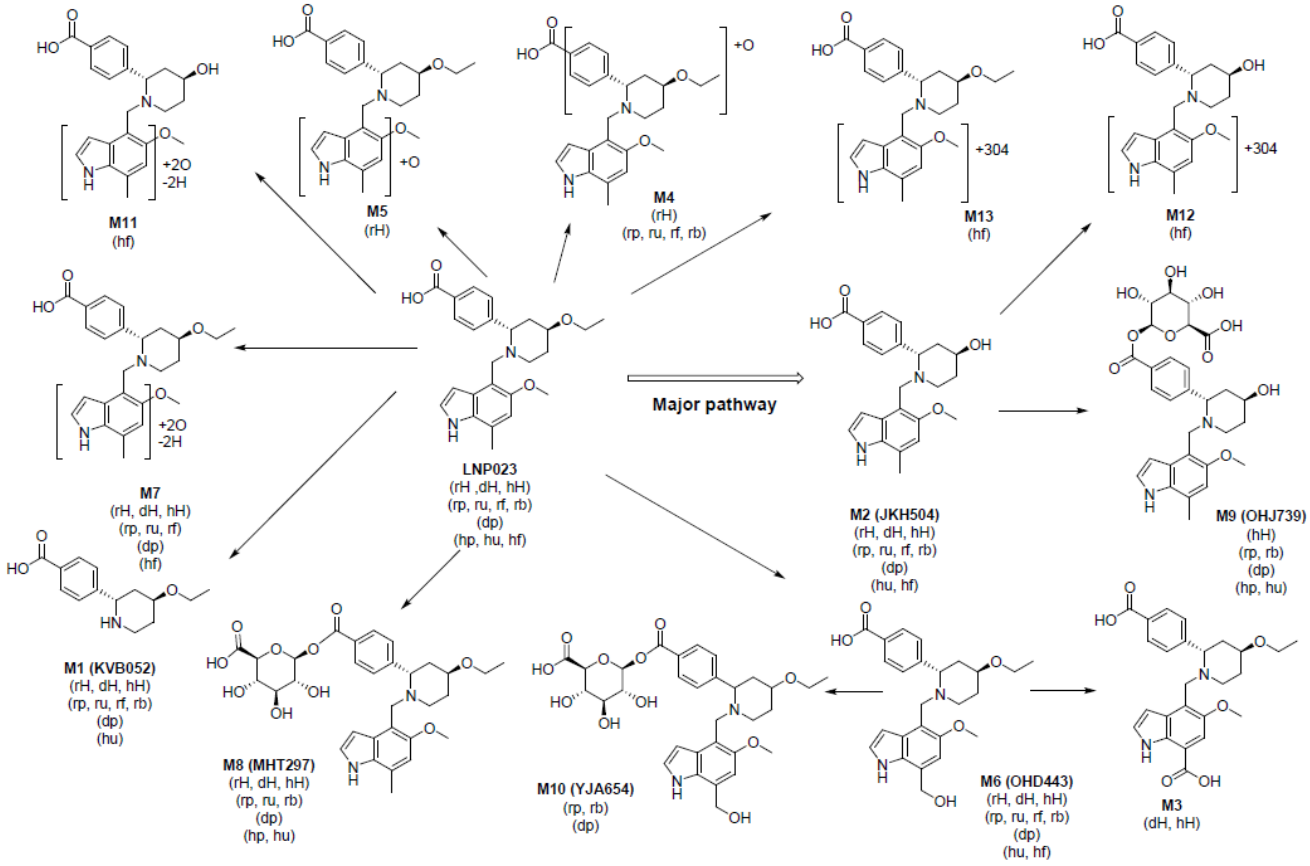
The blood to plasma (Cb/Cp) concentration ratios and plasma protein binding of iptacopan determined *in vitro* were concentration-dependent in all species. Cb/Cp ratios were 0.994 – 3.59 in rat, 0.717 – 1.38 in dog, and 0.6 – 2.14 in human for iptacopan concentrations of 10 – 10000 ng/mL.

The plasma protein binding of iptacopan *in vitro* was also concentration-dependent in all investigated species. At iptacopan concentrations of 10 – 10000 ng/mL, the unbound fractions in plasma (fu) ranged from 6.31 – 37.6% in mice, 4.03 – 37.3% in rat, 9.47 – 35% in dog, and 1.23 – 25.4% in human. With the lowest plasma concentration, the unbound fraction was lowest. With increasing plasma concentration, the unbound fraction increased and the bound fraction decreased, i.e. relatively less iptacopan was bound.

Relatively high tissue concentrations were found in liver, kidney and uveal tract. Some retention of iptacopan-related radioactivity in pigmented tissues of the eye was detected. This process seemed to be at least partly reversible.

Metabolism

Mostly, the metabolites are formed by oxidation, including oxidative dealkylation, and glucuronidation.



rH: rat hepatocytes; dH: dog hepatocytes; hH: human hepatocytes; rp: rat plasma; ru: rat urine; rf: rat faeces; rb: rat bile; dp: dog plasma; hp: human plasma; hu: human urine; hf: human faeces

Figure 13: Overview of the iptacopan metabolites and the matrices in that they were found

The *in vivo* plasma levels of the main iptacopan metabolites in rats, dogs and humans are compared in the following two tables, the ratios rat/human and dog/human, respectively are compiled. Metabolites M1 to M8 were present in similar or higher levels in animals compared to humans. Notably, M9 was present to a much lower extent in rat and dog plasma than in human plasma. M9 is a glucuronidation product of M2 and is – beside M8 – a main metabolite in human plasma.

Table 3: Ratio of LNP023 and metabolite exposures in male and female rat (Day 154, 750 mg/kg/day) versus human (Day 14, 200 b.i.d.)

Components	Ratio male rat / human	Ratio female rat / human
LNP023	3.71	5.19
M1	3.57	2.02
M2	1.06	0.664
M6	2.68	2.34
M7	6.61	5.62
M8	0.688	1.41
M9	0.0223	0.0211

Table 4: Ratio of LNP023 and metabolite exposures in male and female dog (Day 273, 150 mg/kg/day) versus human (Day 14, 200 b.i.d.)

Components	Ratio male dog / human	Ratio female dog / human
LNP023	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

Pharmacological activity of human metabolites

Metabolites M8 and M9, the two metabolites detected in human plasma, and M2 (most abundant metabolite in human faeces) were tested for pharmacological activity and shown to be between 27-fold and 150-fold less potent than parent; IC50 values ranged from 0.27 µM (M2) to 1.52 µM (M9), Study RD-2020-00095. Iptacopan had an IC50 of 0.01 µM.

Excretion

Across species, a large part of iptacopan-related material is recovered in the faeces. Around a quarter to a third of the iptacopan dose is excreted unchanged (table below).

Table 5: Excretion of iptacopan and iptacopan-related radioactivity after single i.v. and p.o. administration

Species **Gender** **Route of administration**	**Rat** **Male i.v.**	**Rat** **Male p.o.**	**Rat** **Male p.o.**	**Human** **Male p.o.**
Dose (mg base/kg)	**2**	**10**	**10**	**1.22**
Excretion in urine				
Radioactivity (% of dose)	5.68	5.09	4.79	24.8
Collection period (h)	0-168	0-168	0-168	0-216
Iptacopan (% of dose)	3.24	2.07	-	17.9
Collection period (h)	0-72	0-72	-	0-96
Excretion in faeces				
Radioactivity (% of dose)	84.6	94.4	92.8	71.5
Collection period (h)	0-168	0-168	0-168	0-216
Iptacopan (% of dose)	19.0	36.1	-	16.8
Collection period (h)	0-72	0-72	-	0.96

Excretion into bile

In bile duct-cannulated male rats dosed iv with 14C-iptacopan, the majority of the administered radioactivity was collected in the bile (79.4%) and only a minor part in the urine (13.0%). The presence of 4.21% of the radiolabelled dose in faeces indicated marginal intestinal secretion of iptacopan-related material. In bile, 11.7% of the dose was recovered as unchanged iptacopan.

M8 was not excreted in either faeces or urine. However, it was excreted in the bile (about 20% of the administered dose). There was no information of metabolism or excretion of M8.

Drug-drug interactions

Iptacopan as a victim drug via CYPs

The metabolism of iptacopan by different CYP enzymes was investigated in Studies DMPK R1500516 and DMPK R1600579.

In Study DMPK R1500516, radiolabelled (C-14) iptacopan was subjected to metabolism *in vitro* by human liver microsomes (HLM), human liver S9 and human cultured hepatocytes. For identifying the individual enzymes responsible for metabolite formation, HLM were incubated with selective inhibitors of various CYP enzymes. The maximal concentrations of the inhibitors were chosen based on published IC50 values. Furthermore, ^{14}C-iptacopan was incubated with commercially available individual CYP enzymes, called supersomes, instead of HLM.

In HLM, the metabolites M1, M2 and M6 in the absence of UDPGA, i.e. when glucoronidation is not possible (figure below). The amount of metabolites formed was small compared to residual parent drug. In the presence of UDPGA but in the absence of NADPH, i.e. when no CYP action is possible, M8 was formed.

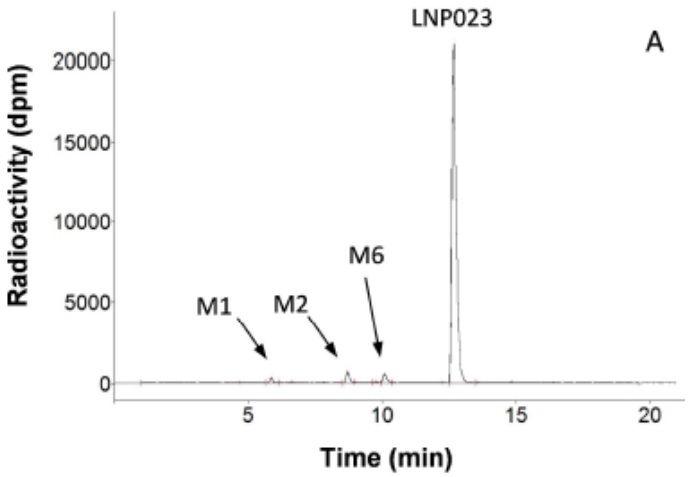


Figure 14: Radio-chromatogram of [14C]LNP023 incubation with HLM [14C]LNP023 was incubated at 10 µmol/L with HLM (2 mg/mL) for 1 hour at 37 °C with 1 mmol/L NADPH

Incubation of ^{14}C-iptacopan with supersomes revealed formation of M1, M2 and M6 by CYP2C8 (figure below). The resulting pattern was highly similar to incubation with HLM. Other CYP enzymes (CYP3A4, CYP1A1, CYP2C9 and CYP2D6) were only able to form M6.

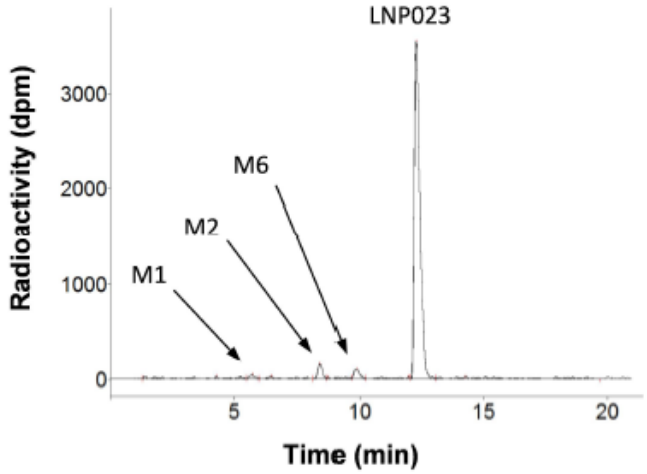


Figure 15: Radio-chromatogram of [14C]LNP023 incubation with CYP2C8 supersomes [14C]LNP023 was incubated at 5 µmol/L with CYP2C8 supersomes (50 pmol/mL) for 1 hour at 37 °C in presence of 1 mmol/L NADPH.

CYP involvement was also studied with selective CYP inhibitors. A relevant inhibition (by around 50% at the highest inhibitor concentration tested) was only seen with montelukast, a CYP2C8 inhibitor.

However, a mixture of inhibitors of different CYP enzymes produced a markedly stronger reduction of iptacopan metabolism than montelukast alone. The strongest inhibition was observed with a combination of an inhibitor of CYP2C8 (montelukast), CYP2C9 (sulfaphenazole), CYP2D6 (quinidine) and CYP3A4 (ketoconazole). Contribution of more than one enzyme is in line with the supersome findings described above.

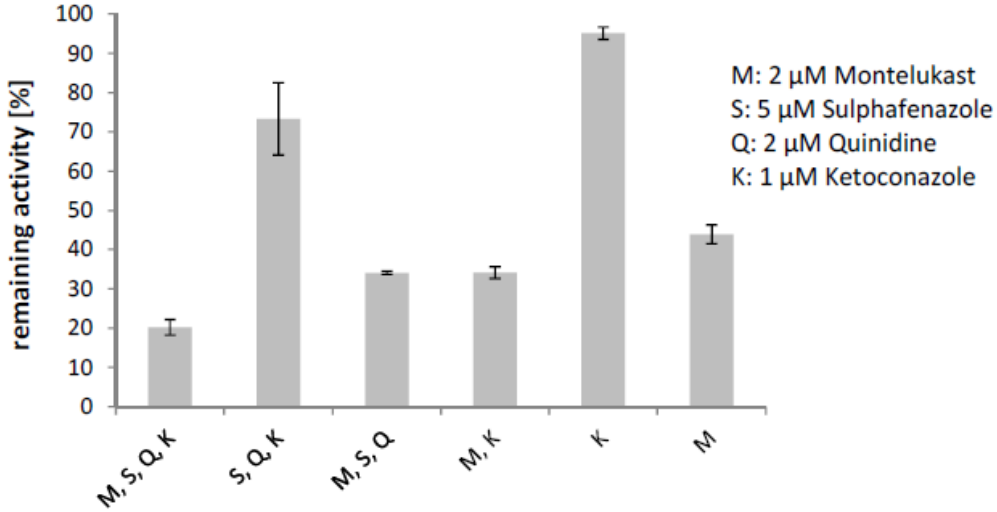


Figure 16: Inhibition of [14C]LNP023 metabolism in HLM by combinations of CYP450 selective inhibitors

In Study DMPK R1600579, recombinant CYP enzymes, expressed in insect cells, were used. The results were similar to those obtained with the supersomes described above. The contribution of the different CYP enzymes as derived from Study DMPK R1600579 is summarised in the figure below. The highest contribution came from CYP1A1. However, it should be noted that CYP1A1 is not present in the liver which diminishes its actual contribution to iptacopan metabolism in the body.

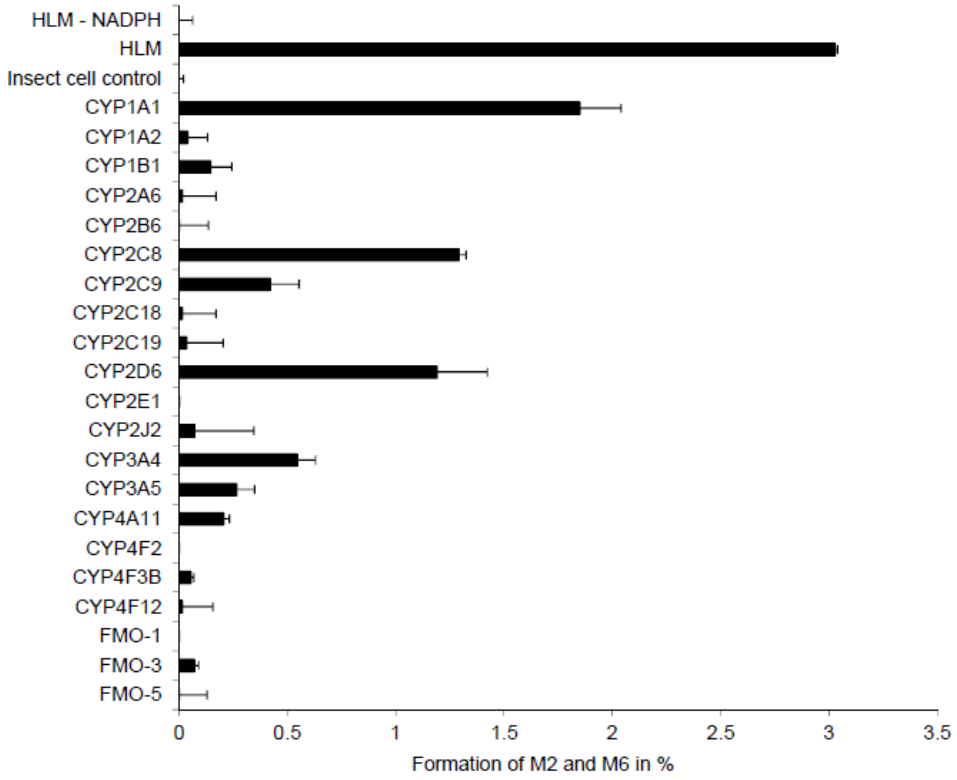


Figure 17: Biotransformation of LNP023 by recombinant human CYPs and FMOs

The biotransformation of [14C]LNP023 (10 µM) by human recombinant enzymes in insect cell microsomes expressing a single cytochrome P450 isoenzyme (50 pmol protein/mL, 60 min), FMOs (0.25 mg/mL, 60 min) and HLM (1 mg protein/mL, 60 min) was investigated. The formation of metabolites was determined by HPLC analysis combined with radio-detection. Mean values of 2 incubations were given.

This study also revealed that most CYP enzymes produced M6 only. M6 is not present in human plasma; in humans, it is only found in urine and faeces. M2, the precursor of M9, one of the main circulating metabolites, was only produced by CYP2C8.

Iptacopan as a victim drug via UGTs

Direct glucuronidation of iptacopan leads to metabolite M8. The UGT isoenzymes involved in its formation were investigated. It turned out that UGT1A1 and 1A8 contributed roughly equally, and 1A3 had a smaller contribution.

Iptacopan as a victim drug via transporters

The applicant tested permeability of Caco-2 cells and human hepatocytes for iptacopan. The former were used in search for efflux transporters and the latter for its ability to enter the liver. Involvement of transporters (uptake and efflux) was assessed by using pharmacological inhibitors of the most common transporters. By this means, the applicant estimated the fraction of carrier-mediated permeability vs. carrier-independent (passive) uptake. Based on the results of the former studies, the applicant tested efflux transporters and OATP carriers in more detail. In the latter study, MDCKII cells overexpressing the respective carrier were used.

Taken together, the applicant concluded that iptacopan is a likely substrate of all transporters tested as listed in the table below.

Table 6: Summary of the obtained results

Transporter assay	Maximum ER	Substrate
BCRP ML	5.98 ± 0.48 (at 10 µM)	Likely*
MDR1 ML	7.86 ± 0.91 (at 400 µM)	Likely*
Transporter assay	**Maximum fold accumulation**	**Substrate**
MRP2 VT	2.71 at 25 µM	Likely#
OATP1B1 UP	2.80 at 1 µM	Likely (K_m=82.5 ± 43.6 µM)**
OATP1B3 UP	4.39 at 0.25 µM	Likely (K_m= 17.1 ± µM)**

ER: efflux ratio (expressed as mean (n=3) ± SD), ML: monolayer assay, VT: vesicular transport assay, UP: uptake transporter assay

* If the efflux ratio is > 2 - and can be inhibited by a known inhibitor of the transporter - the TA can be considered being a substrate of the respective transporter.

\# If the ATP-dependent fold accumulation value is > 2 in transporter containing vesicles and can be inhibited by a known inhibitor of the transporter, then the TA can be considered a substrate of the transporter investigated.

** If the fold accumulation value is > 2 and can be inhibited by a known inhibitor of the transporter, then the TA can be considered a substrate of the transporter investigated.

However, when considering concentration-response relationships, it appears that iptacopan is a weaker substrate for OATP1B when compared to OATP1B3, see figure below.

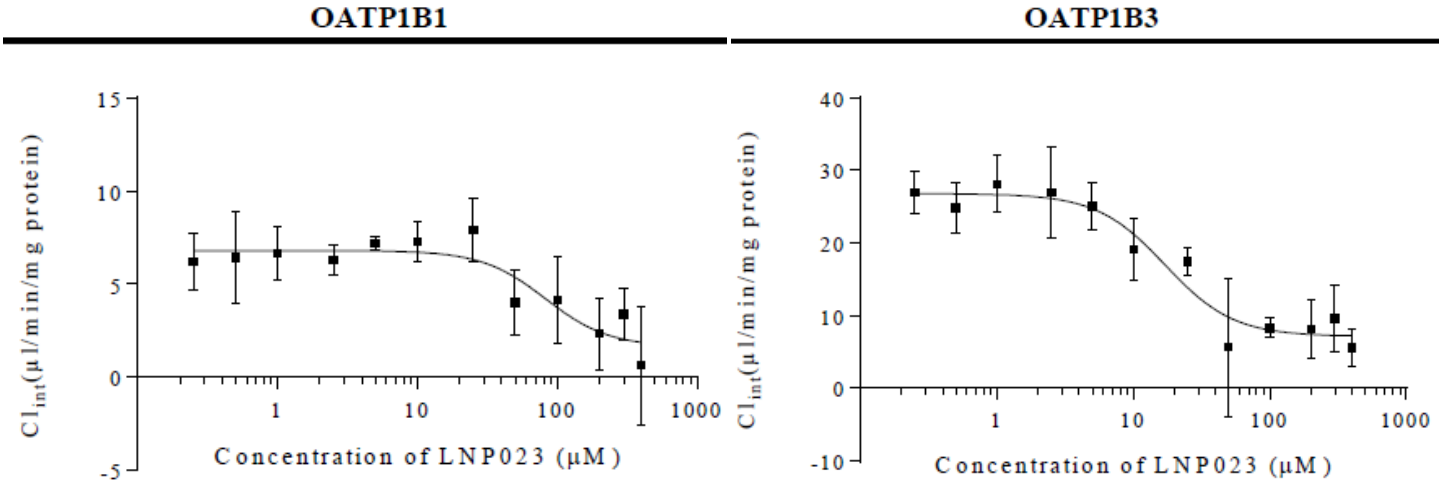


Figure 18: Curve fitting of LNP023 intrinsic clearance in OATP1B1- (left) and OATP1B3- (right) expressing cells in the uptake transporter substrate assay

The applicant performed a clinical DDI study testing iptacopan as victim for inhibitors of CYP2C8, clopidogrel, and of OATPs, cyclosporin. Both perpetrator compounds markedly increased iptacopan AUC by 36% and 50%, respectively.

Iptacopan as a perpetrator drug

The DDI concentration cut-off values which are relevant for the interpretation of the *in vitro* interaction signals according to the EMA guideline are presented in the table below.

Table 7 DDI concentration cut-off values

50×$C_{max(u)}$ (µM)	**25×Inlet $C_{max(u)}$** (µM)	**0.1×Dose/250 ml** (µM)
118,3	145,6	189,3

For the calculation of cut-offs, the following parameters were chosen: C_{max},ss = 4 µg/mL or 9.5 µM, fu=0.25, Cb/Cp=2.14 , F=1, ka= 0.1 min-1, Qh=1600 mL/min.

No inhibition of CYP or UGT enzymes was detected, with the exception of time-dependent inhibition of CYP2C8 by iptacopan, with KI of 179 µM and kinact of 0.0702 min^{-1}. *In vitro*, iptacopan was an inhibitor of OATP1B1 (but not OATP1B3) with a Ki of 24.9 µM, and of PgP (Ki=27.7 µM).

Induction of CYP3A4 mRNA by iptacopan was observed *in vitro*.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

A single-dose study was performed in monkeys. This study included ECG recording, and the most salient finding was QTc prolongation (further discussed in the safety pharmacology section). Pathology and histology were not performed. Laboratory evaluation revealed increase in neutrophils, decrease in lymphocytes and eosinophiles as well as increase in bilirubin, AST and ALT.

2.5.4.2. Repeat dose toxicity

Table 8: Overview of the repeat dose toxicity studies

Species and strain	Method of administration	Duration of dosing	Doses (mg/kg/day)	Additional evaluations	Study number
Rat, Wistar Hannover	Oral (gavage)	2 weeks	0, 100, 300, 1000		1370303
Rat, Wistar Hannover	Oral (gavage)	4 weeks (+ 4 weeks recovery)	0, 100, 300, 1000	Liver gene profiling and micronucleus assessment	1470568
Rat, Wistar Hannover	Oral (gavage)	13 weeks (+ 8 weeks recovery)	0, 50, 150, 500		1570195
Rat, Wistar Hannover	Oral (gavage)	26 weeks (+ 27 weeks recovery)	0, 50, 150, 750		1570193
Dog, Beagle	Oral (gavage)	2-weeks (with a rising dose phase)	50, 100, 300, 600, 1000 (rising dose phase); 0, 100, 300, 1000 (repeated dose phase)	Heart gene profiling	1470220
Dog, Beagle	Oral (gavage)	4 weeks (+ 4 weeks recovery)	0, 15, 50, 300	Heart, thyroid gland, liver gene profiling	1470567
Dog, Beagle	Oral (gavage)	13 weeks (+ 8 weeks recovery	0, 5, 30, 150	Testis gene profiling; bone marrow evaluation (Report 1920095)	1570194
Dog, Beagle	Oral (gavage)	39 weeks (+ 27 weeks recovery)	0, 5, 30, 150	Testis	1570192

The most consistent findings in the repeat-dose studies above were histological alterations in liver, testis/epididymis and thyroid gland. These changes were accompanied by macroscopic changes and alterations in serum parameters. All observations related to liver, thyroid gland or male reproductive organs are summarised in **Table 9** to **Table 11**. In addition to these findings that were consistent across studies, at least in one species, there were various organ findings which occurred in one or two dog studies only, e.g. cardiomyocyte degeneration or lymphoid depletion of lymph nodes. These findings are summarised in **Table 12**. All other inconsistent findings in the repeated-dose studies are considered less informative or were observed at very high doses (1000 mg/kg) only and are therefore not further discussed.

Regarding thyroid, the most consistent finding was follicular cell hypertrophy, which was observed in both toxicology species, rat and dog. Other thyroid findings were more variable. E.g. thyroid weight was either increased or decreased (the latter because of colloid depletion), and serum thyroid hormone levels were either unchanged, increased or decreased. TSH was unchanged in most cases.

Liver changes were mainly observed in dogs, and alterations in serum liver and bile markers imply biliary damage although liver cell necrosis also was observed.

Iptacopan effects on testis and epididymis were observed predominantly in dogs, consisting of testicular tubular degeneration, accompanied by cell debris in the epididymis. In rats, testicular degeneration was minimal if present at all. Increased prostate weight was occasionally found in both species. All described changes were reversible and were largely absent after the recovery periods.

In order to elucidate the mechanisms underlying the observed damage in testis, liver and heart as well as the follicular hypertrophy of the thyroid, the applicant conducted gene expression studies (using tissue from the repeat-dose studies) and conducted dedicated *in vitro* studies using primary cultured cells. However, no clear mechanism could be established. Changes were often highly variable and did not yield a fully consistent picture. Thyroid effects were attributed at least in part by the observation that iptacopan behaved as an antagonist at thyroid hormone receptors at high concentrations in a reporter gene assay.

Regarding the cause of follicular cell hypertrophy, the applicant considers the frequently assumed mechanism of increased hepatic degradation of thyroid hormones unlikely. This assumption is based on gene expression profiling in the liver, done in the 4-wk dog study. This analysis revealed that there was no modulation of thyroid hormone metabolising genes.

In the chronic toxicity study, one male dog at the highest dose level (margin to clinical exposure near 20-fold), was sacrificed 103 days after completed iptacopan administration due to irreversible non-regenerative severe anaemia associated with bone marrow fibrosis. During the treatment phase, haematology findings indicating inflammation and dyserythropoiesis were observed. No mechanism for the observed findings has been identified and a relation to treatment cannot be excluded.

Overview across studies: Liver, thyroid and male reproductive organ findings

Table 9: Liver

	control	low dose	mid dose	high dose
rat 2-wk		100 mg/kg	300 mg/kg	1000 mg/kg
rat 4-wk		100 mg/kg bilirubin ↑	300 mg/kg bilirubin ↑	1000 mg/kg bilirubin ↑, ALP ↑
rat 13-wk		50 mg/kg	150 mg/kg	500 mg/kg
rat 26-wk		50 mg/kg	150 mg/kg bilirubin ↑ (F)	750 mg/kg ALP ↑ (M), bilirubin ↑ (F)
rat 104-wk		150 mg/kg	300 mg/kg	750 mg/kg

		hepatocyte vacuolation	hepatocyte vacuolation	hepatocyte vacuolation
dog 2-wk		100 mg/kg	300 mg/kg	1000 mg/kg AST ↑, ALT ↑, ALP↑, bilirubin ↑; hepatocyte vacuolation
dog 4-wk		15 mg/kg bilirubin ↑ (M)	50 mg/kg bilirubin ↑ (F)	300 mg/kg bilirubin ↑; bile duct hyperplasia & bile pigment (1F)
dog 13-wk		5 mg/kg	30 mg/kg	150 mg/kg bile duct hyperplasia; single cell necrosis; mixed cell infiltrate
dog 39-wk		5 mg/kg	30 mg/kg	150 mg/kg centrilobular hepatocyte degeneration & focal necrosis & extramedullary haematopoiesis (1M); haemosiderin in Kupffer cells

Table 10: Thyroid

	control	low dose	mid dose	high dose
rat 2-wk		100 mg/kg weight ↑	300 mg/kg weight ↑	1000 mg/kg weight ↑
rat 4-wk		100 mg/kg	300 mg/kg	1000 mg/kg weight ↑ (F), weight ↓ (M) follicular cell hypertrophy (F)
rat 13-wk		50 mg/kg T4↑ (M)	150 mg/kg T4↑ (M)	500 mg/kg weight ↑ (M); follicular cell hypertrophy; T4↑ (M)
rat 26-wk		50 mg/kg weight ↑	150 mg/kg	750 mg/kg weight ↑, follicular cell hypertrophy
rat 104-wk		150 mg/kg diffuse C-cell hyperplasia	300 mg/kg diffuse C-cell hyperplasia; follicular cell hypertrophy (M)	750 mg/kg diffuse C-cell hyperplasia; follicular cell hypertrophy
dog 2-wk		100 mg/kg	300 mg/kg weight ↑; follicular cell hypertrophy	1000 mg/kg weight ↓
dog 4-wk		15 mg/kg weight ↓; follicular cell hyperplasia; colloid depletion; T4↓	50 mg/kg weight ↓; follicular cell hyperplasia; colloid depletion; T4↓	300 mg/kg weight ↓; follicular cell hyperplasia; colloid depletion; T4↓
dog 13-wk		5 mg/kg weight ↑ (F)	30 mg/kg weight ↑	150 mg/kg weight ↑; follicular cell hypertrophy
dog 39-wk		5 mg/kg weight ↑ (M); follicular cell hypertrophy (M)	30 mg/kg weight ↑ (M); follicular cell hypertrophy (M); T3↑ (M)	150 mg/kg weight ↑ (M); follicular cell hypertrophy; T3↑ (M)

Table 11: Male reproductive organs

	control	low dose	mid dose	high dose
rat 2-wk		100 mg/kg	300 mg/kg	1000 mg/kg
rat 4-wk		100 mg/kg	300 mg/kg	1000 mg/kg

rat 13-wk		50 mg/kg prostate weight ↑	150 mg/kg prostate weight ↑	500 mg/kg prostate weight ↑; minimal tubular degeneration (testis)
rat 26-wk		50 mg/kg	150 mg/kg Testis weight ↑	750 mg/kg Testis weight ↑; Ki67-positive cells (prostate)
rat 104-wk		150 mg/kg	300 mg/kg	750 mg/kg
dog 2-wk		100 mg/kg	300 mg/kg	1000 mg/kg
dog 4-wk		15 mg/kg	50 mg/kg	300 mg/kg testis weight ↓; epididymis weight ↓; germ cell exfoliation; oligospermia
dog 13-wk		5 mg/kg	30 mg/kg	150 mg/kg prostate weight ↑; testis weight ↑; epididymis weight ↑; tubular degeneration (testis); cell debris (epididymis)
dog 39-wk		5 mg/kg	30 mg/kg tubular degeneration (testis); cell debris (epididymis); prostate weight ↑	150 mg/kg testis weight ↓; tubular degeneration (testis); cell debris (epididymis); prostate weight ↑

Table 12: Other noteworthy findings (beside liver, thyroid and male reproductive organs)

	control	low dose	mid dose	high dose
rat 2-wk		100 mg/kg	300 mg/kg	1000 mg/kg
rat 4-wk		100 mg/kg TG↑ (M)	300 mg/kg proteinuria (M), TG↑ (M)	1000 mg/kg proteinuria, TG↑ (M)
rat 13-wk		50 mg/kg	150 mg/kg	500 mg/kg
rat 26-wk		50 mg/kg	150 mg/kg	750 mg/kg salivation
rat 104-wk		150 mg/kg	300 mg/kg	750 mg/kg
dog 2-wk		100 mg/kg	300 mg/kg	1000 mg/kg cardiomyocyte degeneration/ necrosis; gastrointestinal erosions/ulcers; kidney tubular degeneration; CK↑, creatinine↑, albumin ↓, protein ↓, metabolic alkalosis
dog 4-wk		15 mg/kg	50 mg/kg	300 mg/kg heart rate ↑; cardiomyocyte degeneration
dog 13-wk		5 mg/kg	30 mg/kg lymphoid depletion of lymph nodes	150 mg/kg heart rate ↑; lymphoid depletion of lymph nodes
dog 39-wk		5 mg/kg	30 mg/kg vomiting, salivation	150 mg/kg vomiting, salivation; heart rate ↑

2.5.4.3. Genotoxicity

A standard battery of *in vitro* and *in vivo* genotoxicity tests was performed with iptacopan.

Table 13: Overview of genotoxicity studies performed with iptacopan

Type of test / study ID / GLP	Test system	Concentrations / Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria / 1313007 / No	Salmonella strains TA98/TA100 Miniscreen Ames	+/- S9 (all strains): 0, 5, 15, 12, 250, 500 µg/plate	**Negative** for relevant increase in reverse mutations
Gene mutations in bacteria / 1470563 / Yes	Salmonella strains TA97a/TA98/TA100 /TA102/TA1535	+/- rat S9 (all strains): 0, 5, 16, 50, 160, 500, 1600, 5000 µg/plate Solvent: DMSO Plate incorporation method	**Negative** for relevant increase in reverse mutations Cytotoxicity: slight thinning of the background bacterial lawn at 5000 µg/plate in strain TA102 in the +/- S-9 and strains TA1535 and TA97a + S-9.
In vitro Micronucleus test / 1314004 / No	TK6 cells	+/- rat S9 3h incubation and 21h recovery, - S9 20h incubation (sampling at 48 h) 0 – 500 µg/mL Solvent: DMSO	**No increase in cells with micronuclei** +/- S9 Cytotoxicity: none
In vitro Micronucleus test / 1470562 / Yes	Primary human peripheral blood lymphocytes	+/- rat S9 3h incubation and 21h recovery, - S9 20h incubation (sampling at 48 h) 0 – 459 µg/mL Solvent: DMSO	**No increase in cells with micronuclei** +/- S9 Cytotoxicity: none
In vivo Micronucleus test / 1470568-Appendix 7/ Yes	WI (Han) rats (6/sex/group) micronuclei in peripheral blood reticulocytes as part of a 4-week oral (gavage) toxicity study in rats with a 4-week recovery period	0, 100, 300, 1000 mg/kg Sampling at necroscopy	**No increase** in the frequency of micronucleated reticulocytes (MN-RETs/[RETs+MN-RETs]) as compared to vehicle. TK at 300 mg/kg/day: M: $AUC_{0\text{-}24h}$: 170000 ng*h/mL F: $AUC_{0\text{-}24h}$: 186600 ng*h/mL

2.5.4.4. Carcinogenicity

Iptacopan was tested in carcinogenicity studies in Wistar Hannover rats for 104 weeks (**Table 14**) and in the rasH2 transgenic mouse model for 26-weeks (**Table 15**).

Table 14: Major findings in the rat carcinogenicity study (1770877)

Study ID / GLP	Dose / Route	Exposure (AUC)	Species / No. of animals	Major findings
1770877 / Yes	0 (water), 0 (vehicle), 150, 300, 300, mg/kg/d Oral gavage once daily Vehicle: 0.5% w/w methylcellulose Type 15 cPs, + 0.5% w/w and Tween 80	Day 176 (M+F): 150 mg/kg/d: Total: 59700 ng*h/mL 300 mg/kg/d: Total: 153000 ng*h/mL 750 mg/kg/d: Total: 620000 ng*h/mL Unbound: 343000 ng*h/mL	Wistar Hannover rats / 50 sex/dose TK: 10 sex/dose	**No indication of carcinogenicity at any dose level.** <u>Mortality:</u> at 750 mg/kg/d (M+F): survival ↓ termination of dosing in M at Week 94 after the survival rate reached 20/50 and early euthanasia of F on Week 99-100 after the survival rate reached 15/50 <u>Clinical findings:</u> ≥ 300 mg/kg/d (M+F): abnormal respiration↑ at 750 mg/kg/d: salivation (M+F) ↑; body weight gain (M)↓ ; body weight gain (F) ↑; food consumption (F) ↑ <u>Gross- and histopathology:</u> ≥ 150 mg/kg/d: diffuse C-cell hyperplasia (M+F) ↑; hepatocyte vacuolation, mottled liver (M+F) ↑ ≥ 300 mg/kg/d: thyroid follicular cell hypertrophy (M) ↑; at 750 mg/kg/d: thyroid follicular cell hypertrophy (F)↑; dark thyroids (F) Neoplastic changes In female rats, a statistically significant positive trend and increased incidence, when compared to the vehicle control only, were recorded for benign thymoma and combined benign thymoma/malignant thymoma in females administered 750 mg/kg/day. The incidences of benign thymomas in female rats were 7/49 (14%), 2/48 (4%), 6/50 (12%), 10/49 (20%) and 8/49 (16%) at 0 (water), 0 (vehicle), 150, 300 and 750 mg/kg/day, respectively. One malignant

				thymoma was observed in each of the low and high dose groups and the incidences of combined benign and malignant thymomas in female rats were 7/49 (14%), 2/48 (4%), 7/50 (14%), 10/49 (20%) and 9/49 (18%) at 0 (water), 0 (vehicle), 150, 300 and 750 mg/kg/day, respectively. Thus, a slightly increased incidence is noted in females at ≥300 mg/kg/day.

Table 15: Study details and main findings in 26-week carcinogenicity study in transgenic rasH2 mice (1770876)

Study ID / GLP	Dose / Route	Exposure (AUC)	Species / No. of animals	Major findings
1770876 / Yes	M/F: 0 (vehicle), 0 (water), 100, 300, 1000 mg/kg/d Oral Gavage, once daily Vehicle: 0.5% w/w methylcellulose Type 15 cPs, + 0.5% w/w and Tween 80 Positive control: 75 mg/kg N-methyl-N-nitrosourea (MNU)	Week 22, high dose: Iptacopan (M+F): 277000 ng*h/mL (total) OHJ739: M: 1530 ng*h/mL F: 1890 ng*h/mL (total)	RasH2 (001178-T [hemizygous], CByB6F1-transgenic[HRAS]2Jic) mice Tox: 25 M + F/dose TK: 3 M + 3 F (Co), 10 M + 10 F (treated)	**No indication of carcinogenicity at any dose level.** No macroscopic findings, no clinical findings. Non-neoplastic findings: M ≥100 mg/kg/d, F ≥300 mg/kg/d hepatocyte vacuolation in the liver Positive control: mortality 84-96% due to fatal malignant tumours

2.5.4.5. Reproductive and developmental toxicity

Reproductive toxicity was studied in the relevant animal species rats and rabbits under consideration of ICH S5. All pivotal studies were carried out in compliance with GLP regulations.

A male fertility study was performed in rats at doses up to 750 mg/kg/day. Sperm with morphological abnormalities increased statistically significant with dose. Sperm abnormalities were within historical controls and no correlating findings were observed during microscopic evaluation of testis or epididymis. All other parameters investigated were without findings. Therefore, the NOAEL for male

fertility was established at 750 mg/kg/day with a margin of exposure towards the human therapeutic exposure at the MRHD of 5.7 based on total exposure.

In the fertility and early embryo-embryonic development study, iptacopan doses of 100, 300 and 1000 mg/kg/day were applied to female rats. Iptacopan-related findings were increased % preimplantation losses, increased numbers of early resorptions, increased % post-implantation losses (including two animals [R0705 and R0718] that had 100% implantation loss), and reduced numbers of live embryos for each female were observed at the highest dose of iptacopan (1000 mg/kg/day). In the control group, the 100 mg/kg/day group and the 300 mg/kg/day group of iptacopan, post-implantation losses of 2.9 %, 4.6 % and 7.1 %, respectively, were observed, but were within the historical range. Based on these findings, the NOAEL was established at 100 mg/kg/day, with an estimated margin of exposure (total) of 2.4 compared to the exposure at the MRHD.

In the embryo-foetal development studies in rats, iptacopan showed no maternal toxicity up to the highest dose of 1000 mg/kg/day. Dose-related foetal skeletal variations (reduced ossification of the (inter-)parietal bones of the skull) were recorded in all dosing groups (100, 300, 1000 mg/kg/day) and were considered a non-adverse delay in ossification. All other embryo-foetal parameters were without relevant findings. The maternal and embryo-foetal NOAEL was established at 1000 mg/kg/day with a margin of exposure towards the exposure at the MRHD of approximately 5.4.

A dose-range finding study preceded the pivotal embryo-foetal development study in rabbits. No embryo-foetal toxicity was observed, but maternal toxicity in the high dose group of 600 mg/kg/day. Therefore, the doses were reduced for the pivotal study to 100, 250 or 450 mg/kg/day. In the pivotal study in rabbits, maternal toxicity was observed at 450 mg/kg/day. No substance-related embryo-foetal toxicity was observed in any dose group. Toxicokinetics showed significantly higher plasma exposure in rabbits compared to plasma levels in rats (e.g. 1000 mg/kg/day iptacopan AUC in the rat is about 278000 ng*h/mL whereas in the rabbit iptacopan exposures of already 732000 ng*h/ml were observed at 600 mg/kg/day), which may be the reason for the occurrence of maternal toxicity in the 450mg/kg/day dose group. However, there were no test-article-related malformations in the pups of the dams, treated with 450mg/kg/day. The maternal NOAEL was set at 250 mg/kg/day and the foetal NOAEL at 450 mg/kg/day, with total $AUC_{0\text{-}24h}$-based exposure margins of 3 and 7.8, respectively, compared to exposure at the MRHD.

In a pre- and postnatal development study performed in rats, no iptacopan-related adverse findings were noted during gestation, parturition or lactation in dams and the F1/ F2 generation following oral gavage administration of iptacopan at 100, 300 or 1000 mg/kg/day. The NOAEL was 1000 mg/kg/day with estimated total $AUC_{0\text{-}24h}$ exposure multiples of ~5.4 (or unbound AUC exposure multiples of ~18) compared to the exposure at the MRHD. Milk transfer of iptacopan was not investigated.

Juvenile toxicity studies were conducted in dogs. Findings were in general similar to what was seen in adult dogs. However, increased heart weight and aorta mineralisation observed in juvenile dogs only, appear to be specific to juvenile dogs due to an underdeveloped cardiovascular system.

2.5.4.6. Toxicokinetic data

Animal exposure in the different dose groups of the toxicology studies is tabulated below. Human therapeutic exposure for comparison was derived as follows:

$AUC_{0\text{-}24h}$ was used for comparison. Since in animals iptacopan was administered once daily whereas in humans it is to be administered twice daily the human $AUC_{0\text{-}24h}$ was calculated by doubling the $AUC_{0\text{-}12h}$ value derived from clinical FIH study CLNP023X2101 and measured at steady-state. C_{max} was also taken from this study under steady-state conditions. The following values for human exposure result:

$AUC_{0\text{-}24h}$ (human): 51400 ng*h/mL
C_{max} (human): 4120 ng/mL

Table 16: Data from the 26-week rat and 39-week dog pivotal studies.

Dose mg/kg	Mice		Rats		Dogs		Rabbits	Monkeys	Report
	male	female	male	female	male	female	female	male	
5					35500	32700			1570194
5					39300	37900			1570192
5					25500	30500			1770671
5					50100	46100			1870009
10								25700	1370389
15					91800a	88000a			1470567
30					148000	149000			1570194
30					183000	155000			1570192
30					113000	108000			1770671
30					182000	167000			1870009
50								127000	1370389
50			26000	22300					1570195
50			45700	30900					1570193
50					253000a	224000a			1470567
50							37800		1670322
100								326000	1370389
100			59000						1370303
100			61000	55600					1470568
100					561000				1470220
100	25500	27100							1770876
100				41500					1670321
100							51800		1670323
100		32000							1470564
150			69500	49700					1570195
150			101000	99300					1570193
150					733000	611000			1570194
150					840000	628000			1570192
150					568000	716000			1770671
150			88800	58100					1770877
150	66700	60000							1770875
150					841000	928000			1870009
250							153000		1670323
300								1270000	1370389
300			181000						1370303
300			170000	186000					1470568
300					2280000				1470220
300	63100	56000							1770876
300			170000	136000					1770877
300					2220000a	1810000a			1470567
300				123000					1670321
300							188000		1670322
300					1170000	1280000			1770671
300		127000							1470564
450							400000		1670323
500			249000	181000					1570195
500	152000	158000							1770875
600								1680000	1370389
600							732000		1670322
600						2580000			1770671
750			295000	369000					1570193
750			733000	498000					1770877

a AUC(0-23h) is given

2.5.4.7. Local Tolerance

N/A

2.5.4.8. Other toxicity studies

Impurities

A comprehensive assessment of potentially mutagenic impurities has been provided. All potential impurities were screened for a mutagenic potential by suitable *in silico* methods using expert rule-based (Derek Nexus, Lhasa Ltd.) and statistical-based (Case Ultra, MCASE Inc. and Sarah Nexus, Lhasa Ltd.) systems by using different version numbers during years 2014 – 2022. Four impurities were considered mutagenic and carcinogenic (ICH M7 class 1) and are controlled below AIs listed in ICH M7 or PDEs, which were previously derived and accepted. NHW362, a potential process impurity as well as a potential degradation product for iptacopan, revealed a mutagenic potential in the Ames test and human lymphocytes nucleus assay. An adequate GLP-conform *in vivo* Pig-a gene mutation and micronucleus assay in rats was negative and thus allows controlling it as a non-mutagenic impurity. For the three non-mutagenic impurities NHW362, 1H-imidazole and iodomethane compound-specific PDE limits were derived.

Phototoxicity

One *in vitro* and one *in vivo* study was performed. No clear evidence for phototoxicity was found (table below).

Table 17: Phototoxicity studies (in vivo study GLP-compliant)

Study type	Species and strain	Method of administration	Duration of dosing	Doses / Concentrations	Study number	Brief description
In vitro	Mouse BALB/c fibroblast cell line 3T3 clone A31	In vitro	NA	Up to 1000 µM	1315506	Iptacopan showed a photo irritation factor (PIF) of 7.0 indicating a weak phototoxicity potential.
In vivo	Mouse, BALB/c	Oral (gavage)	3 days	0, 100, 300, 1000 mg/kg/day	1470564	No clear evidence of *in vivo* photoactivation potential: Transient erythema at the first two days in the low- and mid-dose group and slight increase in average ear weight sub-sequent to irradiation.

Mechanistic studies

The following table summarises the mechanistic studies performed to address the organ toxicities observed in the repeated-dose studies. However, no clear conclusions could be drawn.

Table 18: Mechanistic studies (not GLP-compliant)

Study type	Species and strain	Method of administration	Doses (mg/kg/day)	Study number	Brief description
Testicular toxicity					
Testicular toxicity evaluation of LNP023 on the *ex vivo* rat model, Bio-AlteR	Rat, Sprague Dawley seminiferous tubules primary culture	*In vitro*	2, 20 and 200 µM, 3 times per week for 3 weeks	DIS R1720270	According to the applicant, the observed effects suggest an androgen-like effect of iptacopan
Testicular toxicity evaluation of LNP023 on the *ex vivo* dog model, Bio-AlteR	Dog, Beagle seminiferous tubules primary culture	*In vitro*	2, 20 and 200 µM	DIS R1720277	Similar results as in rats, see above
In vitro assessment on histone lysine demethylase enzymes JMJD1A and JMJD1B involved in spermatogenesis	Human recombinant (Sf9 cells)	*In vitro*	0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 µM	RD-2020-00447	These enzymes were investigated as a possible off-target responsible for the testicular toxicity of iptacopan. Iptacopan inhibited JMJD1A at high concentrations; IC50 was 130 µM
In vitro assessment on histone lysine demethylase enzymes JMJD1A and JMJD1B involved in spermatogenesis	Human recombinant (Sf9 cells)	*In vitro*	0.1, 0.3, 1, 3, 10, 30, 100, 200 µM	RD-2020-00448	See above
Thyroid effects					
In vitro assessment of androgen and thyroid hormone receptor activities	Human HEK293 recombinant reporter cells expressing androgen and thyroid hormone receptors	*In vitro*	10,20,40,80, 160, 200 µM	DIS R1820225	Activation of androgen (AR) und thyroid hormone receptor (TH) by iptacopan was tested via reporter gene (luciferase) assay. Iptacopan inhibited T3-activation of TH at ≥80 µM
Rat thyroid receptor binding assay	Wistar Rat liver	*In vitro*	0.03,0.1, 0.3, 1, 3, 10, 30, 100 µM	RD-2019-00025	No binding to rat TH was observed despite the inhibition of T3 action as described above
Mechanistic investigations on thyroid peroxidase activity *in vitro*	Dog thyroid microsomes	*In vitro*	5, 10, 20,40, 60,80, 100 µM	DIS R1470567b	Iptacopan did not inhibit TPO. Propylthiouracil served as positive control.
Haematotoxicity					
In vitro haematotoxicity Study	Stem cells and progenitor cells derived from canine bone marrow mononuclear cells	*In vitro*	0.002, 0.02, 0.2, 2, 20, 200 µM	1920024	Was done to further investigate bone marrow toxicity observed in the 39 wk dog study. Weak inhibition of progenitor cell burst forming unit (P-BFU), stem cells – granulocyte, erythroid, macrophage, megakaryocyte (SC-GEMM) and progenitor granulocyte and macrophage (P-GM) cells at highest iptacopan concentration tested. Positive control was cycloheximide
Gene expression analysis of progenitor erythroid cells (P-BFU) from in vitro haematotoxicity study 1920024	Stem cells and progenitor cells derived from canine bone marrow mononuclear cells	*In vitro*	0.002, 0.02, 0.2, 2, 20, 200 µM	DIS R1920024a	No meaningful changes in gene expression detected

In vitro haematotoxicity study	Stem cells and progenitor cells derived from human and canine bone marrow mononuclear cells	*In vitro*	0.002, 0.02, 0.2, 2, 20, 200 µM	2020007	Possible slight inhibition of P-GM at the highest iptacopan concentration tested
Gene expression analysis of progenitor erythroid cells (P-BFU) from *in vitro* haematotoxicity study 2020007	Stem cells and progenitor cells derived from canine bone marrow mononuclear cells	*In vitro*	0.002, 0.02, 0.2, 2, 20, 200 µM	DIS R2020007a	No meaningful changes in gene expression detected
Off-target effects					
Phenotyping of complement factor B knock out mouse	Mouse, complement factor B knockout (B6;129S4-Cfb<tm1Hrc>)	*Ex vivo*	NA	DIS R1820037	Several organs, including those identified as toxicological target of iptacopan, were investigated from FB KO mice. No changes were detected, indicating that the effects observed in the iptacopan toxicology studies were not related to FB inhibition but were off-target effects

Ecotoxicity/environmental risk assessment

As required by the respective guidelines the applicant provided an environmental risk assessment for the active ingredient iptacopan. Based on prevalence data Fpen has been refined and the calculated $PEC_{surface\ water}$ results in a value of 0.008 µg/l. As the PEC of 0.008 µg/l falls below the action limit of 0.01 µg/l no Phase II assessment was performed. Furthermore, an experimentally derived log K_{ow} of 0.3 was presented leading to the conclusion that no further screening for persistence, bioaccumulation and toxicity was deemed necessary.

Table 19: Summary of main study results

Substance (INN/Invented Name): Iptacopan hydrochloride			
CAS-number (if available): 2447007-60-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD107	0.12 at pH 5 0.3 at pH 7 0.085 at pH 9	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (based on prevalence)	0.008	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

2.5.5. Discussion on non-clinical aspects

Pharmacodynamics

The applicant studied the ability of iptacopan to inhibit Factor B in a series of *in vitro* and *in vivo* assays. Iptacopan binding was assessed in a time-resolved fluorescence resonance energy transfer (TR-FRET) based competitive binding assay using the catalytic domain of human FB. This binding assay was not performed with the full-length human Factor B, only with C-terminal portion (amino acids 460-

764). Hence, actual binding affinity of iptacopan to Factor B might differ to the calculated result of the applicant. However, respective control experiments showed similar binding of the two FB forms.

IC50 values calculated by the applicant (over various assays using serum and full blood) are low indicating effective blocking of the AP by iptacopan. Iptacopan is supposed to exert its effect only on the AP and to leave CP intact. The applicant tested the effect of LNP023 on complement dysregulation also in other diseases *in vitro* using sera from of patients with aHUS, C3G and MPGN.

The applicant conducted several *in vitro* studies in search for off-target receptors of iptacopan. Although not considered relevant by the applicant, iptacopan turned out to inhibit at least partially the oestrogen receptor alpha and the protein kinase mTOR at concentrations that are in the range of the human therapeutic plasma concentration. Thus, it is conceivable that an anti-oestrogenic activity of iptacopan contributed to its effects on male reproductive organs (see toxicology section below). However, if so, effects on the female reproductive tract would also be expected. These were not observed so that most likely this *in vitro* effect does not play a role *in vivo*.

Iptacopan had no effects on respiratory and CNS function in rats. Cardiovascular safety was addressed in rats, dogs and monkeys. In rats, blood pressure (BP) and heart rate (HR) were not affected by iptacopan; ECG parameters were not determined in this species. In dogs, there was a consistent, dose-dependent increase in HR and decrease in BP (systolic and diastolic) across all safety pharmacology studies performed; in general, doses of at least 300 mg/kg were needed to see these changes. Furthermore, a dose-dependent shortening of the PR interval in the ECG was observed as well as a slight prolongation of the QRS complex. The QT interval was shortened due to the increased HR; when corrected for HR, no clear effect of iptacopan on QT (i.e. QTc) remained. In a single-dose monkey study, QTc prolongation was observed at higher iptacopan doses (300 mg/kg, 20 ms prolongation and 600 mg/kg, 44 ms prolongation) that started around 9 hours after dosing and lasted until 20 hours after dosing. It is possible that this biologically implausible late increase in QTc was due to over-correction by the formula used. Nevertheless, even when it is assumed that the effect is true, it is reassuring that there is a rather high margin to human therapeutic C_{max}. In the monkey study, the dose of 100 mg/kg was the NOAEL in respect to QTc prolongation. At this dose, the C_{max} was 35600 ng/mL in the monkeys, whereas the human therapeutic C_{max} is 4120 ng/mL.

In vitro studies with hERG channels revealed that iptacopan inhibits these channels at high concentrations. Inhibition is detectable with 100 µM iptacopan, and the IC50 is 415 µM. This concentration is equivalent to 175,303 ng/mL. For comparison, the human unbound C_{max} is 763 ng/mL according to the applicant so that relevant hERG inhibition during therapeutic use of iptacopan is unlikely. Besides direct hERG inhibition, hERG activity can also be affected by disturbed trafficking of this channel into the cell membrane. The applicant addressed this possibility in a dedicated study, and no hints for impaired trafficking in the presence of iptacopan were found.

Because of the changes in HR, BP and ECG parameters in dogs, the applicant searched for direct effects of iptacopan on human cardiac myocytes *in vitro*. Iptacopan slightly increased the contractility of these cells. However, the underlying mechanism remained unclear, and also gene expression profiling performed with heart tissue from dogs did not yield further insight.

Pharmacokinetics

Iptacopan is orally available with a bioavailability of around 40% to 70%. Part of the reduced availability may be due to first-pass metabolism in the liver, not only to limited intestinal absorption. Half-life in animals is around 7 h; there was a slight increase in exposure with repeated dosing. Plasma protein binding was dependent on the actual plasma concentration. With increasing plasma concentration, the unbound fraction increased and the bound fraction decreased, i.e. relatively less iptacopan was bound. This is in line with a limited number of binding sites.

Iptacopan was mainly distributed in liver and kidney; a relatively high tissue concentration was also reached in the uveal tract of the eye. Notably, there was no distribution to the brain (approximately 2% of plasma concentration). Data suggest an affinity to ocular melanin; pigmented animals exhibited retention in the uveal canal and eyes for up to 336 hours. This process seems to be at least partly reversible. However, no ocular findings were observed in any of the toxicity studies in non-clinical species.

No data concerning iptacopan's potential to traverse the placental barrier and enter breast milk was presented. Relevant warnings regarding pregnancy have been included in SmPC sections 4.6.

Iptacopan is partially excreted unchanged. Otherwise, metabolites are formed by oxidation, including oxidative dealkylation, e.g. M2 and M6, or by direct glucuronidation (M8). M9 is formed by glucuronidation of M2. *In vitro* studies revealed that M2 is virtually exclusively formed by the CYP enzyme 2C8 whereas various CYP enzymes, including 2D6 and 3A4, are able to form M6. However, despite extensive M6 formation *in vitro*, rather little amounts of M6 appear to be formed *in vivo*. This was apparently due to the fact that CYP2D6, mainly responsible for forming M6, is expressed in the liver to a lower extent than CYP2C8, responsible for M2 formation. Furthermore, the substrate turnover rate appears to be markedly lower with 2D6 than with 2C8 at therapeutically relevant iptacopan concentrations. Most *in vitro* assays are optimised for the individual CYP enzymes so that this difference does not always become obvious. *In vivo*, only a small fraction of iptacopan is metabolised by CYP2D6, as demonstrated by using specific pharmacologic inhibitors of individual CYP enzymes, so that M6 is hardly formed. M8 was not excreted in either faeces or urine. However, it was excreted in the bile (about 20% of the administered dose). There was no information of metabolism or excretion of M8. Although the conversion of M8 to aglucones by the intestinal flora is a plausible hypothesis, it is important to recognise that other possibilities cannot be definitively excluded as M8 is a potential reactive metabolite. However, given the distribution data together with the toxicological profile, and that no major metabolites have been identified in humans, there is no imminent concern.

The data submitted by the applicant imply that metabolite M9 is hardly present in animal plasma. However, M9 is a main circulating metabolite in humans (albeit its AUC and steady-state plasma level appear to be below 10% of total iptacopan-related material in human plasma). As M9 is formed from M2 by glucuronidation, M2 can be used for toxicological qualification of M9.

Regarding drug-drug interaction (DDI), the role of CYP enzymes in the victim role of iptacopan are already discussed above. The main circulating human metabolite M8 is formed by direct glucuronidation, but more than one UGT type was involved so that inhibition of individual UGTs is not expected to affect iptacopan PK. Furthermore, iptacopan is a substrate of OATP carriers, mainly OATP1B3, and of efflux transporters, mainly MDR1, but also BCRP, at least according to one in-vitro study.

Iptacopan was able to inhibit several CYP enzymes and transporters, but high concentrations were needed in vitro so that the clinical relevance is most likely low.

The effect of PgP (MDR1) inhibition on iptacopan has been investigated in a clinical study, in the study with the OATP, BCRP and PgP-inhibitor cyclosporin.

Some of the interaction signals/risks were not sufficiently investigated by the applicant, and therefore these aspects need to be addressed further (see recommendations letter attached). These include iptacopan interaction risks via CYP induction (as a perpetrator) as well as interaction risk with iptacopan as a potential time-dependent inhibitor of CYP2C8; see also the clinical part of this overview. Until data becomes available, the proposed warnings are acceptable, with a slight rewording.

Toxicology

The most prominent and consistent findings across species (rat and dog) was follicular cell hypertrophy in the thyroid. Tubular degeneration in the testes, accompanied by cell debris in the epididymis, was mainly found in dogs. Only in the 13-week rat study, minimal testicular tubular degeneration was observed. Accordingly, no major effects of iptacopan fertility were observed in the male fertility study conducted in rats. Only a slightly higher percentage of sperm with morphological abnormalities was observed with iptacopan medium and high dose compared to control. However, the applicant stated that these results were within the historical control range.

In order to estimate the relevance of the testicular findings in animals (mainly dogs) for humans, the applicant defined testicular effects as Adverse Events of Special Interest (AESI) and routinely determined the plasma levels of reproductive hormones (androgens, FSH and LH; see clinical AR). However, sperm parameters such as morphology, count and motility, were not obtained. In dogs, there were small, equivocal increases in androgens in some animals. Sperm parameters in dogs were highly variable, and no clear iptacopan-related changes were observed. Therefore, it is questionable whether sperm analysis in humans would have provided additional relevant information.

Testicular findings were largely limited to the high-dose groups whereas thyroid changes were already observed at low dose (but not in vehicle controls). Signs for biliary liver changes and liver cell alterations (vacuolation, degeneration) were mainly observed in dogs but also – to a much lesser extent – in rats. With some exceptions, these findings were limited to high-dose animals. Cardiomyocyte degeneration was observed in two dog studies employing rather high doses (300 mg/kg and 1000 mg/kg). Less consistent were additional alterations in the male reproductive tract (e.g. changes in prostate weight), and some findings were observed in individual studies only, such as degeneration of renal tubules or lymphoid depletion of lymph nodes.

When thyroid hypertrophy is accompanied by liver changes, it is often assumed that liver enzymes are increased that metabolise thyroid hormones so that the thyroid gland has to increase production which in turn leads to hypertrophy. However, based on gene expression studies, the applicant claimed that thyroid hormone degrading enzymes were not increased. Furthermore, thyroid follicle hypertrophy was also observed in rat although in this species the liver changes were less pronounced than in dogs. In addition, TSH was not increased in most studies, which would be expected in case of faster thyroid hormone turnover. Thus, the mechanism underlying the follicular hypertrophy remains unclear. The applicant has conducted dedicated mechanistic studies. It was observed that iptacopan inhibits thyroid hormone receptors at rather high concentrations (in the range of 100 µM in the presence of 2 nM T3). It is not clear whether this effect is responsible for the observed thyroid effects in the toxicology studies.

Within the toxicology program, a remarkable finding was the variability of findings in the different studies. Although some changes in liver, testes and thyroid were observed in most studies, at least in one species, the actual nature of the findings was rather inconsistent. E.g., thyroid findings included increased as well as decreased weight and increased, decreased or unchanged levels of thyroid hormone levels in the serum. Furthermore, in many studies findings were only made in the high-dose group, but in other studies alterations were already observed in the low-dose group. Histological testicular changes were observed in the repeated-dose studies but not in the male fertility study despite same species, dose and duration were used. It was pointed out that the findings in the reproductive organs in rats were rather mild (they were more pronounced in dogs) so that the difference between the general toxicity study and the fertility study can be explained by normal across-study variability.

Juvenile toxicity studies were conducted in dogs with findings similar to those in adult dogs. However, increased heart weight and aorta mineralisation observed in juvenile dogs only, appear to be specific to

juvenile dogs due to an underdeveloped cardiovascular system. Since iptacopan is currently just indicated for the treatment of adults, observations from the juvenile toxicity studies will be most relevant when children are included in the patient population.

The metabolites M8 and M9 are acyl glucuronides that in general are regarded to possess a potential for reactivity. The potential of iptacopan to form reactive intermediates, forming covalent drug protein adducts was tested in human liver microsomes and hepatocytes. The observed levels of covalent drug-protein adduct formation in both assay systems were below defined thresholds of concern. This indicates that the levels of drug-protein adduct formation are not of concern, and additionally, no signs of liver toxicity were observed in the clinical chemistry parameters in either clinical or non-clinical studies, However, the mechanism behind the bile duct hyperplasia observed in the shorter studies in dogs, has currently not been elucidated.

Two possible iptacopan-related mortalities were presented, one in the 26-week study on rat (skin-lesions and sores) as well as in the 39-week study in dog (bone marrow fibrosis). At the highest dose level in the 39-week study a male dog was sacrificed day 103 of recovery. The cause of demise of the dog was a severe, non-regenerative anaemia associated with bone marrow fibrosis. In addition, increased levels of fibrinogen concentrations consistent with inflammation during the study may have complicated the non-regenerative anaemia. The underlying mechanisms remain unknown and a relation to treatment cannot be excluded.

Bile duct hyperplasia was observed in the shorter studies in dogs together with increased bilirubin, increased Kupffer cell pigmentation and single cell necrosis along with cell infiltrate consistent with inflammation. Single cell necrosis was found simultaneously in one female (13-week toxicity study, female No. 0112), however, lacking other signs of liver injury such as elevated transaminases or microscopic signs of toxicity associated to the metabolites M8 or M9. The increased bilirubin serum levels and pigmentation of Kupffer cells in non-clinical species is a likely result from increased breakdown of red blood cells.

Iptacopan was negative in *in vitro* Ames tests, in *in vitro* micronucleus tests in TK6 cells and primary human peripheral blood lymphocytes and in an oral *in vivo* micronucleus test performed in rats up to exposures approximately 3-4-times (total) and 5-6-times (unbound) the human exposure at the MRHD based on AUC. Based on the provided studies, iptacopan is not considered to be genotoxic *in vitro* and *in vivo*.

Iptacopan was tested in a GLP-compliant oral gavage 26-week carcinogenicity study in transgenic rasH2 mice at 100, 300, and 1000 mg/kg/d. The high dose was based on the NOAEL of dose-range findings studies, the maximal feasible dose and a dosing volume of 10 mg/kg. No macroscopic nor clinical findings were reported. Non-neoplastic findings were restricted hepatocyte vacuolation in the liver. The positive control MNU exhibited the expected carcinogenic effect. There was no indication of carcinogenicity of iptacopan at any dose level. Therefore, iptacopan can be considered as not carcinogenic in transgenic rasH2 mice at doses up to 1000 mg/kg/d (NOAEL). This corresponds to exposure margins approximately 4-times to the human AUC at the MRHD.

Plasma analysis of the metabolite M9 (OHJ739) was also included in the study (non-GLP). The M9 mean AUC_{0-24} at the highest dose 1000 mg/kg/day following repeated administration of iptacopan was 1.71 µg*h/mL in males and females combined. This exposure corresponds approximately to 50% of the estimated M9 exposure based on data from 6 healthy volunteers (Study CLNP023X2203).

Furthermore, a GLP-compliant study evaluating carcinogenicity of iptacopan when administered to rats via oral gavage at 150, 300 and 750 mg/kg/d for at least 104 weeks was provided. The highest dose level of 750 mg/kg/day was selected based on the NOAEL in the 26-week rat toxicity study. Increased mortality was noted for animals administered 750 mg/kg/day, but no cause of demise was considered

directly related to the toxicity of iptacopan. Increased mortality was probably gavage-related due to highly concentrated test-article applied at study start until Week 21. Non-neoplastic iptacopan-related findings consisted of a generally dose-related increase in thyroid follicular cell hypertrophy at ≥ 300 mg/kg/day in males and 750 mg/kg/day in females, a minor increase in the incidence and/or severity of diffuse C-cell hyperplasia for the thyroid and a minor increase in the incidence and/or severity of hepatocyte vacuolation for the liver in all iptacopan-treated groups in line with what has been observed in rat repeat-dose toxicity studies. There was no indication of carcinogenicity of iptacopan at any dose level. Observed neoplasms such as Skin/Subcutis M Squamous cell carcinoma or thymoma were considered of low incidence and incidental. Overall, iptacopan can be considered as not carcinogenic in rats up to 750 mg/kg/d. This corresponds to exposures 12-times (or 44-times unbound fraction) the AUC at the MRHD. (see SmPC section 5.3).

Diffuse C-cell hyperplasia is generally not considered pre-neoplastic (Brändli-Baiocco *et al.* 2018), and no evidence of an increase in focal C-cell hyperplasia or a progression to neoplasia was noted.

It is agreed that no iptacopan-related neoplastic findings were noted in male rats. In female rats, a statistically significant positive trend and increased incidence, when compared to the vehicle control only, were recorded for benign thymoma and combined benign thymoma/malignant thymoma in females administered 750 mg/kg/day. The incidences of benign thymomas in female rats were 7/49 (14%), 2/48 (4%), 6/50 (12%), 10/49 (20%) and 8/49 (16%) at 0 (water), 0 (vehicle), 150, 300 and 750 mg/kg/day, respectively. One malignant thymoma was observed in each of the low and high dose groups and the incidences of combined benign and malignant thymomas in females were 7/49 (14%), 2/48 (4%), 7/50 (14%), 10/49 (20%) and 9/49 (18%) at 0 (water), 0 (vehicle), 150, 300 and 750 mg/kg/day, respectively.

The findings were statistically significant (with trend and pairwise comparison test of high dose versus vehicle control) compared to vehicle controls when evaluated at the 5% level. However, there was no statistical significance increase compared to water controls, and no clear dose-response was noted in females.

Overall, the statistically significant increase of thymomas in female rats, versus only one of the two control groups is regarded as likely incidental and not iptacopan related given the observation in one sex only, the lack of a clear dose response, incidences close to that in the historical control data set and that reported in the literature in female Han Wistar rats. Thus, iptacopan can be considered as not carcinogenic in rats up to 750 mg/kg/day, corresponding to exposures 12-times the AUC at the MRHD. However, it should be noted that malignancy has been added as an important potential risk based on mechanistic plausibility and harmonisation with that of other complement inhibitors.

In the fertility study in male rats, the number of sperms with morphological abnormalities increased statistically significant with dose. However, sperm abnormalities were discussed in context of historical controls. Microscopic evaluation of testis or epididymis did not reveal any correlating findings. In contrast, effects on sperm, as well as testes and prostate, were observed in repeated-dose toxicity studies. (see SmPC section 4.6 and 5.3).

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures between 2- and 8-fold the human exposure at the maximum recommended human dose (MRHD) (see section 5.3). Oral administration of iptacopan during organogenesis did not induce adverse embryo or foetal toxicity up to the highest doses, which correspond to 5-fold (for rats) and 8-fold (for rabbits) the MRHD of 200 mg twice daily based on AUC. There are no data on the effects of iptacopan on milk production, this is reflected in the SmPC section 4.6. A decision must be made weighing the benefit of breastfeeding vs the treatment for the mother.

Iptacopan hydrochloride $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log K_{ow} does not exceed 4.5.

The phototoxic potential of iptacopan was analysed in an in vitro study which showed weak positive results and were followed up by in an in vivo study on mice where slight erythema, transient scabs, dryness (low and high dose) as well as increased ear weight were reported. No clinical adverse events indicative of phototoxicity have been recorded; however, no dedicated phototoxicity study has been performed in humans.

In overall, the *in vitro* PD studies could appropriately characterise the mode of action of iptacopan. *In vivo* PD was limited by the fact that no animal model of PNH exists. PK studies revealed potential for DDI (iptacopan as victim) since a main metabolite in humans appears to be formed by a single CYP enzyme (CYP2C8).

Furthermore, OATP appears to be an important transporter for iptacopan. A complete toxicology program was performed that revealed effects of iptacopan on liver, thyroid, heart and male reproductive organs. The applicant conducted several mechanistic studies, but the cause of these effects could not be elucidated. Therefore, effects on these organs were specifically monitored in the clinical studies.

2.5.6. Conclusion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 20: Overview of studies with clinical pharmacology evaluation in healthy volunteers

Study code	Study type Phase I	Number of healthy subjects	Formulation and strength	Dose
X2101	First in human and food effect	78 iptacopan 22 placebo	CSF 5, 25 and 100mg	SAD (Part 1) fasted: 5, 10, 25, 50, 100, 200, or 400 mg (n=6 per dose group) or Placebo (n=14) MAD (Part 2) fasted: 25, 50, 100 or 200 mg b.i.d. for two weeks (n=6 per dose group) or Placebo (n=8) Food effect (Part 3): SD 100 mg (n=12)
A2101	Mass balance	6	neat capsule	100 mg [^{14}C]iptacopan free base amounted to 100µCi (3.7MBq)
X1102	Japanese ethnic sensitivity	24 iptacopan 6 Placebo	CSF 25 and 100mg	SD of 25, 100 and 400 mg 10 subjects per each cohort (8 iptacopan: 2 Placebo)
A2104	Drug drug interaction	55	CSF 100mg	SD 100 mg
A2105	Hepatic impairment	16 healthy 8 mild HI 8 moderate HI 6 severe HI	FMI 200mg	SD 200 mg
A2107	QTcF exposure-response	24 iptacopan 8 placebo	FMI 200mg	SD Cohort 1: 400 mg (n=6) Cohort 2: 800 mg (n=9) Cohort 3: 1200 mg (n=9)

CSF = early CSF with iptacopan-HCl anhydrate; FMI = late CSF / FMI with iptacopan-HCl monohydrate

Table 21: Overview of studies with clinical pharmacology evaluation in patients

Study code	Study type and Phase	Number of patients	Formulation and strength	Dose
X2201	II	PNH patients on SoC treatment eculizumab Cohort 1 n=10 Cohort 2 n=6	CSF 5, 25 and 100mg	Cohort 1: 200 mg b.i.d.+SoC, Cohort 2: minimum of 50 mg b.i.d. for two weeks followed by dose increase to 200 mg b.i.d + SoC based on LDH. Cohorts 1 and 2: down titration using 25 mg and then 10 mg qd if not entering extension
X2202	II	C3G patients Cohort A n=16 Cohort B n=11	CSF 5, 25 and 100mg	Weekly dose escalation from 10 to 200 mg b.i.d., maintain at 200 mg b.i.d. for nine weeks, then weekly down titration from 200 mg b.i.d. to 10 mg b.i.d. and stop (if not entering extension)
X2203	II	IgAN patients Part 1 n=46 Part 2 n=66	CSF 5, 25 and 100mg	Part 1: placebo b.i.d (n=14) 10 mg b.i.d (n=9) 50 mg b.i.d (n=8) 200 mg b.i.d (n=15) Part 2: placebo b.i.d. (n=11) 10 mg b.i.d. (n=11) 50 mg b.i.d. (n=11) 100 mg b.i.d. (n=22) 200 mg b.i.d. (n=11)
X2204	II	Treatment naive PNH patients Cohort 1 n=7 Cohort 2 n=6	CSF 5, 25 and 100mg	Sequence 1: up-titration from 25 mg to 100 mg to 200 mg b.i.d. Sequence 2: Up-titration from 50 mg to 200 mg b.i.d.
C12301	III SAT	Treatment naive PNH patients n=40	FMI 10 and 200mg	200mg b.i.d.
C12302	III pivotal RCT	PNH patients previously treated with SoC (eculizumab/ ravulizumab) n=97	FMI 10 and 200mg	200mg b.i.d. (n=62) Control/Anti-C5 therapy (n=35)

CSF = early CSF with iptacopan-HCl anhydrate; FMI = late CSF / FMI with iptacopan-HCl monohydrate

Table 22: Overview of PNH clinical studies

Study, purpose and status	Design, population	Duration	No. patients enrolled/ treatment(s)
Pivotal Phase III APPLY-PNH (C12302) Efficacy, safety Ongoing Data cut-off date: 26-Sep-2022	Multicentre, randomised, active-comparator controlled, open-label study Adult PNH patients with residual anaemia despite prior anti-C5 treatment	48 weeks: 24-week randomised treatment period 24-week treatment extension period)	Randomised treatment period N=97: Iptacopan 200 mg b.i.d. (N=62) Anti-C5 treatment (eculizumab vs. ravulizumab) (N=35) Treatment extension period N=94: Iptacopan 200 mg b.i.d.
Supportive Phase III APPOINT-PNH (C12301) Efficacy, safety Ongoing Data cut-off date: 02-Nov-2022	Multicentre, single arm, open-label study Adult PNH patients naïve to complement inhibitor therapy (including anti-C5)	48 weeks: 24-week core treatment period 24-week treatment extension period	N=40 Iptacopan 200 mg b.i.d.
Phase II CLNP023X2204 Efficacy, safety, PK/PD Completed LPLV: 09-Feb-2022	Multicentre, randomised, open-label multiple dose study Adult PNH patients with active signs of haemolysis, without concomitant complement inhibition	12-week core treatment period and treatment extension period up to 2 years	N=13 Cohort 1: N=7 Iptacopan 25 mg b.i.d. (4 weeks) followed by iptacopan 100 mg b.i.d. (8 weeks) Cohort 2: N=6 Iptacopan 50 mg b.i.d., 4 weeks (N=6) followed by iptacopan 200 mg b.i.d. (N=5) 2-year extension period: N=5 Iptacopan 200 mg b.i.d.

Study, purpose and status	Design, population	Duration	No. patients enrolled/ treatment(s)
Phase II **CLNP023X2201** Efficacy, safety, PK/PD Completed LPLV: 28-Feb-2022	Open-label, single arm, multiple dose study Adult PNH patients with signs of active haemolysis on anti-C5 treatment	Cohort 1 Part 1: 13 weeks Part 2: treatment extension up to 3 years Cohort 2 Part 1: 13 weeks Part 2: treatment extension up to 3 years	N=16 Cohort 1: N=10 Iptacopan 200 mg b.i.d.+ eculizumab (N=10) Cohort 2: N=6 Iptacopan 50 mg b.i.d.+ eculizumab with option to switch to iptacopan 200 mg b.i.d. + eculizumab from Day 15 (N=5 patients received 200 mg b.i.d.)
Phase II **CLFG316X2201**** Efficacy, safety, PK Completed LPLV: 24-May-2022	Open-label, single arm study PNH patients with haemolysis	Treatment period 1: 29 days Treatment period 2: 48 weeks Treatment period 3: 260 weeks Treatment period 4: up to 21 weeks*	N=10 (LFG316) N=10 (LFG316) N=10 (LFG316) N=9 Week 1 to Week 4: LGF316 + iptacopan Week 5 to Week 20: Iptacopan 200 mg b.i.d.
CLNP023C12001B **PNH REP** Long-term safety, tolerability Ongoing Safety data cut-off date: 26-Jan-2022	Multicentre, open-label, roll-over extension programme (REP) Adult PNH patients who have completed Phase II or Phase III studies with iptacopan	36 months	N=94 Iptacopan 200 mg b.i.d.

*Only treatment period 4 with iptacopan 200 mg b.i.d. is included in the pooled PNH analyses.
** Of note, in 2015 Novartis initiated clinical investigations of another terminal pathway inhibitor, LFG316 (anti-C5 monoclonal antibody) in PNH patients. The programme ended for strategic reasons and as a result, 9 patients initially enrolled in study LFG316X2201 switched to iptacopan 200 mg b.i.d. treatment and joined the PNH REP study.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacology program of iptacopan included PK evaluation after single- and multiple-dose in healthy subjects and patients with PNH, C3G and IgAN, mass balance in healthy subjects, as well as evaluation of food effect, hepatic and renal impairment and DDI. In addition, PopPK, PKPD and exposure-response modelling was performed.

I*n vitro* studies were performed to characterise the permeability, plasma-protein binding, blood distribution, metabolism and transporter DDI potential.

Methods

Bioanalytical methods

Methods R1600743, R1600744 and R2200309 for plasma, urine and ultrafiltrate (assessment of iptacopan protein binding) consisted of solid phase extraction followed by liquid chromatography tandem mass spectrometry (LC-MS/MS) in multiple reaction monitoring (MRM) mode using electrospray ionisation (ESI) technique.

Method R1900470 (urine and plasma) and method R1501031 were based on protein precipitation followed by dilution of the supernatant and analysis of diluted sample extract by LC-MS/MS in MRM mode using ESI.

Furthermore, in support of study A2105, a method for quantification of unbound fraction of iptacopan in plasma ultra-filtrate was fully validated. Unbound iptacopan was recovered using Ultrafiltration Centrifree device, followed by solid phase extraction and analysis of the processed samples by LC-MS/MS in MRM mode using ESI.

Methods were successfully cross validated between the three respective BA sites. All clinical study samples were analysed within the demonstrated stability period and all analyses met the predefined acceptance criteria described in the BA study plan and standard operating procedures.

In addition, in the mass balance study A2101, acidification of plasma was done to stabilise expected acyl glucuronide metabolites and to investigate the potential impact of sample acidification on LNP023 PK parameters. LNP023 concentrations were measured in non-acidified and acidified plasma.

Evaluation and qualification of models

A one-compartment model with first order absorption lag time and linear elimination was used to describe the PK of iptacopan in patients with IgAN, C3G and PNH indications for the 100 mg and the 200 mg dose. Body weight on CL/F was already included in the base model, while baseline eGFR and ethnicity covariates on CL/F were found to be significant in the final model after applying the full model approach. Retained covariates were increasing apparent clearance with increasing body weight and baseline eGFR; decreasing CL/F in China and other Asians, compared to the rest of the world ethnicities. Parameter estimates are listed below.

Table 23: Parameter estimates of the final popPK model of LNP023 in Phase II and Phase III studies (PopPK pool)

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%)		

*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 m² and reference ethnicity was "rest of the world" (i.e., all ethnicities excluding other Asian, Chinese, and Japanese).
Location: /vob/CLNP023C1/mas/mas_1/model/pgm_001/TASK01_PNH_POPPK_Submission
Code: ScriptsA_04_popPKdiagnostics
Output: Output/mod9/A_04_popPKdiagnostics.docx
Created: Dec 20 2022 06:52:05

A popPK model fitted to all iptacopan doses was used as sensitivity analysis model and led to similar results compared to the final model, differing with regard to bioavailability which was modelled with a sigmoid function in order to account for the under-proportional PK in lower doses. The simulation analysis predicted lower exposure of C3G patients and similar exposure of IgAN patients, compared to PNH patients.

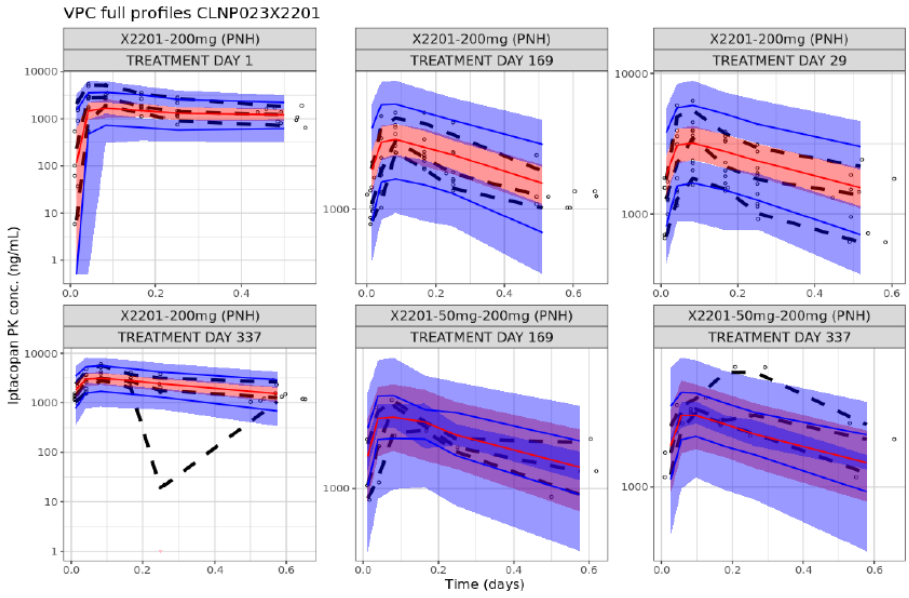


Figure 19: VPC full profiles for PNH patients in study CLNP023X2210

Sigmoid E_{max} direct response models were developed to describe the exposure-response relationships between iptacopan concentrations and complement pathway biomarkers in healthy volunteers and patients with PNH, C3G, or IgAN disease (**Figure 20**). Response parameters of E_{max}, EC50 and EC90 were estimated for all three biomarkers. The Wieslab assay showed the clearest exposure response relationship whereas the relationship was less evident for plasma Bb and soluble plasma C5-b9.

The exposure-response analysis was used to simulate missed dose scenarios and is regarded as supportive for justifying the b.i.d. 200 mg dosing scheme.

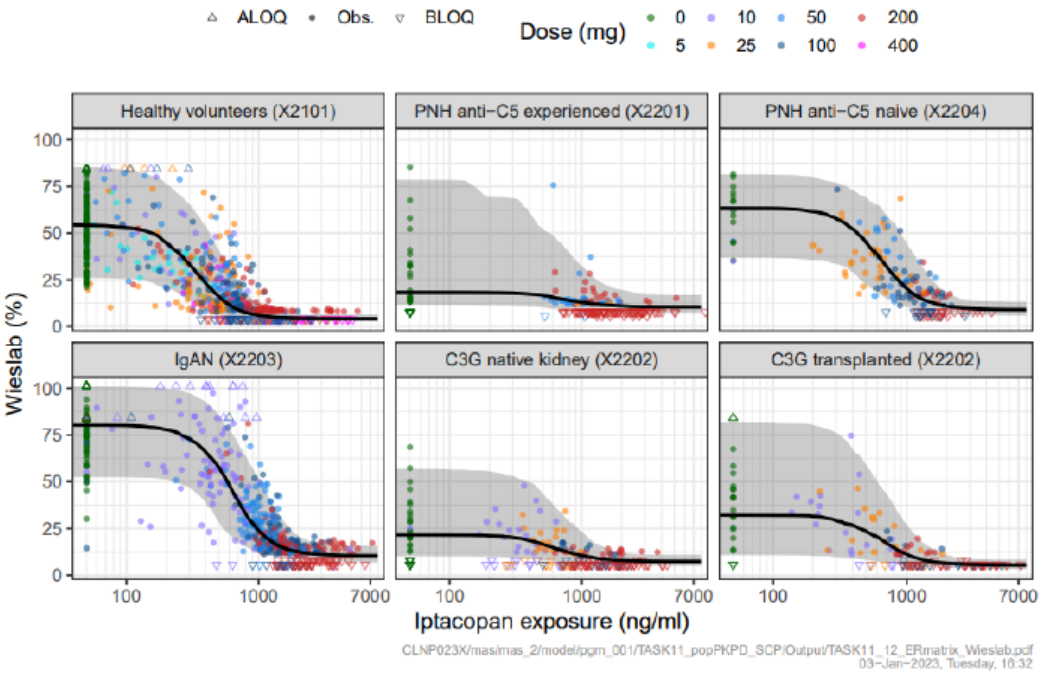


Figure 20: Exposure-response of Wieslab assay

Absorption

In vitro permeability

In study DMPK R1500730, the permeability of iptacopan through Caco-2 cell monolayers was investigated in the concentration range of 0.5-400 µM. The Papp AP-BL direction was $0.727*10^{-6}$ cm/s and Papp BL-AP of $6.32*10^{-6}$ cm/s at the highest concentration. Efflux ratios were > 4 at all concentrations, up to 6.89. It was concluded that LNP023 showed low to moderate passive permeability through Caco-2 monolayers with efflux transporters involved. In the presence of transporter inhibitors, AP-BL permeability was $2.35*10^{-6}$ cm/s. The predicted human absorption in presence or absence of efflux transporter activity (based on Papp and Pm data, respectively) was 47 and 61%.

In vivo absorption

Absolute bioavailability of iptacopan in humans was not evaluated, but data in animals and human mass balance data suggested an absolute bioavailability of approximately 70%.

Study X2101 evaluated PK and PD of ascending single and multiple oral doses of iptacopan in healthy male and female volunteers under fasted and fed (Part 3 only) conditions.

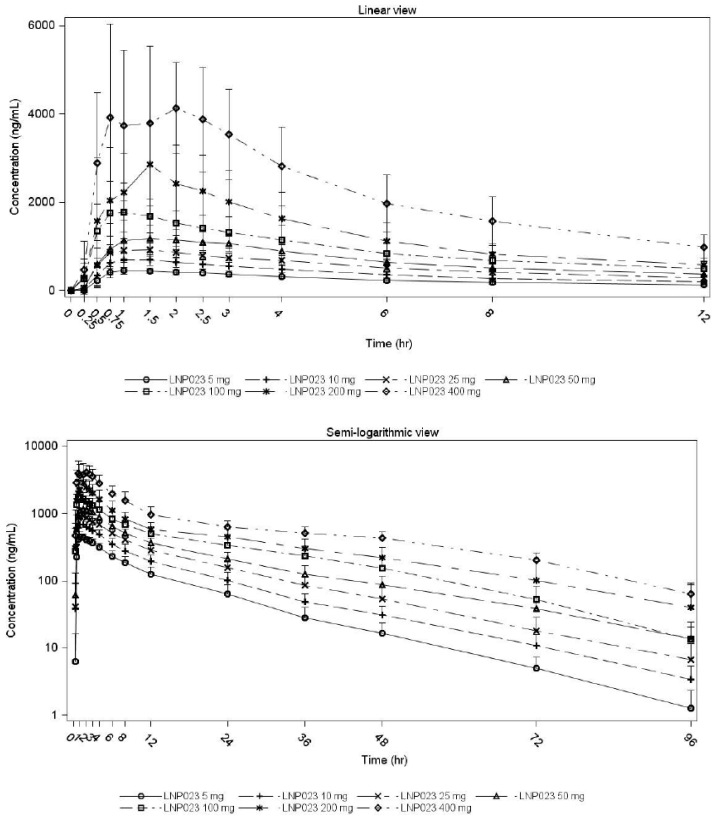


Figure 21: Arithmetic mean (SD) concentration-time profiles SAD cohort Part 1

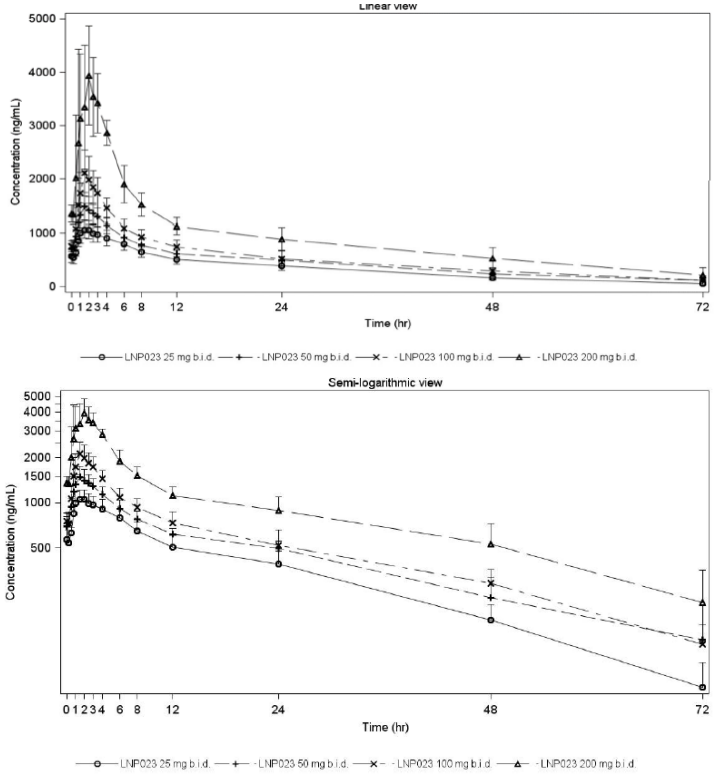


Figure 22: Arithmetic mean (SD) concentration-time profiles Day 14 MAD cohort Part 2

Consistent with a half-life of approximately 24 hours, steady-state was reached by Day 5 with C_{trough} at 200 mg b.i.d. of approximately 1200–1300 ng/mL (**Figure 23**).

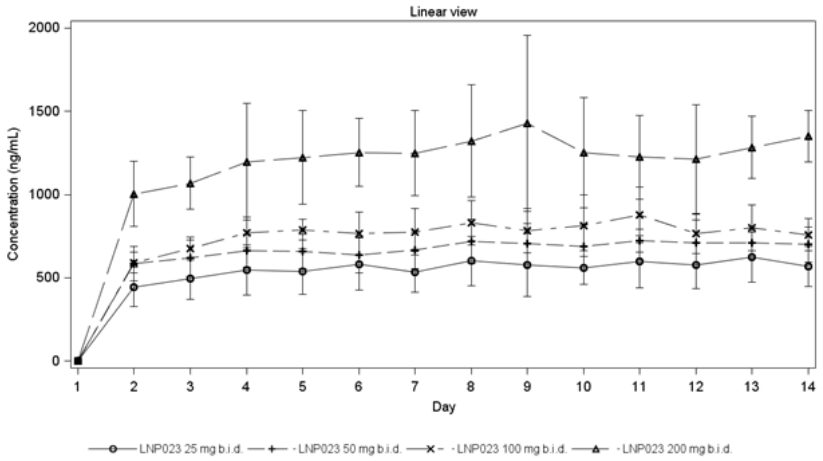


Figure 23: Pre-dose (C_{trough}) iptacopan concentrations by dose after multiple b.i.d. doses from day 0 to day 14 in study CLNP023X2101

Table 24 and Table 25 summarise pharmacokinetic parameters from single and multiple dose studies in healthy volunteers.

Table 24: Pharmacokinetic parameters after iptacopan single doses in HV (geo-mean (%CV); T_{max} median (min-max))

dose (mg)	n	t_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng×h/mL)	AUC_{inf} (ng×h/mL)	$t_{½}$ (h)	CL/F (L/h)	Vz/F (L)	formulation	study
5	6	1.01 (0.767-2.48)	462 (14.3%)	-	5160 (26.5%)	13.8 (17.5%)	0.97 (26.5%)	19.3 (32.1%)	CSF	X2101
10	6	1.00 (0.750-1.52)	703 (18.8%)	-	8240 (24.3%)	15.1 (14.8%)	1.21 (24.3%)	26.4 (22.0)	CSF	X2101
25	6	1.13 (0.750-2.50)	974 (22.6%)	-	12400 (22.1%)	14.8 (31.3%)	2.01 (22.1)	43.1 (40.7%)	CSF	X2101
25	8	1.50 (1.00-3.00)	1140 (19.5%)	12100 (25.6%)	12100 (25.9%)	13.0 (16.8%)	2.06 (25.9%)	38.7 (22.0%)	CSF	X1102 Japanese HV
50	6	1.26 (0.733-3.00)	1360 (11.2%)	-	17200 (19.9%)	17.8 (30.1%)	2.90 (19.9%)	74.4 (38.5%)	CSF	X2101
100	6	1.00 (0.750-2.00)	1930 (26.1%)	-	24700 (28.3%)	13.3 (20.1%)	4.05 (28.3%)	77.8 (25.8%)	CSF	X2101
100	8	1.75 (1.00-5.50)	2360 (32.6%)	27100 (31.9%)	27500 (32.5%)	14.7 (26.9%)	3.64 (32.5%)	77.2 (27.4%)	CSF	X1102 Japanese HV
100	18	1.51 (1.00-4.00)	1940 (24.4%)	27100 (25.5%)	27700 (26.2%)	16.5 (29.3%)	3.61 (26.2%)	85.7 (28.6%)	CSF	A2104 Iptacopan alone Cohort 1
100	20	2.00 (1.00-4.00)	1800 (26.2%)	25900 (23.2%)	26600 (24.8%)	15.8 (34.1%)	3.76 (24.8%)	85.5 (22.8%)	CSF	A2104 Iptacopan alone Cohort 2
200	6	1.13 (0.500-2.50)	3140 (24.6)	-	34800 (35.6%)	16.2 (51.1%)	5.75 (35.6%)	134.0 (26.2%)	CSF	X2101
200	16	2.50 1.00-4.00)	3490 (25.1%)	52300 (23.7%)	52300 (23.8%)	19.6 (32.8%)	3.82 (23.8%)	108 (29.1%)	FMI	A2105 Healthy control
400	6	1.25 (0.750-2.50)	4900 (30.7%)	-	59400 (28.3%)	17.1 (18.6%)	6.74 (28.3%)	166.0 (23.6%)	CSF	X2101
400	6	1.06 (0.833 - 1.98)	10400 (30.6%)	84600 (29.8%)	89900 (34.6%)	21.3 (59.9%)	4.45 (34.6%)	137.0 (44.7%)	CSF	A2107
400	8	2.25 (1.00-3.00)	7890 (18.0%)	75700 (27.8%)	72300 (19.7%)	21.6 (55.2%)	5.53 (19.7%)	149 (28.4%)	CSF	X1102 Japanese HV
800	9	2.00 (1.00-4.05)	11400 (16.6%)	123000 (20.2%)	129000 (24.6%)	20.2 (50.1%)	6.19 (24.6%)	181.0 (25.4%)	CSF	A2107
1200	9	2.52 (0.767-4.00)	16600 (27.0%)	162000 (11.6%)	167000 (11.0%)	20.7 (29.2%)	7.20 (11.0%)	215.0 (31.6%)	CSF	A2107

Table 25: Steady-state PK parameters after iptacopan multiple doses in HV – study X2101 (geo-mean (%CV); T_{max} median (min-max))

dose (mg)	n	study day	t_{max} (h)	C_{max} (ng/mL)	C_{ave} (ng/mL)	$AUC_{tau,ss}$ (ng×h/mL)	$t_{½}$ (h)	CL/F (L/h)	Vz/F (L)	accumulation ratio
25 bid	6	1	1.24 (0.983-2.93)	879 (21.7%)	505 (17.6%)	6060 (17.6%)	6.82 (14.8%)	-	-	-
	6	14	1.51 (0.983-2.03)	1090 (16.6%)	-	9070 (15.1%)	17.8 (25.8%)	2.76 (15.1%)	71.0 (32.5%)	1.51 (6.4%)
50 bid	6	1	1.00 (0.733-1.50)	1380 (18.6%)	668 (12.1%)	8010 (12.1%)	6.73 (23.3%)	-	-	-
	6	14	1.49 (1.00-3.00)	1510 (18.5%)		11400(12.2%)	21.9 (49.2%)	4.38 (12.2%)	138.0 (37.3%)	1.44 (7.4%)
100 bid	6	1	1.75 (1.48-2.50)	1490 (19.3%)	743 (12.2%)	8910 (12.2%)	5.86 (19.7%)	-	-	-
	6	14	1.50 (0.75-2.50)	2220 (20.0%)	-	14300 (12.5%)	22.2 (13.7%)	6.98 (12.5%)	224.0 (15.8%)	1.63 (9.3%)
200 bid	6	1	0.875 (0.50-2.45)	3630 (28.7%)	1560 (18.0%)	18800 (18.0%)	5.31 (39.8%)	-	-	-
	6	14	2.02 (0.75-3.00)	4020 (23.8%)	-	25400 (15.2%)	23.3 (42.1%)	7.89 (15.2%)	265.0 (45.3%)	1.36 (14.4%)

Bioequivalence

The formulation used in the clinical studies was an immediate release hard gelatine capsule for oral administration filled with neat drug substance, i.e., without any excipients.

- The early phase clinical study formulation (CSF) contained iptacopan anhydrous hydrochloride salt modification A in dose strengths of 5, 25, and 100 mg iptacopan hard gelatine capsules.
- The late phase CSF differed from the early phase CSF by the change from the anhydrous to the monohydrate HCl-salt modification HB of iptacopan in dose strengths of 10, 50, 100 and 200 mg iptacopan hard gelatine capsules. For the pivotal phase III clinical studies, the 10 and 200 mg strengths were utilised.
- The final market image (FMI) formulation (200 mg) strength differed from the late phase CSF only by minor changes in capsule colour and imprint.

As the difference between the formulations was not expected by the applicant to impact iptacopan bioavailability, no relative bioavailability study comparing formulations was conducted.

Influence of food

In study X2101 food effect was evaluated after a high-fat high-calorie meal ("standard FDA") and showed no significant effect on PK parameters.

Table 26: Food effect: Summary statistics of PK parameters

PK parameter (Unit)	Fasted N=12	Fed N=12
AUCinf (hr*ng/mL)	26900 ± 7720 (28.7%)	23600 ± 5430 (23.0%)
AUClast (hr*ng/mL)	25700 ± 6410 (24.9%)	23000 ± 4980 (21.7%)
CL/F (mL/hr)	3990 ± 1120 (28.0%)	4480 ± 1150 (25.8%)
C_{max} (ng/mL)	1850 ± 501 (27.1%)	1820 ± 670 (36.8%)
T1/2 (hr)	17.8 ± 7.07 (39.7%)	16.1 ± 4.63 (28.7%)
T_{max} (hr)	1.76 (0.750 - 4.00)	1.26 (0.750 - 4.00)

The mean renal clearance was identical in fasted (662 mL*ng/mL / (hr*ng/mL)) and fed states (661 mL*ng/mL / (hr*ng/mL)), i.e. CLr of 11 mL/min.

Influence of gastric pH

The clinical dose strength of 200 mg iptacopan hydrochloride modification A (CSF) and hydrate HB (FMI and commercial formulations) can be fully dissolved in 250 mL of media, as shown by a solubility of at least 1.22 mg/mL (over the pH range of 1.2-6.8 at 37 °C), indicating a highly soluble drug substance. Therefore, no study was performed to investigate the influence of gastric pH.

Distribution

In equilibrium dialysis in the concentration range of 10-10000 ng/ml the plasma protein binding (PPB) to isolated proteins was 98.8-74.6%, with the highest PPB at the lowest concentration (DMPK 1500362). The fraction bound to human serum albumin was 28.4%, to α1-acid-glycoprotein 9.25% and lipoproteins 16.0% and was not concentration dependent.

In plasma from Factor B knock-out mice no concentration dependency was found while plasma from the wild-type mice showed a concentration dependent binding. These data suggested that the binding of iptacopan to plasma proteins mainly related to saturable high-affinity binding to its drug target Factor B. **Figure 24** illustrates the concentration dependence of the unbound fraction (fu) from plasma

samples from studies X2101 and A2105. At plasma concentrations greater than 750 ng/mL to 1000 ng/mL (inflection point) there was an over-proportional increase in the unbound concentration of iptacopan which the applicant suggested as near-complete saturation of Factor B, consistent with target-mediated drug disposition (Smith *et al.* 2018).

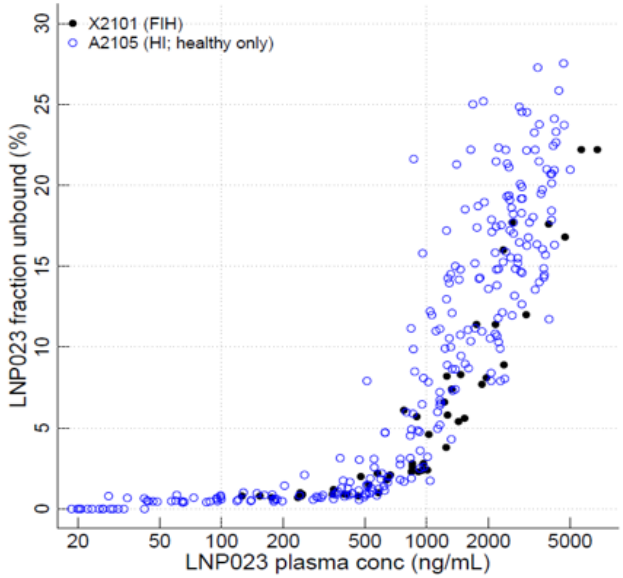


Figure 24: Concentration dependency of PPB of iptacopan in human from studies X2101 and X2105

In vitro at a concentration of 10 ng/ml iptacopan the distribution into human plasma was fp 93.3±1.4% with a mean blood-to-plasma ratio of 0.6.

In study X2101 in HV the apparent volume of distribution increased from (geo-means) 19.3 L at the lowest dose of 5 mg to 215 L at the highest dose of 1200 mg, and 265 L at the proposed 200 mg b.i.d. dose in steady-state.

Elimination

The elimination of iptacopan included multiple hepatic and extrahepatic pathways, predominantly by metabolism in the liver. Based on data of the mass balance study, from *in vitro* human hepatocyte clearance and from assuming that 12% of the dose was the result of biliary elimination (as observed in rats), presumably by PgP, the relative contributions of iptacopan clearance pathways in human were estimated in the PBPK model (report R2270401). CYP, renal elimination, and direct UGT-mediated clearance contributions were estimated to be 57.02%, 20.50%, and 7.63%, respectively, of the total clearance, with CYP2C8, CYP2D6, UGT1A1 and 'other' enzymes contributing 55.88%, 1.14%, 7.63% and 2.85%, respectively.

In study X2101 apparent clearance Cl/F in HV increased from (geo-means) 0.97 L/h at the lowest dose of 5 mg to 7.2 L/h at the highest dose of 1200 mg. Mean apparent elimination half-life increased from 13.8 h to 20.7 hours, respectively. At 200 mg bid at steady-state apparent clearance was 7.9 L/h and $t_{1/2}$ 23.3 hours. The mean percentage after 100 mg LNP023 recovered in urine was slightly higher in fasted state (14.1%) than in fed state (12.6%). The mean renal clearance was identical in fasted (662 mL*ng/mL / (hr*ng/mL)) and fed states (661 mL*ng/mL / (hr*ng/mL)), i.e. CLr of 11 mL/min.

Metabolism

Study CLNP023A2101 was an open-label mass balance study after single oral administration of one capsule containing 100 mg and 3.7 MBq (100 µCi) of [^{14}C] iptacopan in 6 healthy non-smoking male volunteers under fasted conditions.

The arithmetic mean recovery of total radioactivity in urine and faeces was 96.4% (SD: 1.63%), i.e. 96.2 mg of the administered 100 mg dose of [^{14}C]LNP023. Radioactivity was excreted predominantly in faeces (71.5% [SD: 2.79%] or 71.4 mg). Excretion in urine was 24.8% (SD: 1.71%) corresponding to 24.8 mg overall with 22.6 mg within the first 24 hours, indicating the minimum absorption. A mean 93.9% of the dose was recovered within 96 hours in faeces and urine.

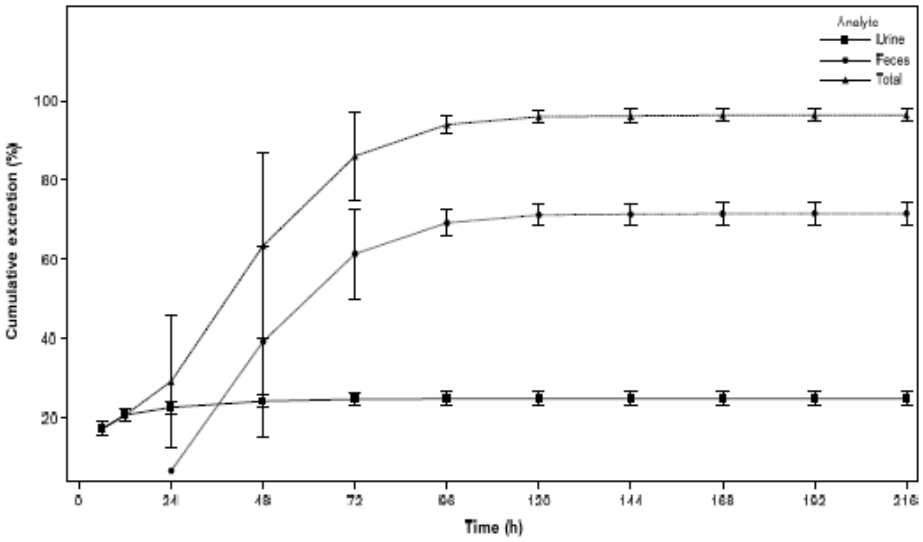


Figure 25: Cumulative excretion of radioactivity in urine and faeces

Plasma exposures for total radioactivity were slightly higher than those for LNP023 indicating that drug-related material seemed to consist primarily of parent and only little of metabolites. Metabolite identification was performed in sample pools of all 6 subjects up to 48 h (plasma) and up to 96 h (urine and faeces) by HPLC-MS/MS with radioactivity detection.

Parent iptacopan represented 83% of the plasma $AUC_{0\text{-}48h}$. Two metabolites were detected in plasma, both below 10% of parent (M8 8.1%, M9 5.2%). In urine, over 98% of excreted radioactivity could be assigned to 7 drug-related components with iptacopan at 17.9% of the dose. In faeces, over 87% of excreted radioactivity could be assigned to 7 drug related components with metabolite M2 (JKH504) with 27.0% of the dose being the most abundant. Other components were LNP023 and metabolite M7 with 16.8% and 8.32%, respectively. Metabolites M8 and M9, and M2 were tested for pharmacological activity and shown to be 27-150-fold less potent than parent.

The mean oral absorption of iptacopan was estimated with at least 70.6% of administered dose calculated from 24.8% of urinary excreted radioactivity plus 45.8% of dose in faeces attributable to metabolites.

Dose proportionality and time dependencies

Dose proportionality after single and multiple doses showed an under-proportional increase in systemic exposure across the entire range of doses. The under-proportional dose-exposure relationship is expected to be a consequence of high affinity binding of iptacopan to its target Factor B in the systemic circulation, with free (unbound) iptacopan cleared from the plasma more rapidly and able to distribute

more broadly than iptacopan bound to FB. At higher doses the dose-exposure relationship approaches dose proportionality (Figure below). The applicant considered this finding consistent with target-mediated drug disposition (TMDD) of a small molecule drug.

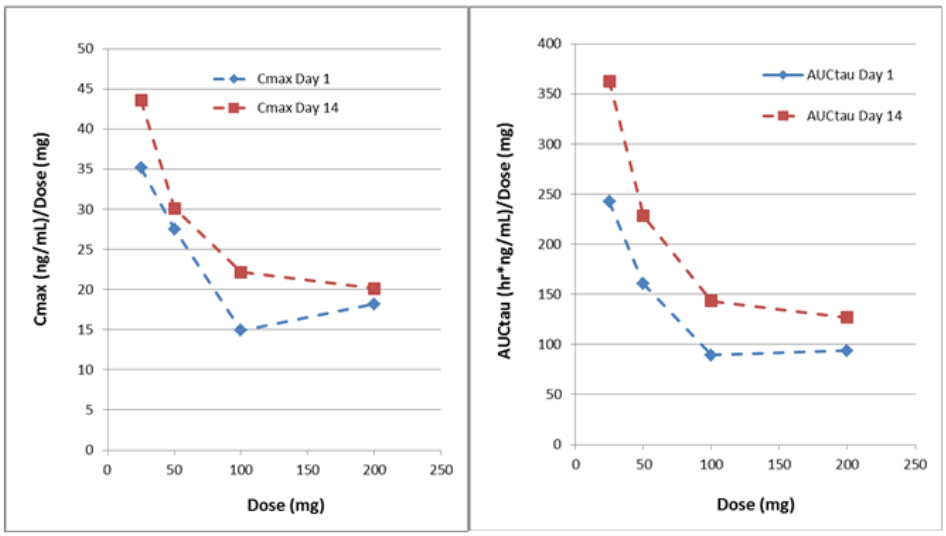


Figure 26: Dose dependency of dose-normalised C_{max} and AUC_{tau} after multiple ascending doses from 25-200 mg b.i.d. – Study X2101

Low accumulation at steady-state was observed for iptacopan with AUCtau increases of <1.7 across all doses and 1.4-fold at the proposed dosing.

Intra- and inter-individual variability

Intra- and inter-individual variability of AUC, C_{max} and C_{trough} in PNH patients at the recommended dose in steady-state was low to moderate with 16-44%.

Pharmacokinetics in the target population

Pharmacokinetics in the targeted PNH population were retrieved from 4 studies:

- X2201 at 50 and 200 mg b.i.d. in combination with anti-C5 antibody in 16 adult PNH patients with signs of active haemolysis despite anti-C5 therapy.
- X2204 at 4 iptacopan dose levels, including 100 and 200mg b.i.d., in 13 treatment-naïve adult PNH patients with active haemolysis.
- C12301-24w at 200mg b.i.d. in 40 PNH patients who had not previously received complement inhibitor therapy, including anti-C5 antibody treatment, and
- C12302-24w in PNH patients with residual anaemia despite prior anti-C5 antibody therapy of which 62 patients were randomised into the iptacopan 200 mg b.i.d. group.

Table 27: Summary statistics of steady-state PK parameters at 200 mg b.i.d. in PNH studies (geo-mean (%CV); T_{max} median (min-max))

Study population	n	study day	T_{max} (h)	C_{max} / C_{2h} (ng/mL)	C_{trough} / C_{min} (ng/mL)	$AUC_{tau,ss}$ (ng×h/mL)
X2101 HV / Part 2	6	14	2.02 (0.75-3.00)	4020 (23.8%)	-	25400 (15.2%)
X2201	10	29	2.00 (1.00-2.00)	3280 (40.4%)	1110 (42.0%)	23000 (39.0%)
X2204	5	57	2.00 (1.00-4.13)	4320 (34.3%)	1460 (29.9%)	32300 (29.0%)
C12301	38	28	-	4662.1 (49.0%)	1909.2 (40.5%)	-
C12302	57	7	-	3575.3 (61.9%)	1365.7 (57.9%)	-
C12302	58	28	-	3659.3 (39.2%)	1380.0 (39.7%)	-
C12302	48	168	-	3887.7 (51.5%)	1597.0 (46.6%)	-
C12302	45	196	-	3764.0 (42.7%)	1657.5 (45.2%)	-
C12302	27	336	-	4490.5 (44.1%)	1583.3 (42.0%)	-

Exposure was estimated by popPK with median (90% prediction interval) AUC_{0-24} of 2626.2 (1666.6-4338.6) ng*day/ml, median C_{max} 3403.4 (2138.1-6202.1) ng/ml and median C_{min} 1886.2 (946.9-3033.1) ng/ml. In the popPK pool CL/F was estimated with 196 (4%) L/d and Vc/F with 3 (7%) L.

By PKPD the effect of missed doses was simulated. After one day, i.e., 2 missed doses, the mean iptacopan C_{trough} dropped below the sC5b-9 EC_{90} threshold in >50% of patients with 100 mg b.i.d., while a concentration above the Bb and sC5b-9 EC_{90} was maintained with 200 mg b.i.d. After 3 missed doses, the mean C_{trough} dropped below EC_{90} of Bb in >60% of patients with 100 mg b.i.d., while exposure was maintained ≥EC_{90} of Bb with 200 mg b.i.d. in 50% of patients. Based on this, the applicant considered the 200 mg b.i.d. dose regimen to provide a more acceptable tolerance to missed doses than the 100 mg b.i.d. regimen.

Special populations

Renal impairment

eGFR was identified as a significant covariate on iptacopan apparent clearance in the final model. AUC_{0-24} in patients with eGFR 34.3 mL/min/1.73m^2 (5th percentile) was expected to be 38% higher than a reference patient with eGFR 87.5 mL/min/1.73m^2. Changes <15% were observed in the 25th, 75th and 95th percentiles of the eGFR distribution. The applicant concluded that renal function had no clinically relevant impact on iptacopan PK and dose adjustment was not required in patients with mild or moderate renal impairment.

Hepatic impairment

Study A2105 evaluated PK of 200 mg iptacopan in 8 participants each with mild, moderate and severe HI based on Child-Pugh classification and 16 healthy matched controls.

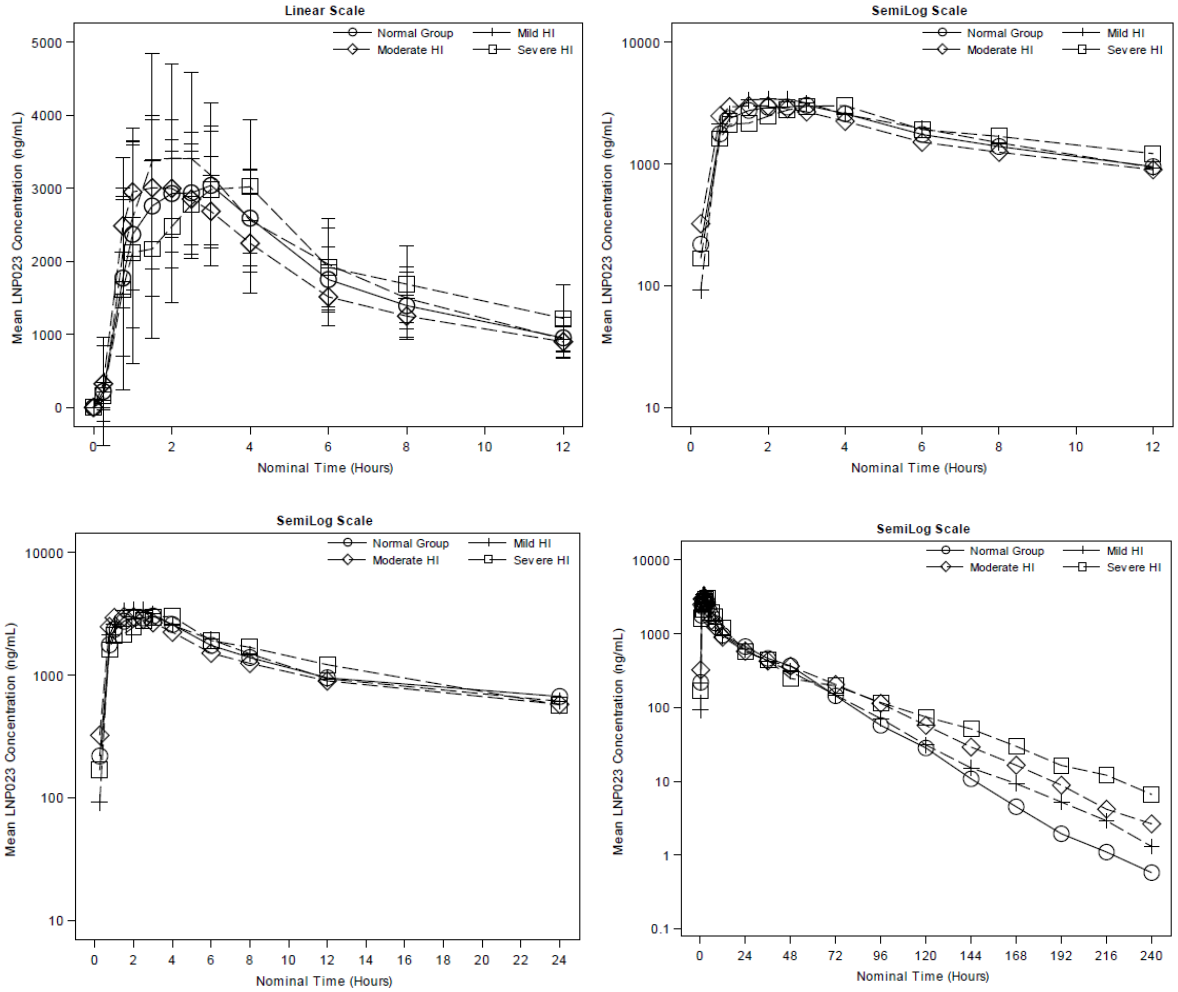


Figure 27: Arithmetic mean (±SD) concentration profiles of total iptacopan – HI study A2105: upper panels 0-12 hr, lower panels semi-logarithmic view of 0-24 h and 0-240 h

All geo-mean ratios comparing the primary PK parameters of mild, moderate, or severe HI groups compared with the control group were within ±10% of 1.00 with all 90% CIs within 80-125% including unity. There was no statistical evidence of an effect of hepatic impairment on the PK of total iptacopan.

For the PK of unbound plasma iptacopan in subjects with HI exposure increased with severity. Geo-mean increases for mild, moderate, and severe HI were: C_{max} (1.38, 1.67 and 2.11-fold), AUClast (1.48, 1.58 and 3.72-fold) and AUCinf (1.48, 1.58 and 3.71-fold). T½,u (gCV%) ranged from 14.0 hr (healthy matched controls) to 14.5 hr, 19.6 hr, and 18.4 hr (mild, moderate, and severe HI).

In study X1102 PK and PD of single ascending-doses (25, 100, 400 mg) were evaluated in 30 healthy male Japanese volunteers. Pharmacokinetics were dose dependent. Mean elimination half-lives ranged from of 13.2 h (25 mg) to 24.7 h (400 mg). Vz/F increased from 39.5 L to 155 L and total systemic clearance CL/F increased from 2.12 L/h (25 mg) to 5.63 L/h (400 mg), respectively. The mean renal clearance ranged from 0.4 L/h to 2.4 L/h until 24 h post dose.

From popPK simulations it was concluded that the ethnicity effect of Asian countries on exposure appeared to be limited and no ethnicity-related dose adjustments were needed.

Body weight did not have a clinically meaningful effect on iptacopan PK, i.e. 11% higher and 10% lower $AUC_{0\text{-}24}$ in patients with low body weight (5th percentile of 47.4 kg) and high body weight (95th percentile of 100 kg), respectively, compared to reference patients (69.5 Kg).

Age had no influence on PK and no dose adjustments are needed in elderly subjects.

Participants by age category and PK trial in healthy volunteers and patients are shown below.

Table 28 Participants by age category and PK trial in healthy volunteers

PK trial	Age 65-74 (Older participants number / total number)	Age 75-84 (Older participants number / total number)	Age 85+ (Older participants number / total number)
CLNP023X1102	0/30	0/30	0/30
CLNP023X2101	0/100	0/100	0/100
CLNP023A2101	0/6	0/6	0/6
CLNP023A2104	0/55	0/55	0/55
CLNP023A2105	10/38	1/38	0/38
CLNP023A2107	0/32	0/32	0/32

Table 29 Participants by age category and PK trial in patients

PK trial	Age 65-74 (Older participants number / total number)	Age 75-84 (Older participants number / total number)	Age 85+ (Older participants number / total number)
CLNP023X2201	0/16	1/16	0/16
CLNP023X2202	2/27	0/27	0/27
CLNP023X2203	3/112	0/112	0/112
CLNP023X2204	0/13	0/13	0/13
CLNP023C12301	2/40	1/40	0/40
CLNP023C12302	19/97	7/97	0/97

Gender was not found to have a significant (p=0.62) effect on iptacopan pharmacokinetics.

Pharmacokinetic interaction studies

In vitro, iptacopan was an inhibitor of OATP1B1 with an IC_{50} of 25.6 µM, but not for OATP1B3. No inhibition of UGT1A1 up to 100µM was observed. Time-dependent (irreversible) inhibition of CYP2C8 with a KI of 179 µM was observed.

Iptacopan is a substrate for the efflux transporters PgP, BCRP and MRP2 and characterised by a high solubility and moderate permeability. No saturation of any of the transporters was observed *in vitro* (up to 800 µM for PgP and BCRP and up to 400 µM for MRP2).

Iptacopan treatment was not expected to affect the hepatic efflux transporters, PgP (Ki=27.7 µM), MRP2 (no inhibition), BCRP (no inhibition) and MATE1 (Ki=327.1 µM), based on *in vitro* measured inhibition compared to the unbound systemic exposure in human plasma (DMPK R1600716). Potential inhibition of the bile salt export pump (BSEP) was also tested and no inhibition was found up to 300 µM.

Study A2104 investigated the DDI of 75 mg clopidogrel (CYP2C8 inhibitor; cohort 1) and 175 mg cyclosporine (OATP inhibitor; cohort 2) on PK of 100 mg iptacopan and the effect of multiple doses of 200 mg b.i.d. iptacopan on the PK of a cocktail (cohort 3) of 0.25 mg digoxin (PgP substrate) and 10 mg rosuvastatin (OATP substrate).

CYP2C8 inhibitor clopidogrel

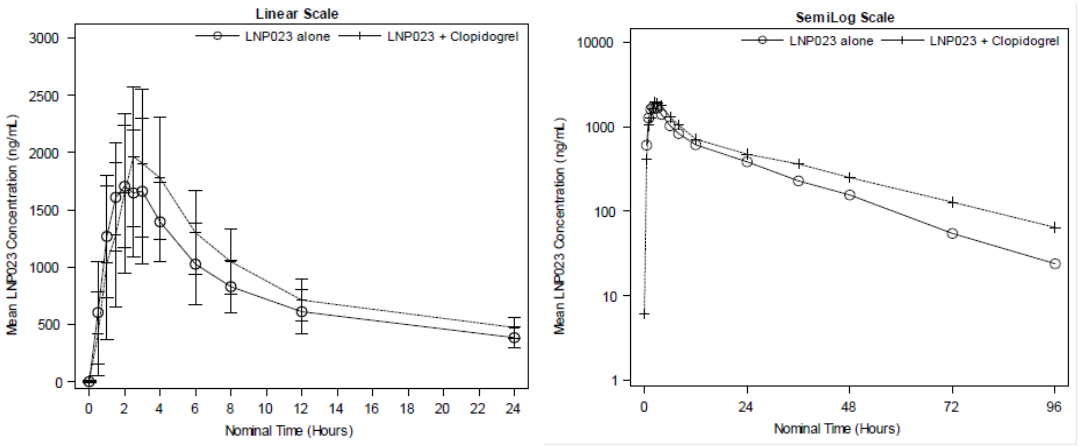


Figure 28: Mean (SD) profiles of in the presence and absence of clopidogrel (Cohort 1)

In urine, in the presence of clopidogrel, iptacopan CLr0-24 and CLr0-48 showed an increase compared to iptacopan alone, with GMR (90% CI) of 1.20 (1.13, 1.27) and 1.14 (1.08, 1.21), respectively. The amount excreted in urine (Ae) increased from geo-mean 15.9 mg to 22.3 mg.

OATP inhibitor cyclosporine

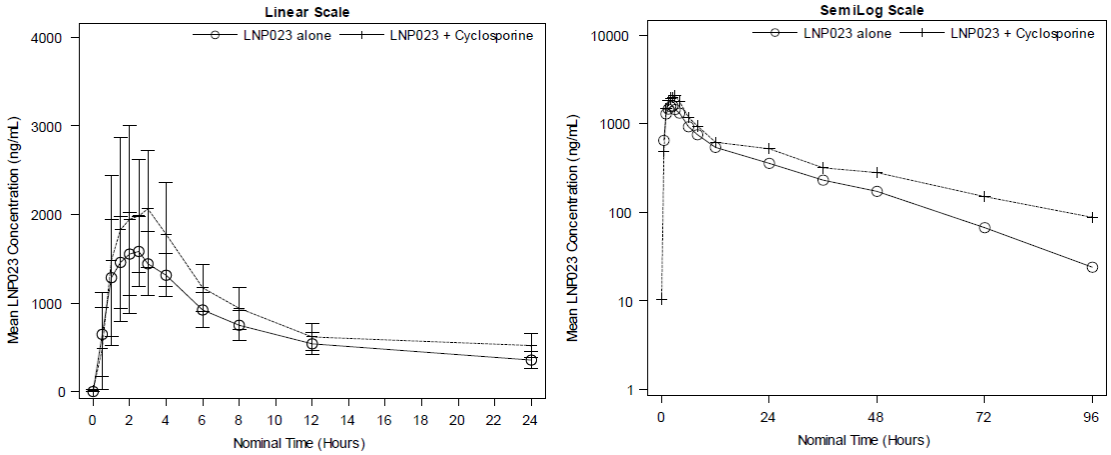


Figure 29: Mean (SD) profiles of in the presence and absence of cyclosporine (Cohort 2)

In urine, in the presence of OATP inhibitor cyclosporine, iptacopan CLr0-24 and CLr0-48 showed an increase compared to iptacopan alone, GMR (90% CI) of 1.33 (1.13, 1.57) and 1.28 (1.08, 1.51), respectively. The amount excreted in urine (Ae) increased from geo-mean 14.3 mg to 24.3 mg.

In the presence of OATP inhibitor cyclosporine, iptacopan CLr0-24 and CLr0-48 showed an increase compared to iptacopan alone, GMR (90% CI) of 1.33 (1.13, 1.57) and 1.28 (1.08, 1.51), respectively. The amount excreted in urine (Ae) increased from geo-mean 14.3 mg to 24.3 mg.

The table below summarises the plasma PK parameters of iptacopan or digoxin and rosuvastatin as victims.

Table 30: PK parameters in DDI study A2104 Cohorts 1 - 3 (geo-mean (%CV); T_{max} median (min-max))

treatment	n	t_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng*h/mL)	AUC_{inf} (ng*h/mL)	$t_{½}$ (h)	CL/F (L/h)	Vz/F (L)
iptacopan alone	18	1.51 (1.00-4.00)	1940 (24.4%)	27100 (25.5%)	27700 (26.2%)	16.5 (29.3%)	3.61 (26.2%)	85.7 (28.6%)
+ clopidogrel	18	2.5 (1.5-5.98)	2040 (29.5%)	35900 (25.5%)	38100 (29.5%)	21.5 (29.7%)	2.62 (29.5%)	81.5 (17.3%)
iptacopan alone	20	2.00 (1.00-4.00)	1800 (26.2%)	25900 (23.2%)	26600 (24.8%)	15.8 (34.1%)	3.76 (24.8%)	85.5 (22.8%)
+ cyclosporine	15	2.5 (1.00-4.03)	2450 (30.7%)	36800 (25.8%)	37800 (28.0%)	23.7 (21.5%)	2.65 (28.0%)	90.5 (17.2%)
Digoxin alone	17	1.00 (0.50-2.00)	978 (31.5%)	13900 (24.1%)	15500 (22.7%)	41.4 (27.0%)	16.1 (22.7%)	963 (27.0%)
+ iptacopan	17	1.00 (0.50-2.05)	1050 (31.7%)	13900 (26.9%)	15800 (25.2%)	41.3 (28.3%)	15.8 (25.2%)	944 (25.2%)
Rosuvastatin alone	17	4.00 (3.00-10.00)	4.94 (43.5%)	61.5 (48.0%)	66.2 (44.4%)	13.00 (50.7%)	151 (44.4%)	2830 (55.5%)
+ iptacopan	17	4.00 (2.00-6.00)	4.95 (40.8%)	63.5 (48.1%)	66.9 (45.7%)	12.6 (21.0%)	149 (45.7%)	2710 (40.9%)

Consistent with *in vitro* studies there were only minimal to mild effects (<50%) observed for iptacopan being either a victim or perpetrator drug. These effects were not considered to be clinically relevant and the applicant concluded that no dose adjustments with concomitant drug treatment were required.

Table 31: Geo-mean ratios for C_{max} and AUC for iptacopan – study A2104

				Geo-metric mean ratio (90%CI)		
Cohort	**Iptacopan status**	**Pathway tested**	**Probe drug**	**C_{max}**	**AUClast**	**AUCinf**
1	Victim	CYP2C8	Clopidogrel	1.05 (0.97-1.14)	1.33 (1.26-1.40)	1.36 (1.28-1.45)
2	Victim	OATP	Cyclosporine	1.41 (1.35-1.47)	1.46 (1.39-1.52)	1.50 (1.42-1.59)
3	Perpetrator	P-gp	Digoxin	1.08 (0.94-1.24)	1.00 (0.90-1.11)	1.02 (0.93-1.12)
3	Perpetrator	OATP	Rosuvastatin	1.00 (0.87-1.15)	1.03 (0.92-1.16)	1.01 (0.91-1.12)

PBPK Modelling

PBPK modelling was used to simulate the PK of iptacopan after single and multiple b.i.d. 100-200 mg doses with the available clinical data in healthy subjects and to simulate the DDI magnitude at different iptacopan dosing. Furthermore, iptacopan PK after a single 200 mg dose in hepatic impaired populations was simulated. Then the iptacopan PBPK model was applied to predict the potential impact of rifampicin (induction) on the iptacopan PK, to predict the potential impact of iptacopan, as a CYP2C8/OATP inhibitor, on the PK of repaglinide (a CYP2C8/OATP1B1 substrate) and to predict the PK of iptacopan in patients with severe renal impaired function, which had not been evaluated clinically.

Exposure relevant for safety evaluation

At steady-state in PNH patients at 200 mg b.i.d., as derived from non-compartmental analyses, the exposure at 2 hours/C_{max} ranged from 3280-4662 ng/ml, the C_{min} from 1110-1909 ng/ml.

In the popPK exposure was estimated with median (90% prediction interval) AUC_{0-24} 2626.2-(1666.6-4338.6) ng*day/ml, median C_{max} 3403.4 (2138.1-6202.1) ng/ml and median C_{min} 1886.2 (946.9-3033.1) ng/ml.

2.6.2.2. Pharmacodynamics

Mechanism of action

Patients with PNH are highly susceptible to complement-mediated haemolysis by the membrane attack complex (MAC). Anti-C5 monoclonal antibodies have changed the natural course of the disease by

targeting the terminal part of the complement cascade and preventing the MAC formation. However, anti-C5 antibodies also induce proximal C3-mediated extravascular haemolysis, which may be responsible for residual anaemia and transfusion dependence.

Iptacopan is a first-in-class, orally administered factor B inhibitor. Factor B is an acute phase protein normally present in plasma at a concentration of approximately 200-300 µg/mL, but it can increase in the context of infection or inflammation. Inhibition of factor B prevents the activation of the C3 convertase related to the alternative pathway, thus preventing the downstream generation of the C5 convertase and the formation of the MAC. Iptacopan specifically targets the alternative pathway while leaving the lectin and classical pathways intact. As a result, iptacopan targets the central pathophysiology of PNH and is expected to prevent the emergence of C3-mediated extravascular haemolysis.

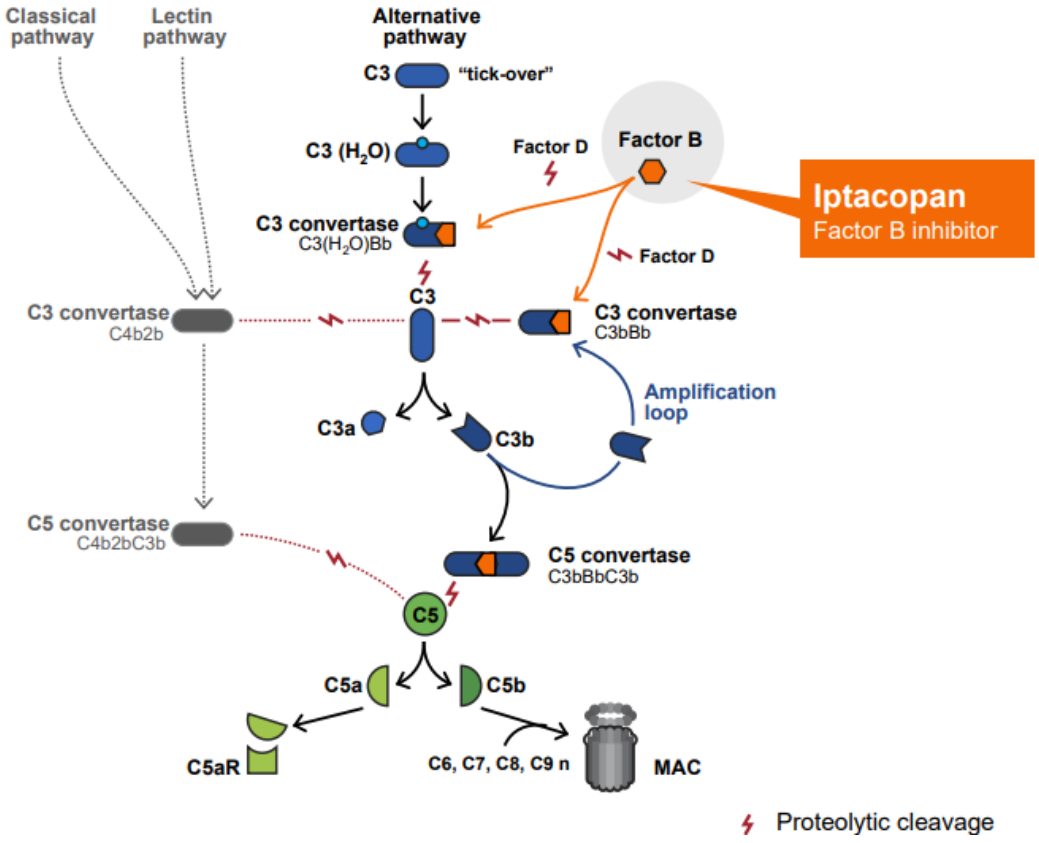


Figure 30: Iptacopan is a proximal complement inhibitor that specifically binds to FB to inhibit the activation of the AP and amplification loop. AP, alternative pathway; FB, Factor B; MAC, membrane attack complex. (Rizk *et al*. 2023)

The biomarkers selected for PD studies can be divided into three types: 1) blood biomarkers related to the mechanism of action; 2) other blood biomarkers; and 3) urine biomarkers related to the mechanism of action. In addition to these soluble biomarkers, C3 fragment (C3d) deposition on red blood cells (RBCs) was determined in PNH studies. The following table shows the soluble biomarkers analysed in blood in each study.

Table 32: Soluble complement biomarkers described in final study reports

Biomarker class	Soluble complement biomarker endpoint	X2101 FIH	X1102 Japanese	X2201 PNH	X2204 PNH	X2202 C3G	X2203 IgAN
Blood based target and mechanism related complement biomarkers	Factor B (µg/mL, plasma)			X		X	X
	Bb (ng/mL, plasma)	X	X	X	X	X	X
	sC5b-9 (ng/mL, plasma)	X		X	X	X	X
	Wieslab (iu or %, serum)	X	X	X	X	X	X
Blood based other complement biomarkers	CH50 (KU Eq/L, serum)	X		X			
	C3 (g/L, plasma/serum)					X	X
	C4 (µg/mL, plasma)					X	X
	Factor H (µg/mL, plasma)					X	X
	Properdin (µg/mL, plasma)					X	X

The most important soluble biomarkers related to iptacopan's mechanism of action (MoA) are:

- Factor B levels: Factor B is an essential component of the alternative pathway of complement activation. Factor B is activated after binding to C3b and subsequently cleaved to C3bBb (C3 convertase) and Ba peptides. Iptacopan inhibits the proteolytic activity of C3bBb, thus preventing the alternative pathway amplification loop. Since the activation of the alternative pathway increases factor B consumption, inhibition of this pathway would be expected to increase plasma factor B levels. However, factor B levels may also increase in case of inflammation or infection because it is an acute phase protein.
- Serum Wieslab assay: This assay measures the amount of *ex vivo* C5b-9 formation in serum after alternative pathway activation. To ensure that only the alternative pathway activation is measured, specific blockers are used. The result is reported as a percentage of the activity of the positive control. Iptacopan therapy would be expected to reduce the C5b-9 formation induced by the activation of the alternative pathway, hence reducing the activity of the Wieslab assay.
- Plasma Bb assay: The activation of the alternative pathway results in the cleavage of factor B into Ba and Bb. Iptacopan therapy would therefore be expected to decrease plasma Bb. However, since low levels of factor B cleavage ("tick over") independent of iptacopan treatment can still occur, iptacopan would not be expected to achieve complete inhibition of Bb production.
- Plasma soluble C5b-9 levels: sC5b-9 is the terminal product of complement activation, also known as the soluble MAC (sMAC) or terminal complement complex (TCC). Unlike the Wieslab assay, the sC5b-9 is not specific of the alternative pathway given that all pathways (classical, alternative and lectin) contribute to sC5b-9 production. However, for diseases that activate the alternative pathway, such as PNH, it can be assumed that most sC5b-9 production reflects

alternative pathway activation. In patients with PNH, iptacopan would be expected to reduce plasma sC5b-9, and the degree of reduction would be expected to be associated with the baseline sC5b-9 production.

Among other soluble biomarkers evaluated in the blood, not directly related to iptacopan's MoA, were CH50 assay, serum C3 levels, plasma/serum C4, plasma factor H and plasma properdin. Only the CH50 assay was systematically evaluated in PNH studies. As a marker of complement activation via the classical pathway, this assay would not be expected to be affected by iptacopan therapy.

Urine biomarkers were not evaluated in PNH studies.

The deposition of C3 fragments (C3d) on RBCs was evaluated in PNH studies. In patients with PNH, intravascular haemolysis is mediated by sC5b-9 (sMAC), whereas extravascular haemolysis is mediated by opsonisation induced by C3d. In patients on anti-C5 therapy, intravascular haemolysis is completely blocked, and extravascular haemolysis becomes the predominant cause of residual anaemia. Because of its ability to inhibit the production of C3 fragments, iptacopan therapy would be expected to decrease the deposition of C3d on RBCs from patients with PNH.

Primary and Secondary pharmacology

Primary:

The following soluble biomarkers were selected to evaluate the effect of iptacopan treatment on the complement pathway:

Factor B levels

Baseline factor B levels were evaluated in 3 studies: X2201, X2202 and X2203. Patients with PNH had higher factor B levels (420-460 µg/mL) than healthy subjects (200-300 µg/mL). Of note, patients with C3G had lower baseline factor B levels than patients with IgAN or PNH.

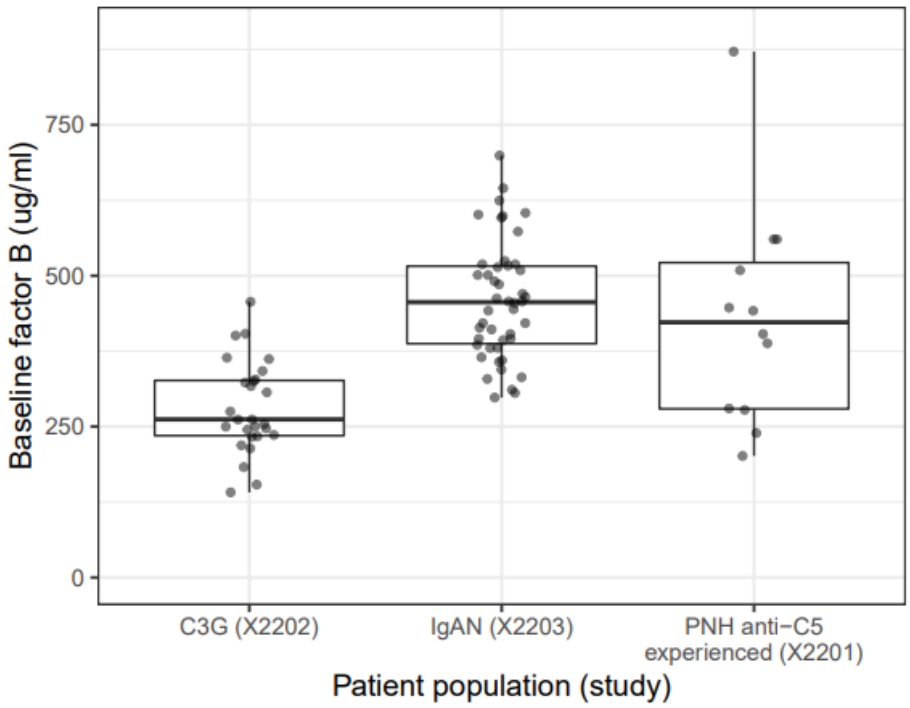


Figure 31: Baseline plasma Factor B concentration by population

Other conditions associated with higher baseline factor B levels are systemic inflammatory conditions (Behçet's or Crohn's disease), sepsis and infection. Assuming a factor B concentration of >420 µg/mL

(as shown in study X2201), an iptacopan dose of 200 mg twice daily would reach an approximately equimolar concentration with factor B in the intravascular compartment over the 12-hour dosing interval. This means that, when administered at this dose, the concentration (in molecules per unit of volume) reached by the drug (iptacopan) in the blood compartment is equivalent to that of the target (factor B). As a result, the 200 mg dose provided the most effective and consistent inhibition over the dosing interval in healthy subjects and patients with PNH. In contrast, doses lower than 200 mg twice daily were insufficient to fully inhibit factor B, especially in the setting of increased factor B levels as seen in patients with PNH.

Factor B levels on iptacopan therapy were measured in studies X2201, X2202 and X2203. Compared to baseline and placebo, factor B levels increased on iptacopan treatment by approximately 20-30%. This may be due to decreased consumption and/or increased production.

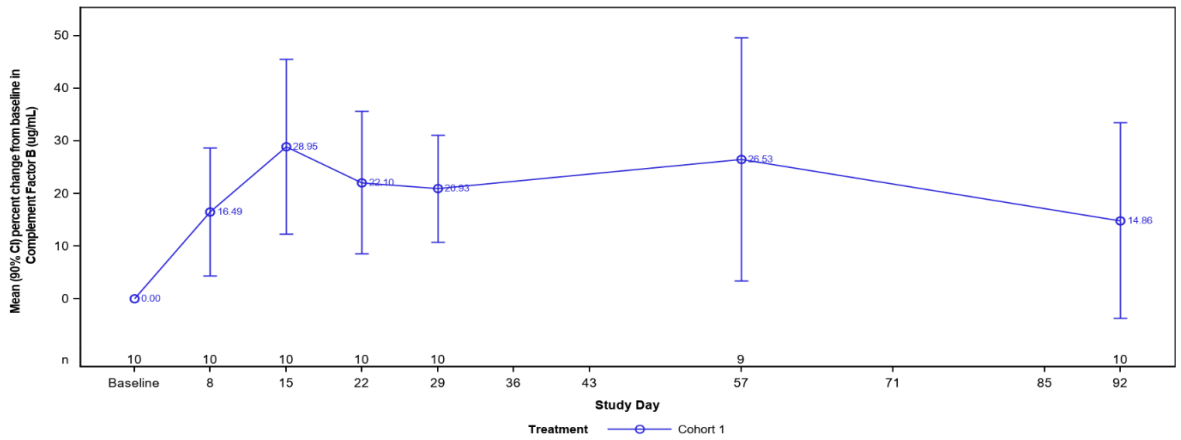


Figure 32: Mean (90% CI) of factor B plasma concentration as a function of time post iptacopan treatment initiation in PNH patients (Cohort 1, Study CLNP023X2201)

Wieslab assay

Single doses of iptacopan from 10 to 400 mg resulted in >81% reduction of Wieslab in healthy subjects compared to baseline at 2 h post-dose, whereas the placebo cohort had no appreciable change in Wieslab. At 12 h from administration, sustained inhibition of Wieslab was dose-dependent and only observed after a single dose of 200 or 400 mg. At 48 h, Wieslab values returned to baseline except in the 200 and 400 mg cohorts.

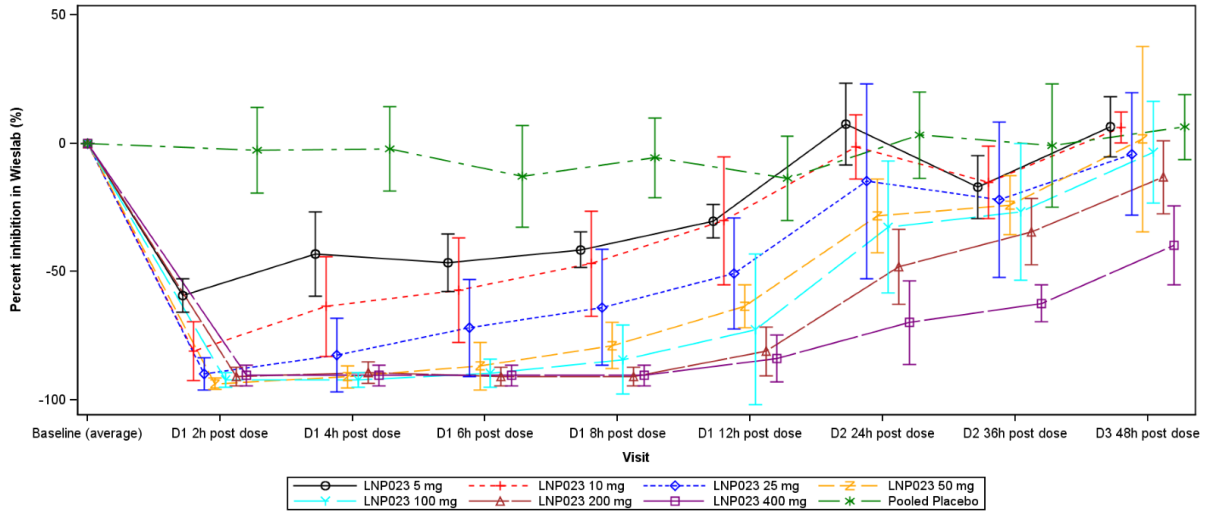


Figure 33: Mean (± SD) percentage inhibition in Wieslab assay compared to baseline by single dose, healthy subjects, treatment cohort (Study CLNP023X2101)

Multiple doses of iptacopan from 25 to 200 mg twice daily led to rapid and near complete (>87%) inhibition of Wieslab in healthy subjects compared to baseline 2 h after the first dose. However, a consistent inhibition (>60%) was generally sustained throughout the 14 days for the 100 and 200 cohorts only. Duration and magnitude of inhibition appeared dose-dependent, being maximal and more consistent (with a lower standard deviation) in the 200 mg cohort.

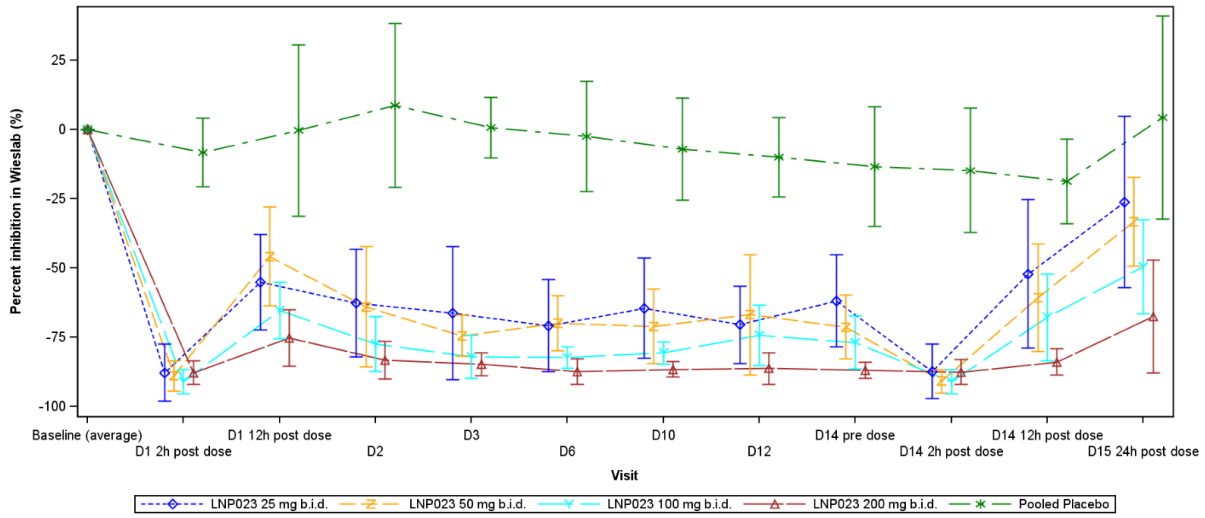


Figure 34: Mean (± SD) percent inhibition in Wieslab assay compared to baseline by multiple dose, healthy participant, cohort (Study CLNP023X2101)

Wieslab assay was evaluated in patients with PNH recruited in the X2201 and X2204 studies. The same dose-response correlation was observed compared to healthy volunteers up to the 200 mg twice daily dose. Of note, the baseline values of Wieslab were lower in patients with PNH (compared to healthy subjects) because they were on anti-C5 treatment prior to iptacopan therapy. Despite the lower baseline values, iptacopan therapy resulted in additional inhibition of the alternative pathway in them.

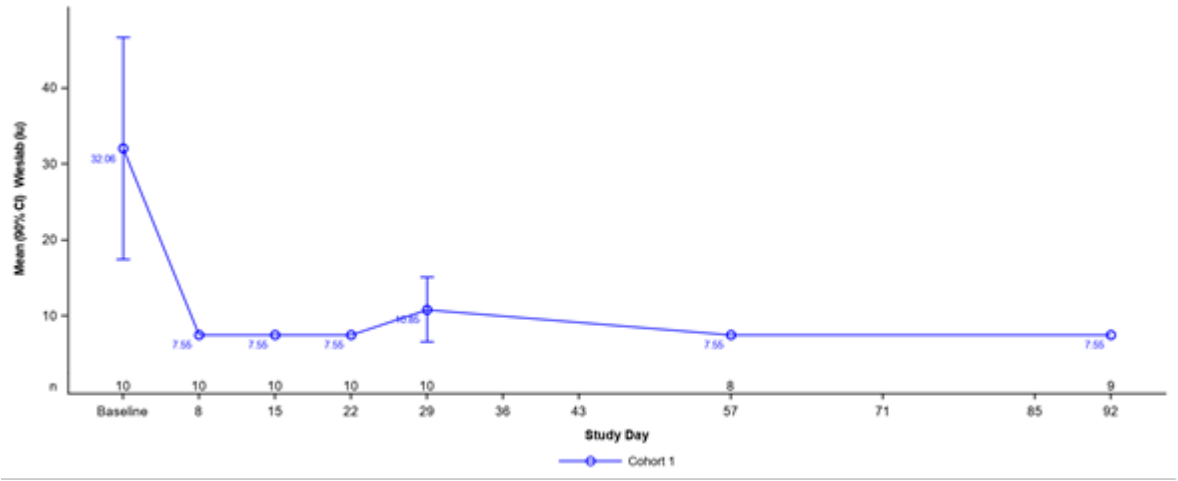


Figure 35: Mean (90% CI) Wieslab assay (%) compared to baseline in PNH patients starting iptacopan 200 mg b.i.d. and already on anti-C5 treatment in Cohort 1 (Study CLNP023X2201)

Plasma Bb levels

Plasma Bb levels from healthy subjects receiving placebo remained like baseline, whereas a significant decrease from baseline was observed at 2 h post-dose for all single dose iptacopan cohorts. Only the 200 mg and 400 mg cohorts displayed a nadir level through 24 h post-dose with a slow upward trajectory at later timepoints.

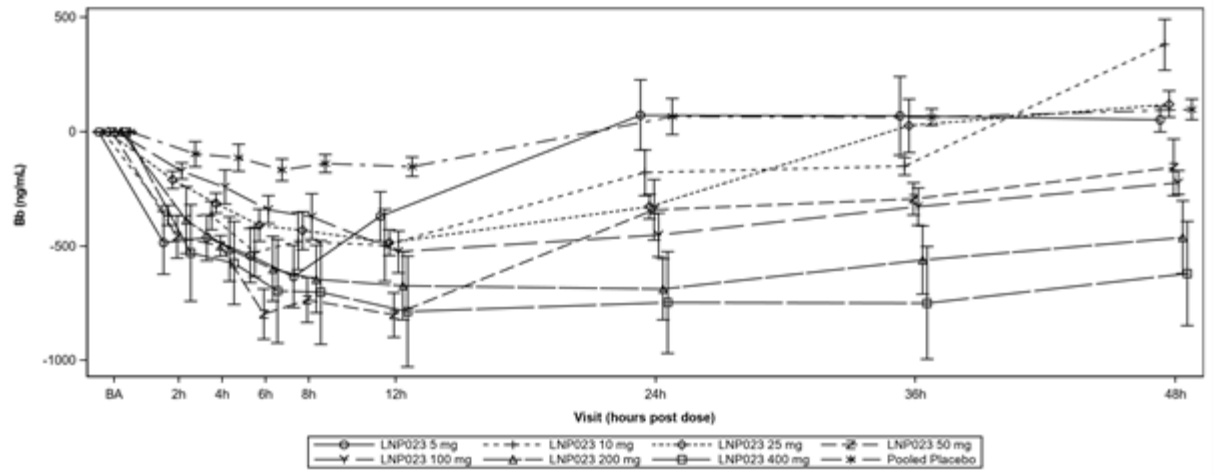


Figure 36: Mean (± SE) change from baseline of plasma Bb level after a single dose treatment in Study CLNP023X2101

Multiple dose administration of iptacopan achieved a similar Bb level decrease, regardless of the dose (i.e. there was no obvious dose-response). However, the 200 mg cohort showed a more persistent inhibition of the pathway upon treatment discontinuation at 14 days.

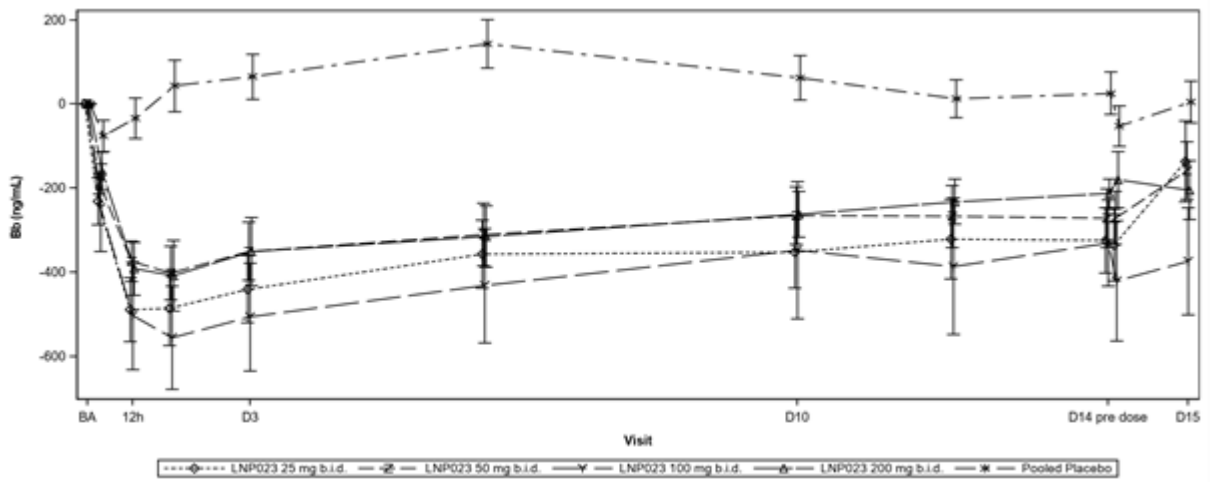


Figure 37: Mean (± SE) change from baseline of plasma Bb level after multiple dose treatment in (Study CLNP023X2101)

In patients with PNH recruited into the X2201 and X2204 studies, iptacopan decreased Bb levels up to 80% from baseline, with a more consistent inhibition of Bb levels for patients taking 200 mg twice daily.

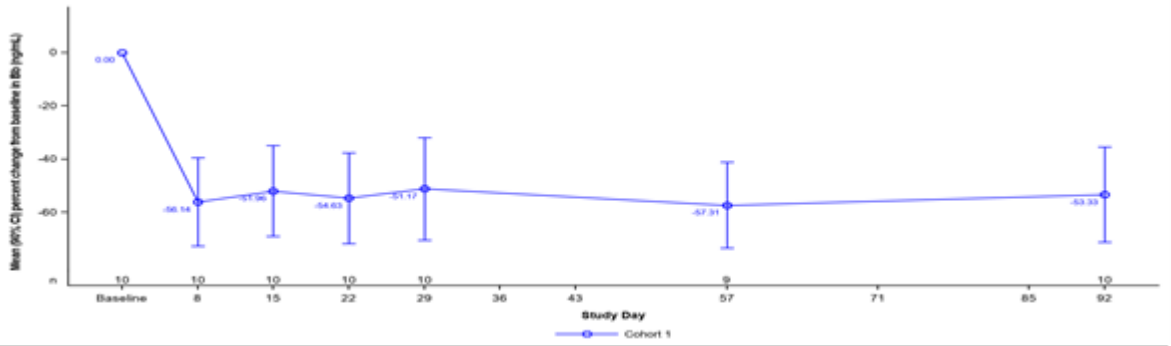


Figure 38: Mean (90% CI) of plasma Bb in PNH patients starting iptacopan 200 mg b.i.d. and already on anti-C5 treatment in Cohort 1 (Study CLNP023X2201)

In summary, iptacopan therapy induced a rapid, up to 80% decrease in Bb levels and patients with PNH. The Bb level decrease was not clearly dose-dependent in healthy subjects, but it was for patients with PNH, being maximal for those taking 200 mg twice daily.

Plasma sC5b-9 levels

In healthy subjects, baseline levels of sC5b-9 (sMAC) were highly variable across single dose treatment cohorts, with a trend towards a rapid onset of action 2 h post-dose, but without any obvious dose-response.

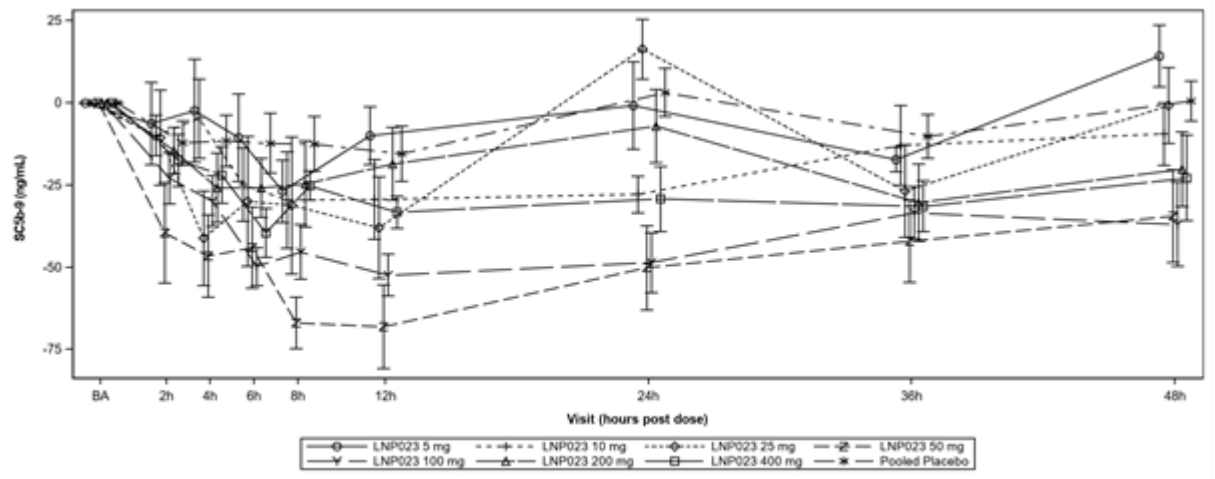


Figure 39: Mean (± SE) change from baseline of plasma sC5b-9 level after single dose treatment in Study CLNP023X2101

With multiple doses, a decrease in sMAC was also observed in healthy subjects after iptacopan administration, but a smaller decrease was also documented for patients taking placebo. Once again, no obvious dose-response was observed.

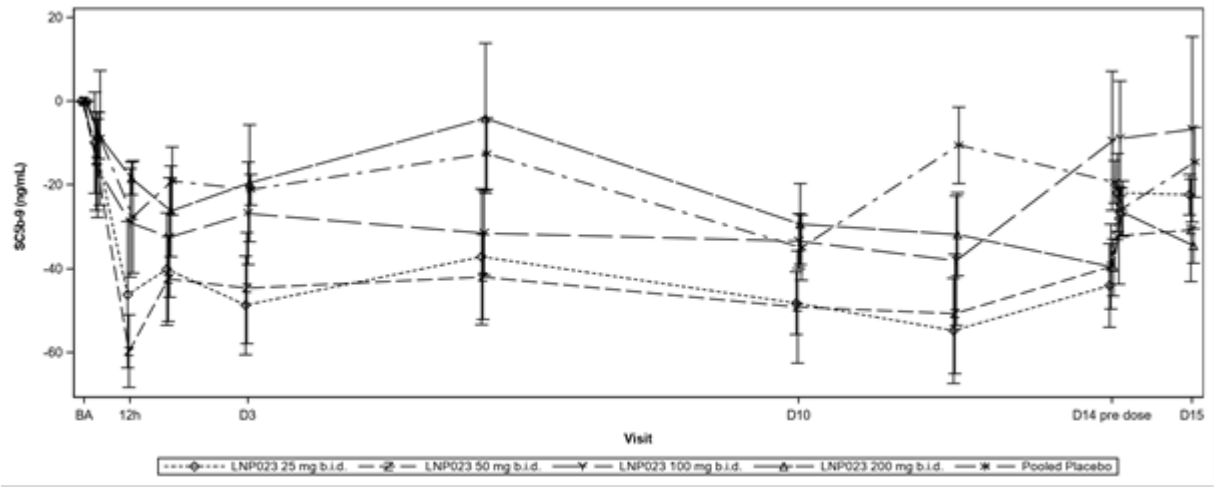


Figure 40: Mean (± SE) change from baseline of plasma sC5b-9 level after multiple dose treatment in Study CLNP023X2101

In patients with PNH, it was not possible to detect a clear effect of iptacopan therapy on sMAC levels, probably due to the relatively normal (<300 ng/mL) baseline sMAC levels observed in these patients.

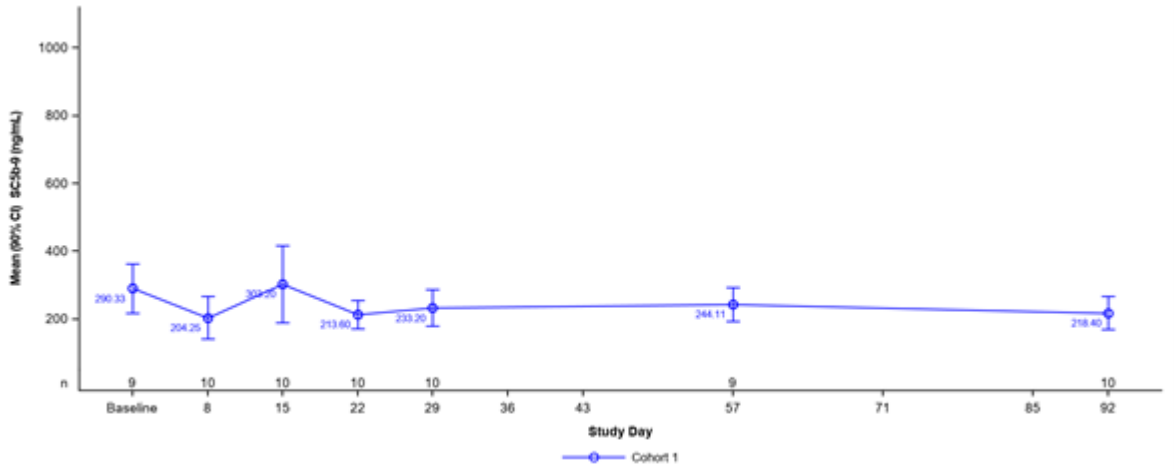


Figure 41: Mean (90% CI) plasma sC5b-9 levels in PNH patients starting iptacopan 200 mg b.i.d. and already on anti-C5 treatment in Cohort 1 (Study CLNP023X2201)

In patients with C3G and IgAN, who had elevated baseline sMAC levels, there was a substantial inhibition of sMAC upon iptacopan therapy.

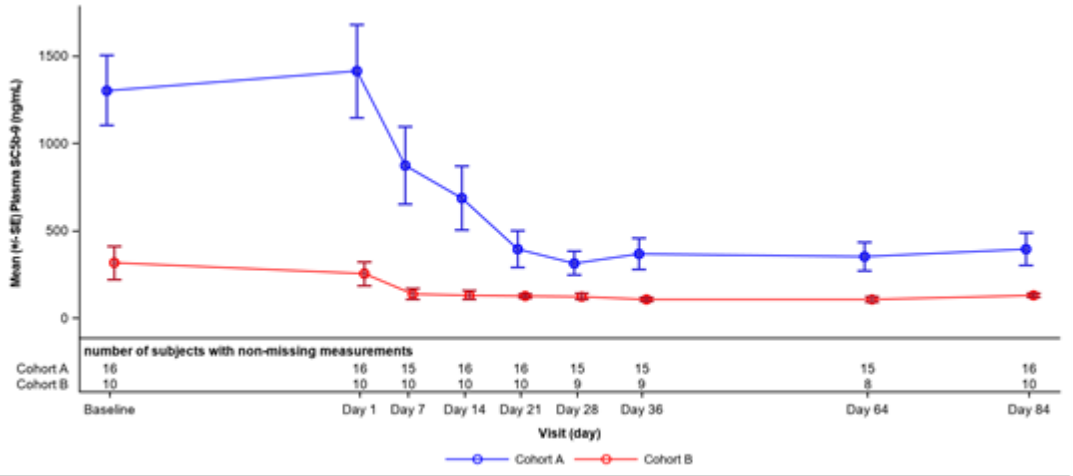


Figure 42: Mean (+/- SE) plasma sC5b-9 for Cohort A (native) and B (transplant) in C3G patients (Study CLNP023X2202)

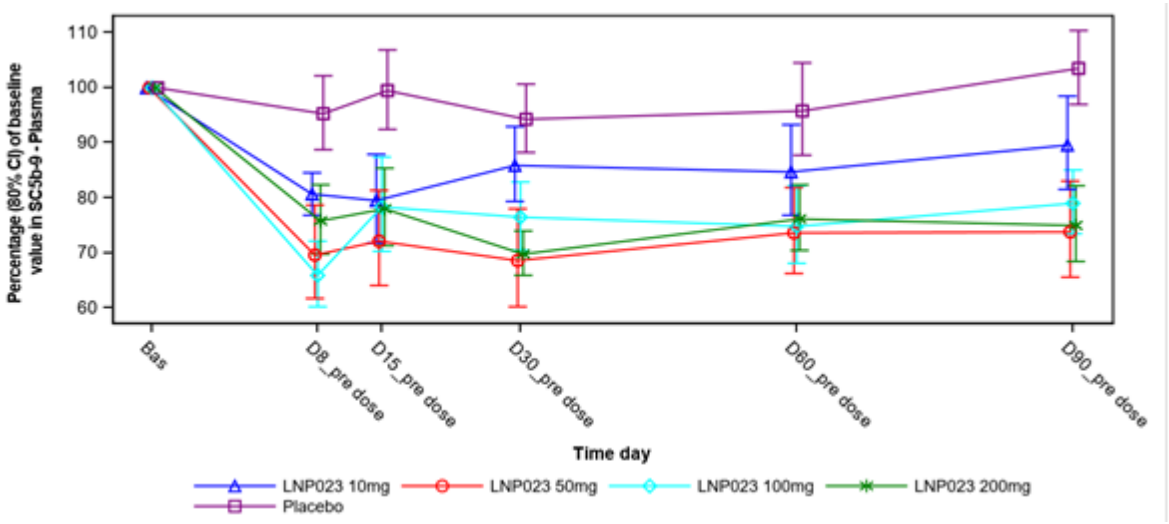


Figure 43: Mean (80%CI) percentage of baseline of plasma sC5b-9 in IgAN patients (Pooled Parts 1 and 2) (Study CLNP023X2203)

CH50 assay

As expected, in healthy volunteers iptacopan therapy had no effect on CH50 compared to placebo, and the same lack of effect was observed in patients with PNH.

C3d deposition on RBCs

In patients with PNH, haemolysis can occur in two compartments: intravascular and extravascular. However, extravascular haemolysis, which is caused by the deposition of C3 fragments (C3d), becomes predominant in patients already on anti-C5 treatment. An early, sustained and marked decrease in C3d deposition in RBCs was observed in patients receiving iptacopan in the X2201 study. The mean percentage change from baseline at day 92 was approximately –90%. This decrease persisted over the >1 year duration of observation, even in patients in whom anti-C5 therapy had been stopped and patients were only taking iptacopan.

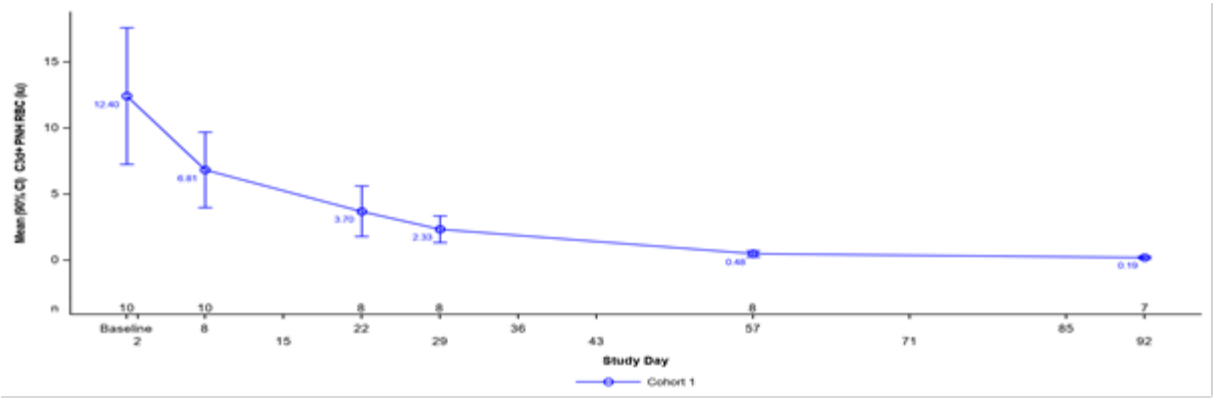


Figure 44: Mean (90% CI) C3d+ PNH (Type II and III) RBC (%) in PNH patients (Cohort 1 of Study CLNP023X2201)

In treatment-naïve patients recruited into the X2204 study, C3d deposition was negligible at baseline and did not change during iptacopan therapy, probably due to the predominance of intravascular haemolysis in these patients.

In conclusion, in patients on anti-C5 treatment, iptacopan inhibited the C3d deposition on RBCs and this effect persisted when anti-C5 treatment was discontinued, whereas in therapy-naïve patients, iptacopan treatment did not induce C3d deposition on RBCs.

Secondary:

The secondary (off-target) pharmacology of iptacopan was evaluated in terms of heart rate, blood pressure and QT interval.

Heart rate: In study X2101, there was no effect of iptacopan on healthy subjects' heart rate with doses up to 400 mg (single or multiple doses). The same lack of effect was observed in patients recruited into studies X2202, X2203 and X2204. In a study extension evaluating doses of iptacopan up to 1200 mg, no effect on heart rate was documented.

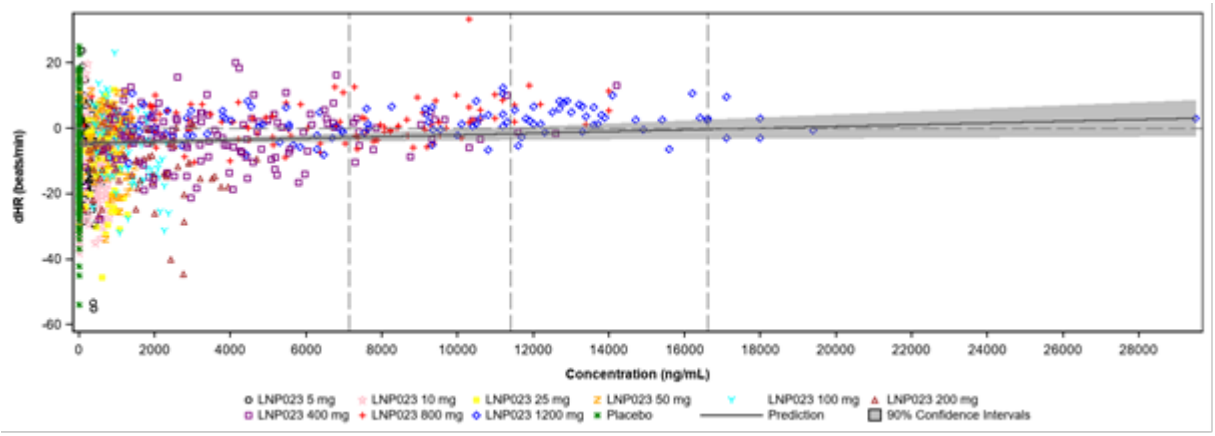


Figure 45: Scatter plot and 90% CI of Holter ECG measured heart rate change between time-matched baseline (Day -1) and Day 1 versus iptacopan concentration (n=88)

Blood pressure: Ambulatory blood pressure monitoring was used in study X2101 at multiple time points before and after the administration of up to 400 mg of iptacopan. There was no effect of iptacopan therapy on blood pressure in healthy volunteers.

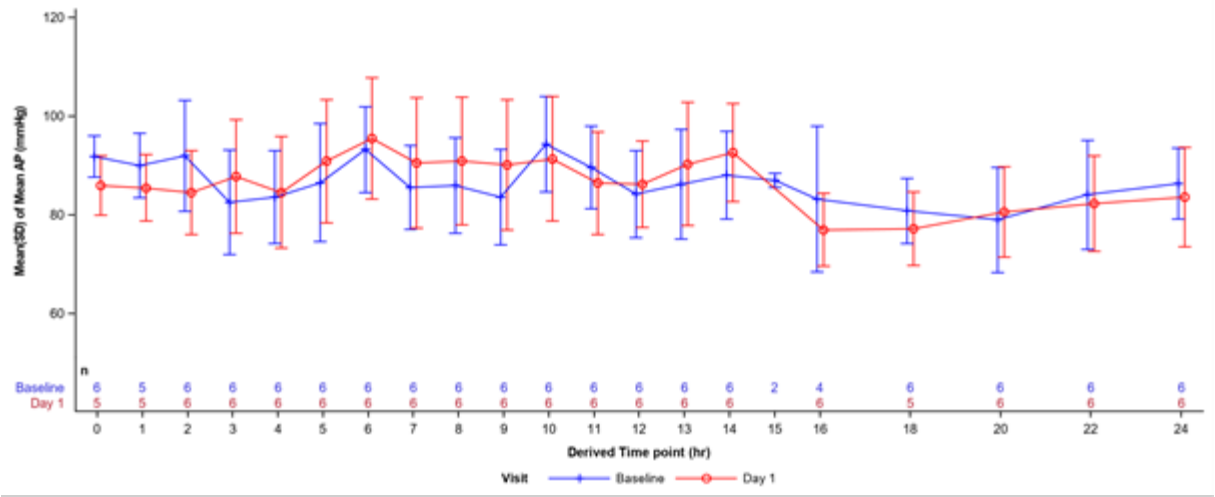


Figure 46: Mean of the MABP by time on Day -1 and Day 1 in the iptacopan 200 mg at time 0 and 12 hour treatment group (n=6) – Part 2

QT interval: The relationship of iptacopan exposure and the QT interval was assessed in healthy subjects receiving single doses of up to 1200 mg (X2101 study and extension). There was a flat relationship between iptacopan concentration and QT interval.

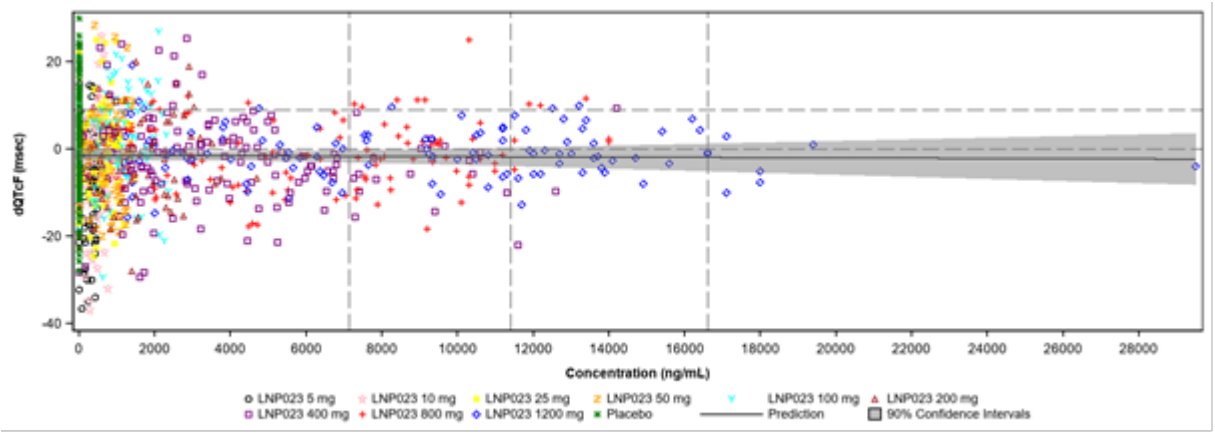


Figure 47: Scatter plot and 90% CI of Holter Electrocardiogram (ECG) measured QTcF change from time matched baseline versus iptacopan concentration ((Study CLNP023X2101) + (Study CLNP023A2107) pooled analysis)

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Iptacopan was investigated in clinical studies in healthy volunteers and in patients for various indications. For the underlying clinical pharmacokinetics assessment the patient studies in indications other than PNH are not specifically discussed, except that the PK values were included in the data pool for modelling purposes.

Iptacopan in plasma and urine was analysed after liquid chromatography or after protein precipitation by LC-MS/MS in multiple reaction monitoring mode using electrospray ionisation. Methods were validated in three labs and cross-validated. LLOQ was adequate for the observed concentrations and method performances acceptable. In study A2101 an acidified sample was analysed for glucuronide metabolites which was adequate to prevent acyl migration and hydrolysis of acyl glucuronide metabolites.

Absorption

Permeability was tested in Caco-2 cells at concentrations including clinically relevant range of Cave ~4.7µM. Based on high solubility and moderate permeability iptacopan is classified as BCS class III compound.

Bioequivalence

Iptacopan was formulated as a conventional, immediate release solid oral dosage form with neat drug substance in hard gelatine capsules. The form of salt is the only differences between the formulations in the early phases (anhydrous hydrochloride salt) compared to late phases (monohydrate

hydrochloride salt). In accordance with ICH M9 for an immediate release oral product the conditions for BCS class III define that dissolution profiles at all required conditions of pH 1.2 – 6.8 should display very rapid dissolution, i.e. ≥ 85% in ≤ 15 minutes. However, at the lowest pH 1.2 (i.e. USP simulated gastric fluid; and also 0.1 N HCl) these conditions were not fulfilled in the comparative dissolution tests between biobatches of highest strengths of early CSF (100 mg, batch 1010014270, used in study X2201) and late CSF (200mg, batch 1010034622, used in pivotal study C12301), whereas dissolution at pH 2.0 (0.01 N HCl), 4.5 and 6.8 was similar. (See also discussion on Quality) .

Two-stage dissolution in bio-relevant media comparably showed slower dissolution at low pH values (1.6 and 1.0) but rapid dissolution after increase of pH. A biopharmaceutics risk assessment to justify the acceptability of non-similar profiles at pH 1, concluded that it is acceptable that no bioequivalence study in fasted state was performed between early and late CSF formulations.

Influence of food

Food did not have a significant effect on PK parameters of iptacopan. With a high-fat high-calorie meal C_{max} and AUC decreased by 3 and 10-11%, respectively, with all CIs within bioequivalence ranges. Mean renal clearance was identical with either food or fasted state. In the pivotal PNH study, study drug intake was performed regardless of food, therefore all efficacy and safety results were obtained with the late CSF/FMI formulation under assumption of a clinically irrelevant food effect. The SmPC states this accordingly.

However, the food effect study was performed with the early CSF capsule containing the anhydrate modification A that showed a slightly better dissolution a lower pH than the later capsule with the monohydrate modification HB. As this was not found in module 3, the applicant is asked to clarify the solubility and lipophilicity of modification A vs. HB to support that the food effect of the later CSF and FMI capsules would not be larger than with the early CSF capsule supporting that food-effect results can be extrapolated between formulations. Based on the responses, it is evident that both API modifications are highly soluble in aqueous buffer media, simulated intestinal fluids and water (anhydrate modification A is slightly more soluble than monohydrate modification HB). Regarding the lipophilicity (logD), the applicant stated that changes in lipophilicity at the site of absorption are not expected due to the same high aqueous solubility throughout the physiological range (pH >2) of both drug substance modifications.

No study was performed under concomitant intake of PPI and this is not necessary considering that either capsule formulation was highly soluble at pH ≥ 2.

Bioavailability

No data on absolute oral bioavailability of iptacopan has been generated. The applicant claims that: 'assuming that iptacopan and metabolites are stable against intestinal bacterial enzymes, the mean oral absorption of iptacopan could be estimated as at least 70.6% based on urinary excreted radioactivity (24.8%) plus 45.8% of dose in faeces attributed to metabolites'. No data on stability in faeces has been presented and the fraction absorbed may be overestimated. However, since no claims in the SmPC are made regarding fraction absorbed and that iptacopan is considered a BCS class III drug, this is acceptable.

Pharmacokinetics after single and multiple doses

One phase I study (X2101) was performed in healthy volunteers, were SAD and MAD and food effect was investigated. Iptacopan was tested as a single dose of 5, 10, 25, 50 100, 200 and 400 mg and multiple doses of 25, 50, 100 and 200 mg b.i.d. After single and multiple doses iptacopan was rapidly absorbed with median T_{max} ranging from 1-2.5h. Plasma exposure increased with dose in an overall less than proportional manner, which was especially pronounced up to doses of 100 mg. At steady-

state (day 14) there was a nearly 2-fold increase between the 100 mg and 200 mg b.i.d. dose for AUC_{tau} and C_{max}. Thus, the increase can be considered dose proportional in this range at steady-state. In HV at 200 mg b.i.d., geo-mean $C_{max,ss}$ was 4020 (23.8%) ng/ml and $AUC_{tau,ss}$ was 25400 (15.2%) ng*hr/ml. At higher doses ≥ 200 mg, double peaks or shoulders were observed, possibly resultant from intestinal reabsorption of iptacopan from cleaved glucuronides.

In addition, the PK after supratherapeutic single doses of 400, 800, and 1200 mg were evaluated in HV in study A2107, and to facilitate pooling of data, the study conduct was identical to that of study X2101 (Part 1). The results were overall in agreement with the results in X2101. However, the C_{max} was doubled following the 400 mg dose in study A2107, compared to the same dose of 400 mg in study X2101. When comparing the mean concentration-time profiles, the profile of the 400 mg dose in study X2101 exhibits an extended (shoulder) peak whereas the profile of the 400 mg dose in study A2107 exhibits a sharp peak. The applicant points out that less of a difference was noted for AUC_{inf} (approximately 50% higher for the 400 mg dose in study A2107 compared to the same dose in study X2101), which indicates that the rate of absorption was more affected than the extent of absorption. The difference observed between the single dose C_{max} for the 400 mg dose arms is hence likely a result of small sample sizes (n=6) in combination with an increased variability of T_{max} with increasing dose, and that more subjects in A2107 had an earlier C_{max} than subjects in X2101.

In PNH patients, PK was investigated in four studies at doses up to the proposed dose of 200 mg b.i.d. In steady-state geo-mean C_{trough} ranged from 1110 - 1909 ng/mL, concentration at T_{max} of 2 hours ranged from 3280 - 4662 ng/mL. Low accumulation was observed with ~1.3-, 2.0- and 1.6-fold for C_{min}, C_{max} and AUC_{tau}. Intra- and inter-individual variability of these exposure parameters in PNH patients was low to moderate with 16-44%.

Distribution

Based on the *in vitro* study DMPK R1500362, iptacopan was highly bound to plasma proteins, but its binding was also concentration dependent. Fraction unbound (fu) in human increased over the tested range of concentrations from 1.23% to 25.4%.

At iptacopan plasma concentrations > 750 - 1000 ng/mL, corresponding to doses at and above 100 mg b.i.d., an over-proportional increase in the unbound concentration of iptacopan appeared. From *in vitro* studies, the protein binding was evaluated as being a result of binding to its target Factor B, which is abundant (143-315 µg/ml in HV) in plasma and prevents both clearance and distribution into tissues. The rapidly increasing unbound fraction at higher doses (inflection point) suggested near-complete saturation of Factor B.

Apparent volume of distribution increased from 19.3 L at the lowest dose of 5 mg to 215 L at the highest dose of 1200 mg, and 288 L at the proposed 200 mg b.i.d. dose in steady-state. The increase of Vz/F (and CL) was less between the highest doses, but was likely related to the high-affinity binding at the target Factor B. It is noted that Table 3-8 in module 2.7.2 does not state the correct values for Vz/F after multiple dose compared to the referenced CSR source table 11-6 and table 14.2-1.2b.

Elimination

Cl/F increased with dose from 0.97 L/h at 5 mg to 7.2 L/h at 1200 mg. $T_{1/2}$ was on average 13.5-18.4 h after a single dose and 18-25 h across doses on day 14, so longer $T_{1/2}$ was seen at steady-state. At the proposed dose of 200 mg b.i.d. in steady-state Cl/F was 2.9 L/h and $t_{1/2}$ 23.3 hours.

The mean percentage of a 100 mg dose recovered in urine as unchanged parent was slightly higher in fasted (14.1%) than in fed state (12.6%) whereas the mean renal clearance was identical in fasted (662 mL*ng/mL / (hr*ng/mL)) and fed states (661 mL*ng/mL / (hr*ng/mL)), corresponding to

CLr of 11 mL/min. It is agreed with the applicant's calculations that for an unbound fraction of 18% for iptacopan at C_{max} of a 200 mg dose and an average human GFR of 95 mL/min, the calculated CLr for iptacopan would roughly amount to 17 mL/min, so that active renal secretion is unlikely.

In the study X1102, a dose dependent increase was observed for the percentage of iptacopan recovered from urine with mean 16.2, 22.6 and 31.9% of the dose of 25 mg, 100 mg and 400 mg, respectively. The amount recovered during 24h (A_{e0-24}) increased from 3.68, 21.0 to 118 mg, resp. The amount for the 100 mg dose within the first 24 hours is comparable to that recovered in the mass balance of mean 22.6 mg.

In the mass balance study, total recovery of 96.4% of radioactivity in urine and faeces was above the guideline-recommended lower limit of 90% so the mass balance study was able to adequately evaluate the elimination. This included multiple hepatic and extrahepatic pathways, predominantly via metabolism in the liver and subsequent excretion via faeces. Recovery of radioactivity in faeces was 71.5% (with 16.8 % unchanged drug and 45.8% attributed to metabolites) of total dose).

Radioactivity collected in urine was 24.8% (17.9% unchanged drug) of total dose with 22.6 mg within the first 24 hours so this would indicate the minimum absorption.

The dose of 100 mg investigated in the mass balance study is nevertheless acceptable for evaluation of elimination and can be extrapolated to the proposed clinical dose of 200 mg b.i.d. even considering the dose dependency of the elimination due to the low unbound fraction at low iptacopan exposures.

Maximal radioactivity in plasma was about 25% higher than iptacopan C_{max}, indicating the presence of radioactive metabolites. But as half-life of radioactivity in plasma was only slightly longer (14.7 vs. 12.3 hours) than that of parent, half-life of metabolites was not relevantly longer and most radioactivity in plasma could be ascribed to iptacopan.

Metabolism

In the mass balance study parent iptacopan was the most abundant compound in plasma with 83% of AUC_{0-48h}. Two metabolites were detected in plasma, the acyl glucuronides M8 and M9, with 8% and 5%, respectively. In urine, unchanged iptacopan was excreted with 17.9% of the dose and 6 metabolites < 3.8%. In faeces the most abundant structure was M2 with 27.0% and 16.8% unchanged drug. The Guideline on interactions recommends that more than 80% of the excreted dose should be identified, this was fulfilled as 87.4% of the dose was identified (24.8% in urine and 62.7% in faeces), iptacopan and 5 metabolites < 8.3%, respectively. Please refer to the non-clinical part for details on metabolism.

No further investigation of PK of metabolites was performed except for calculating AUC_{0-48} for the two metabolites M8 and M9 detected in plasma in the mass balance study, and an exploratory PK analysis at steady-state in the IgAN study, an indication not sought here. Both metabolites had T_{max} at 2-3 hours and the exploratory exposure analysis revealed 17.8% for M8 and 6.5% for M9 of total AUC. This is higher compared to mass balance study were both M8 and M9 were below 10 %. However, since this was % of total circulating material it is likely an overestimation as well as expected accumulation at steady state. When comparing the AUC of M8 and AUC of M9 to the AUC of iptacopan, it was 23% and 9%, respectively. Thus, neither M8 nor M9 can be defined as a major metabolite. Also, the applicant has provided an *in vitro* study supporting that the metabolites have low reactivity. Therefore, there are no concerns regarding theses metabolites. As both metabolites M8 and M9 are glucuronides it can be assumed that they do not exhibit any activity at the target structure and as so, their measured activity was 27-150-fold less than parent. Considering this and their low percentage of total plasma exposure it is acceptable that pharmacokinetics of metabolites have not further been measured in clinical studies.

The contribution of individual enzymes to the *in vitro* metabolism of iptacopan was also investigated in different systems including human liver microsomes and recombinant enzymes. CYP2C8 appeared to have the most relevant contribution, with some involvement of CYP2D6, CYP1A1, UGT1A1, UGT1A3 and UGT1A8 enzymes. Elimination pathways were also estimated in the PBPK model, however, the results retrieved from the PBPK modelling are not considered to be adequate.

Metabolism of iptacopan includes enzymes and transporters which show polymorphism, here UGT1A1, CYP2C8 and OATP1B1. The results of a pooled genetic analysis from 2 studies (X2101 and X1102) showed a statistically significant association of certain CYP2C8 and OAT1B1 genotypes with higher Clearance and lower exposure. As UGT1A1 metabolism is only responsible for 8% of clearance via glucuronidation, the impact of polymorphism was deemed not clinically relevant. However, as these analyses were based on very small sample sizes, further evaluation in larger studies seems relevant, even if the effects might be smaller than with intake of concomitant enzyme inhibitors.

The applicant has clarified and provided reference literature to show that acidification of plasma samples is a standard procedure used to prevent both acyl migration and hydrolysis of acyl glucuronide metabolites. It was also shown that the pharmacokinetics of iptacopan was not affected by the acidification process used in the human ADME study.

Special populations

No dedicated renal impairment study was performed. It was already discussed in the EMA scientific advice procedures that PK data from patients with severe RI are planned to be collected in the ongoing IgAN Phase 3 study CLNP023A2301 to determine whether a dose adjustment may be required. Results will be available after study completion in 2026 (see RMP?). PopPK modelling indicated a change in $AUC_{0\text{-}24}$ between 38% increase and 13% decrease between 27-143 ml/min/1.73m² which is considered not relevant with regard to clinical safety and (lack of) efficacy. Considering that renal elimination is not a major pathway, it can be accepted that no dose adjustment is proposed for mild and moderate RI when no further conditions are additive, e.g. concomitant medications are taken affecting also renal elimination.

In studies X2202 and X2203 median eGRF was 59 and 48 ml/min/1.73m², both studies are included in the popPK datapool. It was stated in the popPK report that "*As would be expected for the PNH patient population, there was a trend for higher eGFR, compared to patients with non-PNH disease*." with medians between 93-116 ml/min/1.73m² in the 3 studies X2204, C12301 and C12302. Thus, for the underlying PNH disease, cases of severe renal impairment might be less often than in the other study patients' population. As the EMA renal impairment guideline requests that "[…] *dose recommendations for a renally eliminated drug should be based on absolute GFR (or other measure for renal function in ml/min), and not on GFR normalised to a body surface area of 1.73 m²*. As no data are available for severe renal impairment or on dialysis, this is also stated in section 4.2 of the SmPC.

In the dedicated HI study, total plasma AUC and C_{max} did not increase relevantly (within ±10%) with increasing severity of HI according to Child-Pugh, but $t_{1/2}$ increased from 19.6 h up to 26.5 h, i.e. by 35%. In contrast, unbound C_{max} and AUC increased significantly by 2.11-, 3.72- and 3.71-fold, for mild, moderate and severe HI, respectively. A strong correlation of the unbound exposure fraction with albumin concentrations (negative) and Prothrombin Int ratio (positive) with increasing severity of hepatic impairment was demonstrated. Additionally, a hypothetical mechanism for the increase in unbound plasma iptacopan may be decreased liver production of Factor B due to liver impairment. Factor B is the high affinity, high plasma concentration target of iptacopan. However, Factor B levels were not measured in this HI study in order to confirm this hypothesis. The impact of decreased Factor B levels in severe HI with additional dysfunction of the kidneys would probably result in even higher exposure (see SmPC section 4.2).

To confirm that the selected HI categories were truly representative/relevant for the PK objective of the HI study, the applicant was requested to present individual Child-Pugh sub-scores. Individual scores for hepatic encephalopathy and ascites were provided but not for albumin, bilirubin and prothrombin. However, median values are presented and show that within each parameter there is a gradual worsening thar correlates to Child-Pugh score. Although the Child-Pugh score classification for each group of hepatic impairment is according to guideline recommendations, it should be noted that moderate group is at the lower end of the Child Pugh B score.

By PBPK modelling it was sought to account for Factor B decreases using a specific Child-Pugh and-Factor B-adjusted modelling, however, the model underpredicted C_{max} and AUCinf for the HI groups. Despite the lack of safety issues in the severe HI group, the group size, with n=6 is small, and the risk of increased AE cannot be excluded at a 3.7-fold increased AUC. Thus, a more conservative approach would be preferred, for example by initiating treatment with iptacopan at 200mg once daily in the severe HI population, and increasing the dose in case the response is insufficient and the treatment is well tolerated. Instead of decreasing the dose to correct for the increased unbound exposure in subjects with severe hepatic impairment, the applicant proposes not to recommend iptacopan in this group of patients, as it is unclear whether an efficacious dose would be reached with 200 mg once daily. This cautious approach is endorsed and reflected in section 4.2 of the SmPC.

Gender did not have a relevant impact on iptacopan PK. No relevant effect of race/ethnicity on PK was observed in the Japanese HV study and in the popPK, the effect of Asian ethnicity on PK was limited, therefore no dose adjustments are needed. In the range of 35-120 kg bodyweight no clinically relevant decrease or increase of exposure was estimated with up to 22%. Age was not a significant covariate and no dose adjustments are needed.

Drug interactions

Iptacopan is a substrate for the efflux transporters PgP, BCRP and MRP2. Based on the maximal gut concentration of 200 mg iptacopan of 568 µM, its fa of 71% and the results from the clinical DDI study A2104 no further clinical DDI studies for PgP, BCRP and MRP2 were warranted. A study for investigation of the DDI potential of iptacopan was performed, with iptacopan as victim for metabolism and elimination pathways concerning CYP2C8 and OATP1B1 and as perpetrator for PgP and OATP. Overall, the utilised inhibitors and substrates in this DDI study were the recommended substances according to the draft ICH M12 guideline for drugs in clinical DDI studies, or for clopidogrel as recommended from US FDA:

- Clopidogrel at the dose of 75 mg is a moderate inhibitor of CYP2C8, and also inhibits OATP1B.
- Cyclosporine is an inhibitor of OATP1B but also inhibits MRP2, PgP and BCRP
- Digoxin is a substrate of PgP, both at intestinal and hepatic and renal level
- Rosuvastatin is a substrate of OATP1B1/3 but also of BCRP, OAT3 and OATP2B1.

The inhibition by clopidogrel had nearly no effect on C_{max} (+5%) but increased AUC by ~35%, $t_{1/2}$ was prolonged by ~40%, CL/F decreased by ~30% and urinary elimination (Ae and CLr) of iptacopan increased by ~40%, respectively, which would be classified as mild effect.

However, it is emphasised that clopidogrel at the used dose of 75 mg is only a moderate inhibitor of CYP2C8 (instead of "strong" as stated in the SmPC), so higher increases may be possible in combination with a strong inhibitor. As no selective strong inhibitor of CYP2C8 is currently recommended, and gemfibrozil, which is listed in draft ICH M12 Table 13 also inhibits OATP1B1 and would have hence possibly also inhibited hepatic uptake of iptacopan, the decision to selectively investigate the 2C8 interaction with clopidogrel as inhibitor seems reasonable. The metabolism via 2C8 was estimated with ~55% of dose, i.e. >65% of the hepatically eliminated iptacopan. Therefore, while

it may be concluded from the mild DDI results on exposure that no dose adjustments would be necessary under concomitant treatment with moderate CYP2C8 inhibitors, the effect of strong inhibitors especially e.g. with concurrent hepatic impairment was questioned. In the clinical study A2104, the 35% increase in AUC when clopidogrel is administered with iptacopan is relatively small, and it can be expected that a stronger inhibitor of CYP2C8 would give a larger effect. However, gemfibrozil is unlikely to be co-administered with iptacopan in patients with severe HI, as it is contraindicated in these patients.

Considering the upper boundary of therapeutic window, there is no need for dose adjustment for co-administration with moderate CYP2C8 inhibitors, PgP, BCRP or OATP inhibitors, and, despite no data being available, it is also likely that the use of strong CYP2C8 inhibitors would not impact on safety, given the small magnitude of the exposure increase in the study with clopidogrel.

The inhibition by cyclosporine increased plasma exposure as of C_{max} and AUC to 41-50%. $T_{1/2}$ was prolonged by ~50%, CL/F decreased by ~30% and the amount eliminated in urine (Ae) of iptacopan increased by ~70%, respectively. This would also be also classified as mild DDI effects.

However, several interactions with the strong OATP1B1 inhibitor cyclosporine are envisaged: hepatic uptake via OATP1B1, and gut absorption and biliary secretion of iptacopan via PgP. No dose adjustments are proposed in the SmPC.

In general, it is emphasised that no long-term clinical safety data are available to justify exposures higher than the normal observed range.

Regarding its effects as a perpetrator, multiple doses of iptacopan showed only marginal inhibition on the plasma exposures of digoxin at PgP and rosuvastatin at OATP1B1/3 and BCRP, so that a clinically relevant effect of iptacopan on such substrates could be excluded.

Considering the plasma C_{max} of ~10 µM, the maximal concentration in gut of 568 µM and that *in vitro* no saturation of PgP and BCRP up to 800 µM and of MRP2 up to 400 µM was observed, and that iptacopan had no effect on absorption digoxin and rosuvastatin, the applicant's argumentation is deemed acceptable that no further clinical DDI studies for these 3 transporters are necessary. As all share the same efflux directions into gut, bile and urine, the marginal DDI effect observed here can be considered the net effect.

No study was performed for iptacopan as UGT1A1 substrate. The applicant argues that the glucuronide metabolite M8 in plasma is only found at about 8% so that the contribution of glucuronidation to metabolic pathway might be low. In addition, it is known that UGTs can be induced by PXR agonists, e.g. strong CYP3A inducers. In the absence of data on the effect of inducers on iptacopan, the concomitant administration with a strong inducer should not be recommended. SmPC warnings to avoid concomitant use of strong inducers, with a monitor for lack of efficacy, for example signs of haemolysis, in the case it is not possible to refrain from using a strong inducer are included (see SmPC section 4.4 and 4.5).

The potential for clinically relevant induction of CYP3A4 by iptacopan and of time dependent inhibition of CYP2C8 by iptacopan could not be excluded based on in vitro data, basic kinetic modelling or the mechanistic static model. SmPC warnings have been proposed, which are acceptable. In order to follow up the mentioned interaction potential, the applicant was recommended to, and committed to conduct a dedicated clinical study with iptacopan (multiple dose) as a potential clinical CYP2C8 time-dependent inhibitor together with repaglinide as a sensitive CYP2C8 substrate (**REC**).

The applicant also committed to further investigate induction potential of iptacopan towards CYP3A4 substrates conducting a RIS assessment with one qualified hepatocyte batch (**REC**). The SmPC texts may be revised once this data becomes available.

Pharmacometrics / exposure-response modelling

The effect of missed doses was calculated and simulated by PKPD. Based on an average 200 mg b.i.d. C_{min} of 1350 ng/mL, the iptacopan concentrations after one, two or three missed doses were calculated with ~960 ng/mL, ~680 ng/mL and ~470 ng/mL, respectively. Considering pharmacodynamic EC_{90} thresholds, 3 missed doses, i.e. 1.5 days would still result in high enough concentrations in 50% of patients for clinically meaningful protection against haemolysis (as of 520 ng/mL for $C_{min,ss}$ of the 25 mg b.i.d. regimen). Regarding the dosing recommendations given in the SmPC to take missed doses asap even if it is shortly before the next scheduled time point, the applicant discussed that increasing the dose to 400 mg in such a situation would not result in safety problems which is acceptable. However, the lower boundary was not discussed. Information has been included in section 4.2 and in the PL.

Overall, diagnostic plots showed an acceptable fit of the model. However, the evaluation of the model separated by different studies indications and time points resulted in VPCs with a low number of observations and broad predicted confidence intervals which did not always contain the observed values (n=159 patients divided into different subpopulations). VPCs combining data from different studies for the PNH indication for relevant time points to facilitate a better evaluation of the absorption phase showed an acceptable fit of the model.

As the platform is not qualified for the intended purpose PBPK modelling results was not to be used to justify dose recommendations regarding drug-drug-interactions or organ impairment in the SmPC. Modelling results tended to underestimate C_{max} whereas concentrations during elimination phase were overpredicted, indicating that the model was not able to describe the PK of iptacopan adequately.

In the popPK exposure was modelled for a PNH patient with eGFR of 81ml/min/1.73m² and 70 kg. Median (90% prediction interval) AUC_{0-24} was 2626.2 (1666.6-4338.6) ng*day/ml, median C_{max} 3403.4 (2138.1-6202.1) ng/ml and median C_{min} 1886.2 (946.9-3033.1) ng/ml. From a mean C_{max} of ~4 µg/mL and a mean C_{ave} of ~2 µg/mL and a molecular weight of 422.52 Da, the iptacopan mass concentrations can be calculated to correspond to molar concentrations of ~10 µM ((0.004 µg/L/422.52)=9.5 µM) and ~5 µM ((0.002 µg/L/422.52)=4.7 µM), respectively.

The conclusions from the E_{max} response models regarding the optimal dose relied mainly on the Wieslab assay. It should be kept in mind that Wieslab assay results are influenced by the concentration of iptacopan itself, leading to lower results in the assay with increasing concentrations of iptacopan. Under these circumstances, the validity of the assay is regarded as limited.

Pharmacodynamics

Iptacopan is a selective inhibitor of factor B and its activated form Bb, an acute phase protein implicated in the alternative pathway (AP) of complement activation. The PD effect of iptacopan therapy was evaluated by measuring the plasma concentration of activated factor B (Bb) and the Wieslab assay, which estimates the AP activation specifically. A third test (sC5b-9 or soluble membrane attack complex [sMAC]) does not fully reflect AP activation and displayed only a weak response to iptacopan but correlated well with the other tests. The applicant pointed out that sC5-9 is also formed by other complement pathways, not only by AP. Nevertheless, one could expect some reduction when one of the pathways (AP in this case) is inhibited. However, complement inhibition by anti-C5 up-regulated baseline sC5-9, indicating that AP inhibition may up-regulate other complement activation pathways. In consequence, sC5-9 concentration would be hardly affected by AP inhibition, in line with the observation. All 3 biomarkers revealed an AP inhibition approximately 2 hours after iptacopan intake across healthy subjects and patients with PNH and other complement-related disorders. The factor Bb assay showed no clear dose- and time-dependency (i.e. when factor Bb level was measured

repeatedly after one iptacopan administration) particularly after a single iptacopan dose. Multiple dosing yielded clearer results. It should be noted that iptacopan inhibits the protease activity of factor Bb but should not diminish its amount. However, as pointed out by the applicant, factor B must bind to factor C3b before it can be cleaved. Long-term inhibition of the AP will decrease the amount of C3b so that eventually also less cleavage of factor B to form Bb will occur. Other biomarkers such as CH50 confirmed that both the classical and lectin complement pathways were left untouched. Overall, the evidence presented by the applicant was convincing of the selective effect of iptacopan on AP complement inhibition.

The primary pharmacology studies for iptacopan mostly rely on the Wieslab assay, which can measure complement activation by any pathway. Pooled PKPD analyses of 247 patients/healthy volunteers (29 PNH patients) with a dose range of 5-400 mg (PNH: 25-200 mg) were conducted. The data in PNH patients is limited and the results should be interpreted with caution. In patients on anti-C5 treatment, iptacopan was shown to prevent C3 fragment deposition on PNH RBCs, thus preventing extravascular haemolysis after anti-C5 therapy was stopped. A clear dose-response correlation was observed in healthy volunteers and in patients and the highest magnitude of AP inhibition, also in the setting of increased baseline factor B levels (as seen in patients with PNH), was observed for the 200 mg twice daily dose. This was confirmed by exposure-response analysis of Wieslab, Bb and sMAC, where the maximal and most consistent AP inhibition was observed with the 200 mg dose twice daily, even after missed doses for 1-2 days.

The applicant conducted a C-QTc analysis for iptacopan on pooled concentration and QT data from studies X2101 (Part 1) and A2107. Data from single doses of 5, 10, 25, 50, 100, 200, 400, 800, 1200 mg or placebo were included in the analysis. There is no indication of any clinically relevant treatment effect on the heart rate, blood pressure and QT interval, neither in the primary analysis nor in any of the sensitivity analyses presented. The decision to choose the 200 mg twice daily dose was clearly supported by the evidence presented, even in situations of high factor B levels or imperfect adherence to therapy.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacokinetics development can overall be considered adequate. PK in severe renally impaired patients is under ongoing investigation in a phase 3 study in another indication which is acceptable. The applicant accepted two recommendations from the CHMP that entail studying the time-dependent inhibition of CYP2C8 in a dedicated multiple dose clinical study with repaglinide and the induction of CYP3A4 by iptacopan in a qualified hepatocyte batch using RIS.

Iptacopan’s mode of action has been clearly described and characterised; Iptacopan blocked lysis of erythrocytes from PNH patients in vitro and prevented deposition of C3 activation fragments on these cells. Further, a clear dose-response correlation was observed in healthy volunteers and patients, and secondary pharmacology studies confirmed a lack of impact on heart rate, blood pressure and QT interval. The decision to choose the 200 mg twice daily dose was adequately justified.

Overall, the pharmacological profile supports the use of iptacopan in patients with PNH.

2.6.5. Clinical efficacy

The iptacopan PNH development programme includes a total of 170 PNH patients. The primary efficacy and safety data supporting the PNH indication are provided by:

- Pivotal Phase III study CLNP023C12302 (APPLY-PNH), a randomised, active-controlled study, comparing 200 mg twice daily iptacopan monotherapy to anti-C5 treatment in 97 PNH patients with residual anaemia despite prior anti-C5 therapy,
- Supportive Phase III study CLNP023C12301 (APPOINT-PNH), a single arm, open-label, study, evaluating 200 mg twice daily iptacopan monotherapy in 40 PNH patients who were naïve to complement inhibitor treatment,

Supportive evidence had been generated by:

- Two open-label Phase II PNH studies in 29 PNH patients (CLNP023X2201 in anti-C5 experienced patients and CLNP023X2204 in complement inhibitor-naïve patients) providing a minimum of 2 years of long-term efficacy and safety data with 200 mg b.i.d. iptacopan monotherapy.

2.6.5.1. Dose response studies

A dose of 200 mg bid iptacopan was applied in the phase 3 studies and recommended in the label (section 4.2 of the SmPC). The iptacopan 200 mg b.i.d. dosing was selected for the phase 3 studies based on the available PK/PD, efficacy and safety data from the Phase I first-in-human study (Study X2101) and the phase II studies in patients with PNH, Studies X2204 and X2201. Both studies showed numerically better inhibition of IVH (assessed by LDH changes) with the iptacopan 200 mg bid regimen compared to the lower doses investigated. The phase 2 studies are described under "supportive studies" on this report.

2.6.5.2. Main study

APPLY-PNH

Study design

APPLY-PNH was a randomised, open-label, active-comparator trial which enrolled 97 adult PNH patients with residual anaemia (Hb <10g/ dL) despite receiving a stable regimen of anti-C5 antibody therapy (eculizumab or ravulizumab) for at least 6 months prior to randomisation.

Treatments

Patients received iptacopan monotherapy 200 mg b.i.d. (n=62) or continued their anti-C5 regimen (n=35) for 24 weeks (randomised treatment period).

Study population

The study population was representative of PNH patients with residual anaemia despite anti-C5 treatment with a mean (SD) baseline Hb of 8.9 g/dL and 58% of patients being transfusion dependent during the 6 months prior to randomisation.

Randomisation and blinding

This was an open label study. Patients were randomised in an 8:5 ratio to receive iptacopan monotherapy 200 mg twice daily or the same regimen and interval of their prior anti-C5 treatment for the duration of the 24-week randomised trial period (RTP). Patients were stratified at randomisation based on the type of prior anti-C5 treatment (eculizumab or ravulizumab) and transfusion history reported during the 6 months prior to randomisation (transfusion received or transfusion not received). Of note, the initiation of iptacopan treatment had an overlap of 1 week (eculizumab) and 2 weeks (ravulizumab) with prior anti-C5 antibody therapy.

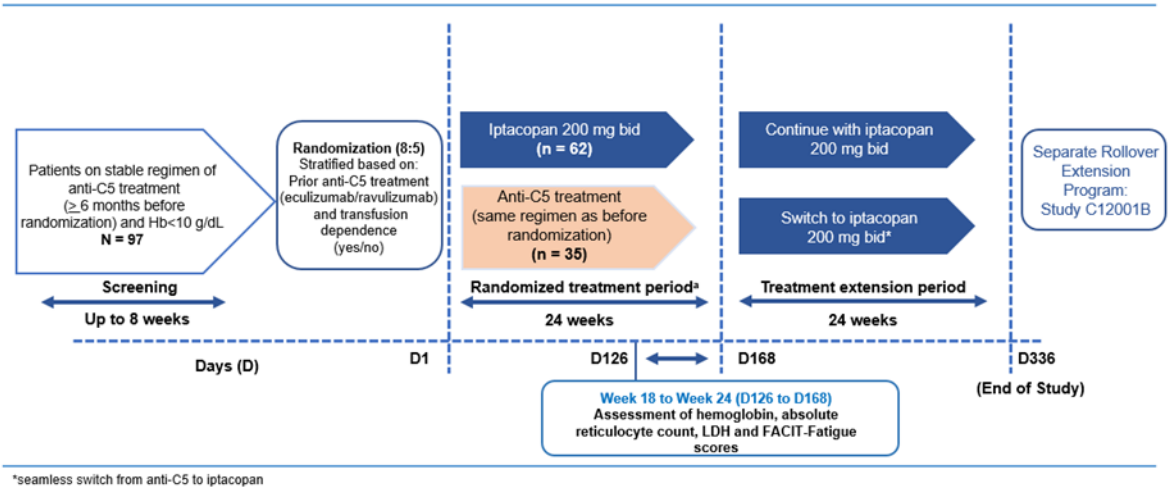


Figure 48: APPLY-PNH study design

Methods

Study participants

Patients with residual anaemia despite anti-C5 treatment during the 6 months prior to randomisation were included.

Main inclusion criteria:

- 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 of anti-C5 antibody treatment (eculizumab or ravulizumab) for at least 6 months prior to randomisation
- Mean Hb level <10 g/dL (historical data over at least 4 months confirmed by central lab data during screening)
- Vaccination required against *Neisseria meningitidis* infection and vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* recommended if available. Vaccine was to be given according to local regulations, at least 2 weeks prior to first dosing. If treatment had to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment was required to be initiated.

Main exclusion criteria:

- Known or suspected hereditary complement deficiency at screening
- History of Hematopoietic Stem Cell Transplantation
- History of recurrent invasive infections caused by encapsulated organisms, or active infection (within 14 days prior to study drug administration)
- Laboratory evidence of bone marrow failure (reticulocytes < 100×10^9/L; platelets < 30×10^9/L; neutrophils < 500×10^6/L)

- Major concurrent comorbidities including but not limited to severe kidney disease, advanced cardiac disease, severe pulmonary disease or hepatic disease
- Concomitant use of systemic corticosteroids was prohibited if not on stable regimen for at least 4 weeks, or immunosuppressants if not on stable regimen for at least 8 weeks prior to screening

Outcomes/endpoints

Primary endpoints

The primary efficacy analysis of the RTP was based on two haematological responder endpoints:

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

A patient was a responder meeting the criterion for the two primary endpoints if they:

- Achieved a sustained haematological response, defined as 3 out of 4 assessments between Day 126 and Day 168.
- Did not receive a transfusion or met one of the following pre-defined criteria for transfusion: 1) Hb between >7 and ≤ 9g/dL with signs/symptoms of sufficient severity to warrant a transfusion or 2) Hb ≤7g/dL regardless of presence of clinical signs and/or symptoms.

Secondary endpoints

- Transfusion avoidance (absence of RBC transfusions) between Day 14 and Day 168
- Average change in Hb (g/dL) from baseline as mean of visits between Day 126 and Day 168
- Improvement in fatigue from baseline, using the FACIT-Fatigue questionnaire as mean of visits between Day 126 and Day 168
- Average change in absolute reticulocyte counts (ARC) from baseline as mean of visits between Day 126 and Day 168
- Rate of clinical breakthrough haemolysis (BTH) reported between Day 1 and Day 168
- Rates of major adverse vascular events (MAVEs) including thrombosis reported between Day 1 and Day 168
- Average percent change in LDH levels from baseline as mean of visits between Day 126 and Day 168.

Estimands

The intercurrent events of RBC transfusion, treatment discontinuation, BTH events, MAVEs and rescue medications were considered in the protocol as potentially important for interpretation of the trial results, hence estimands for all primary and secondary endpoints were defined.

For the two primary haematological response endpoints, absence of RBC transfusion is an integral part of the endpoint definition, such that patients receiving transfusion or meeting criteria for transfusion between Day 14 and Day 168 were automatically considered as failures. All other intercurrent events

were reflected in the primary estimands following a treatment policy strategy, meaning that the efficacy benefit would be assessed regardless of these events occurring.

The efficacy estimands break down into three main categories:

- Treatment policy estimand – To assess the efficacy benefit regardless of the occurrence of intercurrent events such as treatment discontinuation, breakthrough haemolysis events and MAVEs. All data are included in the analysis.
- Direct efficacy estimand – To assess the direct efficacy benefit of iptacopan vs anti-C5, not including any efficacy benefit derived from RBC transfusion use. In this case, the impact of transfusion use is factored out through the analysis approach.
- Including-transfusion estimand – To assess the benefit of iptacopan vs anti-C5 in conjunction with RBC transfusion use as part of a treatment strategy. All data are included in the analysis.

Statistical methods

The overall study Type I error was one-sided 0.025. Superiority of iptacopan in achieving a larger proportion of patients who reached a sustained haemoglobin response compared to anti-C5 antibody treatment was tested by the null hypothesis of an odds ratio of 1 comparing the probability of response in iptacopan to the probability of response on anti-C5 antibody treatment for both endpoints.

For each of the two primary endpoints, the test of hypothesis was initially implemented by fitting a conditional logistic regression model, which conditioned on stratum within which patients were randomised, and included as covariates both sex, age (indicator of age ≥ 45 years), and an indicator variable of baseline haemoglobin above 9 g/dL. However, these analyses models did not converge due to zero responders in the anti-C5 arm.

As per Protocol v00 Section 12.4.7, cases of non-convergence due to sparsity of events were handled with a penalised likelihood (Firth) approach. Hence, the test of the hypotheses associated to the two primary endpoints were carried out by fitting a logistic regression model, based on Firth's penalised maximum likelihood method (Heinze, Schemper 2002, Firth 1993).

The models included treatment, the randomisation stratum, sex, age (indicator of age ≥ 45 years), and an indicator variable of baseline haemoglobin ≥ 9 g/dL as covariates. The summary measures provided were: the odds ratio (and 95% CI); marginal proportions and difference in marginal proportions (and 95%); ratio of marginal proportions (and 95% CI). The confidence intervals for the difference as well as for the ratio of proportions will be derived by use of bootstrap. The term 'marginal proportion' can be interpreted as the population average probability of being a responder for each treatment group. These values include adjustment for baseline covariates and missing data has also been taken into account. Hence these values will not be identical to the observed proportions.

The multiplicity adjustment to be applied for the test of two primary endpoints as well as to the secondary endpoints for which the study wise Type I error was controlled, is described graphically in Figure 9-2 of the study report.

To adjust for multiplicity of the simultaneous test of two primary endpoints, a weighted permutation test with equal weights to each of the two endpoints was applied. The reference distribution of the p-values was derived using 50,000 permuted realisations of the treatment labels within each randomisation stratum and obtaining the p-values of each of the two endpoints for each realisation of permuted treatment labels. The observed p-values from each fit with the actual treatment labels were compared with the 1.25th percentiles of the 50,000 resulting p-values from fits with permuted treatment labels for each of the two endpoints (Westfall 2008, Westfall 1997, Westfall *et al*. 1993).

The alpha propagation rules following principles described in Bretz *et al*. (Bretz *et al*. 2009, Bretz *et al*. 2011) which can be summarised as follows:

1. Hypotheses H1 and H2 were tested using the permutation test described above. The available ½ study alpha may be distributed between the two as shown in the figure by shifting 10% from a successfully rejected hypothesis.
2. Secondary endpoints H3 and hypotheses H41, H42, and H43 denoted by the node H4i were tested if at least one primary endpoint hypothesis was rejected. A weighted Simes procedure was used to test H3 and H4i.
3. Secondary endpoints in H5i: H51, H52, and H53 were tested after successful rejection of hypotheses in H1, H2, H3, and H4i.

Results

Patient disposition

All 97 patients completed the 24-week RTP (96 were on treatment). No patients discontinued treatment due to an adverse event (AE) during the 24-week RTP; one patient in the iptacopan arm discontinued study treatment because of pregnancy but continued all study assessments until the end of the extension treatment period.

Table 33: Patient disposition in APPLY-PNH (FAS)

	LNP023 200mg b.i.d. N=62	Anti-C5 antibody N=35	Overall N=97
Disposition/Reason	**n (%)**	**n (%)**	**n (%)**
Randomized treatment period			
Completed treatment	61 (98.4)	35 (100.0)	96 (99.0)
Discontinued from treatment	1 (1.6)	0	1 (1.0)
Reason for discontinuation			
Pregnancy	1 (1.6)	0	1 (1.0)
Completed treatment period	62(100.0)	35(100.0)	97(100.0)
Discontinued treatment period	0	0	0
Extension treatment period			
Treatment ongoing #	28 (45.2)	14 (40.0)	42 (43.3)
Completed treatment	32 (51.6)	19 (54.3)	51 (52.6)
Discontinued from treatment	1 (1.6)	0	1 (1.0)
Reason for discontinuation			
Pregnancy	1 (1.6)	0	1 (1.0)
Completed treatment period	33 (53.2)	19 (54.3)	52 (53.6)
Discontinued treatment period	0	0	0

n is the number of non-missing observations in each row category.
N = number of patients in Full analysis set.
Percentages are based on no. of patients in Full analysis set.
Ongoing at the time of the data cut-off date 2022-09-26

Baseline demographics and clinical disease characteristics

The mean age was 51 years, 69.1% of patients were female, and 64.9% and 35.1% had received prior eculizumab and ravulizumab, respectively, for a mean duration of 4 years. The mean (SD) baseline Hb level was 8.904 (0.7749) g/dL, and the majority (57.7%) of patients required transfusion in the 6 months prior to randomisation. Further, 74.2% of the patients were from Europe and 8.2% patients were from the US.

Table 34: Patient demographics and baseline disease characteristics (Full Analysis Set) - APPLY-PNH

Characteristic Categories/Statistics	LNP023 200 mg b.i.d. N=62 n (%)	Anti-C5 antibody N=35 n (%)	Overall N=97 n (%)
Age (years)			
Mean (SD)	51.7 (16.94)	49.8 (16.69)	51.0 (16.79)
Age category (years) - n (%)			
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)
Gender - n (%)			
Male	19 (30.6)	11 (31.4)	30 (30.9)
Female	43 (69.4)	24 (68.6)	67 (69.1)
Race - n (%)			
White	48 (77.4)	26 (74.3)	74 (76.3)
Black or African American	2 (3.2)	2 (5.7)	4 (4.1)
Asian	12 (19.4)	7 (20.0)	19 (19.6)
Disease duration (years)[1]			
Mean (SD)	11.88 (9.813)	13.55 (10.937)	12.48 (10.208)
Anti-C5 medication history - 6 months prior to randomisation -n (%)			
Eculizumab	40 (64.5)	23 (65.7)	63 (64.9)
Ravulizumab	22 (35.5)	12 (34.3)	34 (35.1)
Duration of Anti-C5 Treatment (yrs)[2]			
Mean (SD)	3.79 (3.534)	4.23 (3.868)	3.95 (3.644)
Eculizumab dose administered (mg)			
N	40	23	63
Median (Min – Max)	900.0 (900 - 1200)	900.0 (900 - 1500)	900.0 (900 - 1500)
Ravulizumab dose administered (mg)			
N	22	12	34
Median (Min – Max)	3300.0 (3000 - 3600)	3300.0 (3000 - 3600)	3300.0 (3000 - 3600)
Baseline Haemoglobin -n (%)			
< 9 g/dL	32 (51.6)	18 (51.4)	50 (51.5)
>= 9 g/dL	30 (48.4)	17 (48.6)	47 (48.5)
Baseline Haemoglobin (g/dL)			
Mean (SD)	8.933 (0.7026)	8.853 (0.8975)	8.904 (0.7749)
Min - Max	6.80 - 9.95	6.20 - 9.90	6.20 - 9.95
LDH levels at baseline-n (%)			
<= 1.5x LDH	58 (93.5)	31 (88.6)	89 (91.8)
>1.5x LDH	4 (6.5)	3 (8.6)	7 (7.2)
LDH levels at baseline (U/L)			
Mean (SD)	269.1 (70.14)	272.7 (84.80)	270.4 (75.34)

Characteristic Categories/Statistics	LNP023 200 mg b.i.d. N=62 n (%)	Anti-C5 antibody N=35 n (%)	Overall N=97 n (%)
Min - Max	150 - 539	133 - 562	133 - 562
Transfusion in the last 12 months prior to screening -n (%)			
Yes	37 (59.7)	22 (62.9)	59 (60.8)
No	25 (40.3)	13 (37.1)	38 (39.2)
Transfusion in the last 6 months prior to randomisation -n (%)			
Yes	35 (56.5)	21 (60.0)	56 (57.7)
No	27 (43.5)	14 (40.0)	41 (42.3)
Number of transfusions in the last 6 months prior to randomisation -n (%)			
< 2	38 (61.3)	21 (60.0)	59 (60.8)
>= 2	24 (38.7)	14 (40.0)	38 (39.2)
Number of transfusions in the last 6 months prior to randomisation among patients who had a transfusion			
N	35	21	56
Mean (SD)	3.1 (2.62)	4.0 (4.39)	3.4 (3.38)
Min - Max	1 - 13	1 – 19	1 - 19
Platelets (10^9/L), Blood			
Mean (SD)	160.2 (63.83)	147.3 (77.01)	155.6 (68.77)
Min - Max	33 - 348	39 – 355	33 - 355
Absolute reticulocyte count (×10^9/L), Blood			
Mean (SD)	193.22 (83.637)	190.59 (80.922)	192.27 (82.254)
Min - Max	51.0 - 562.8	90.3 - 411.6	51.0 - 562.8
Baseline FACIT-Fatigue total score			
N	62	33	95
Mean (SD)	34.7 (9.82)	30.8 (11.45)	33.4 (10.52)
History of MAVE -n (%)			
Yes	12 (19.4)	9 (25.7)	21 (21.6)
No	50 (80.6)	26 (74.3)	76 (78.4)
History of aplastic anaemia -n (%)			
Yes	9 (14.5)	5 (14.3)	14 (14.4)
No	53 (85.5)	30 (85.7)	83 (85.6)
Vaccination history -n (%)			
Meningococcal Serogroup A	61 (98.4)	34 (97.1)	95 (97.9)
Meningococcal Serogroup C	62 (100)	34 (97.1)	96 (99.0)
Meningococcal Serogroup W-135	61 (98.4)	34 (97.1)	95 (97.9)
Meningococcal Serogroup Y	61 (98.4)	34 (97.1)	95 (97.9)
Meningococcal Serogroup B	52 (83.9)	30 (85.7)	82 (84.5)
H. Influenzae Type B	54 (87.1)	26 (74.3)	80 (82.5)
Pneumococcal Polyvalent	58 (93.5)	30 (85.7)	88 (90.7)
Other	3 (4.8)	2 (5.7)	5 (5.2)

[1] Disease duration is derived from the start date of PNH in medical history page up to the date of screening.
[2] Duration of anti-C5 treatment is calculated as treatment end date – treatment start date +1 regardless of the dose regimen.
SD = standard deviation
n is the number of non-missing observations in each row category.
Percentages are based on number of patients in Full Analysis Set in each treatment group or overall.
The baseline value is defined to be the last result obtained at or prior to start of study treatment Day 1, except for Hb. The baseline value of Hb is defined to be the mean of the two measurements taken during screening. In patients who received a transfusion after the first confirmatory measurement, the baseline is the first measurement.
Vaccination history is defined as any vaccination with a start date before Day 1.

History of MAVE

Overall, 21 (21.6%) patients, including 12 (19.4%) in the iptacopan group, had a history of MAVE. The most common history of MAVE was thrombophlebitis/deep vein thrombosis (11 patients overall (11.3%): 6/62 in iptacopan group (9.7%) vs 5/35 in anti-C5 group (14.3%), followed by Hepatic/portal vein thrombosis (Budd Chiari syndrome) (4 patients overall (4.1%): 2/62 in iptacopan group (3.2%) vs 2/35 in anti-C5 group (5.7%)).

PNH clone size at baseline

The mean (range) PNH clone size was 62.028% (*9.82* - 99.88) for total clone size in RBCs, with slight differences in the distribution of Type II and Type III RBCs between the two treatments groups (64.65% iptacopan, 57.39% anti-C5). The mean (range) proportion of C3d+ PNH RBCs (Type II and III) was 18.60 % (0.039 - 71.762).

Concomitant medication

The vast majority of the patients in both the treatment groups (iptacopan: 100% vs anti-C5 97.1%) were being treated with at least one concomitant medication between Day 1 and last dose of study treatment. The proportion of patients with most common medications class were:

• Folic acid and derivatives: iptacopan 64.5% vs anti-C5 65.7%

• Other viral vaccines (COVID-19 vaccinations): iptacopan 33.9% vs anti-C5 20.0%

• Proton pump inhibitors: iptacopan 21.0% vs anti-C5 28.6%

• Anilides: iptacopan 19.4% vs anti-C5 25.7%

• Iron chelating agents: iptacopan 14.5% vs anti-C5 22.9%.

Immunosuppressants: two patients (3.2%) in the iptacopan group and one patient (2.9%) in the anti-C5 group were receiving ciclosporin. One patient (2.9%) in the anti-C5 group was receiving tacrolimus and azathioprine. Systemic corticosteroids: Nine patients (14.5%) in the iptacopan group and two patients (5.7%) in the anti-C5 group were receiving glucocorticoids (prednisolone, methylprednisolone, prednisone and dexamethasone in the iptacopan group and prednisone in the anti-C5 group). One patient in the iptacopan group was receiving 'corticosteroids for systemic use, combinations' (betamethasone/chlorphenamine maleate).

- **Outcomes and estimation**

Primary endpoint

Iptacopan monotherapy 200 mg b.i.d. was statistically significantly superior to anti-C5, with an estimated treatment difference (95% CI) of:

1. 80.3% (71.3, 87.6) for Hb increase ≥ 2 g/dL from baseline in the absence of transfusion (unadjusted two-sided p-value <0.0001)
2. 67.0% (56.3, 76.9) for Hb ≥12 g/dL in the absence of transfusion (unadjusted two-sided p-value <0.0001).

The marginal proportion of patients by treatment arm is shown in the table below. Note that for both of the primary endpoints and to demonstrate a sustained effect, the Hb criterion had to be achieved at

the end of the RTP (i.e., between Days 126 and 168 and in at least 3 out of 4 of the scheduled measurements).

Based on evaluable/non missing observed data, 51 out of 60 patients in the iptacopan arm vs 0 out of 35 patients in the anti-C5 arm were responders for Hb increase ≥ 2g/dL from baseline in absence of transfusion, and 42 out of 60 patients in the iptacopan arm vs 0 out of 35 patients in the anti-C5 arm were responders for Hb ≥ 12g/dL in absence of transfusion.

As supportive analyses, hypothesis tests for the primary endpoints were also performed using a Cochran-Mantel-Haenszel (CMH) test. These analyses further confirmed the primary efficacy results by yielding an identical p-value (p<0.0001).

Table 35: Responder analysis of haemoglobin between Day 126 and Day 168 in the absence of RBC transfusions between Day 14 and Day 168 (Full Analysis Set) – Treatment policy estimand - APPLY-PNH

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

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

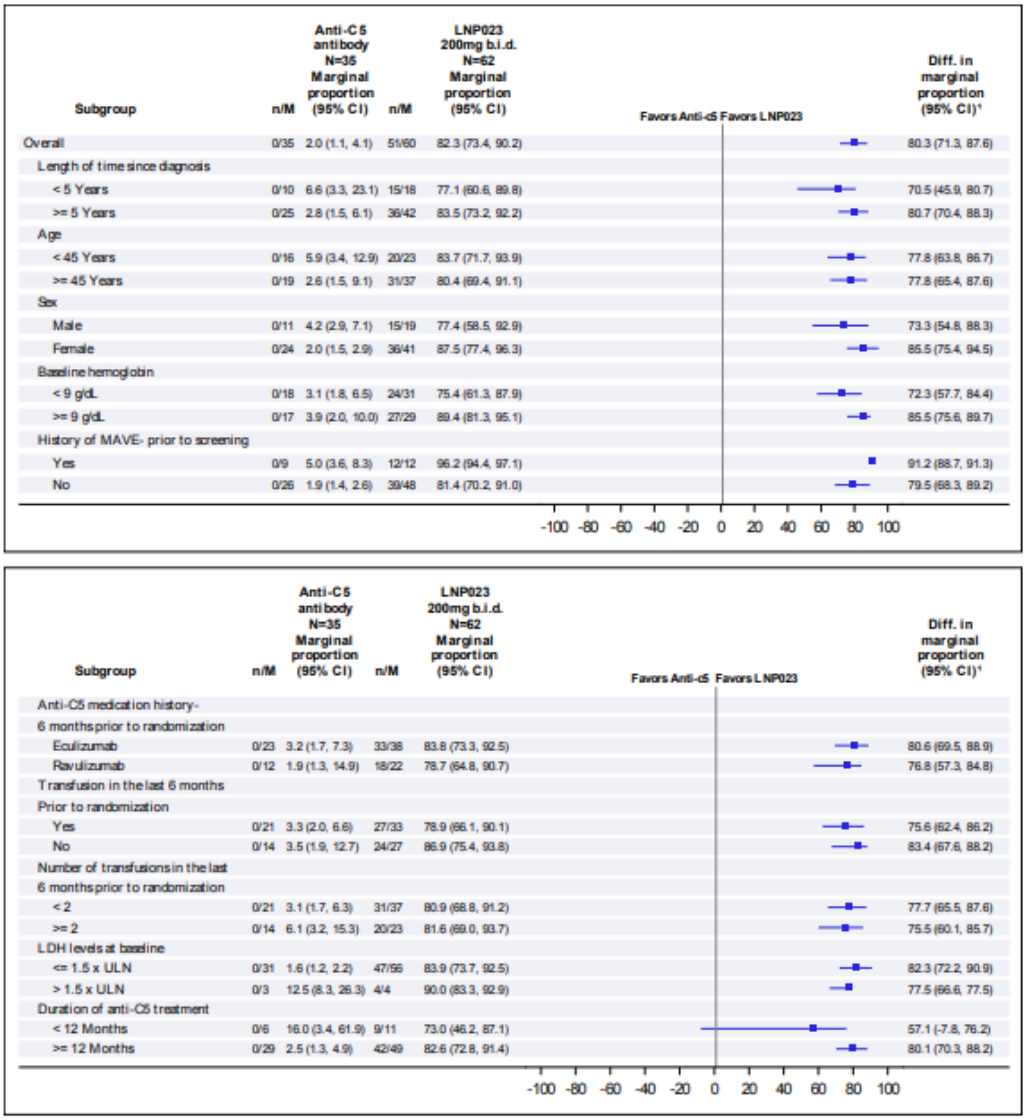
Subgroup analyses

Subgroup analyses were conducted on the primary endpoint for APPLY-PNH, to assess the consistency of effect size across different variables of interest. Subgroups were defined as follows:

Table 36: Definitions for subgroup variables of interest for APPLY-PNH and APPOINT-PNH

Subgroup analyzed	APPLY-PNH	APPOINT-PNH
Age categories	<45 years, ≥ 45 years AND <65 years, ≥ 65 years[1]	<45 years, ≥ 45 years
Race	White, non-White[1]	NE
Region	America, Asia, Europe[1, 2]	China, countries other than China
Sex	male, female	male, female
Baseline hemoglobin	<9 g/dL, ≥9 g/dL	<8 g/dL, ≥8 g/dL
Baseline LDH levels	≤ 1.5 x ULN, > 1.5 x ULN	NE
Baseline platelet count	$<100x10^6$/mL, ≥ $100x10^6$/mL[1]	NE
Length of time since diagnosis	<5 years, ≥5 years	< 3 years, ≥ 3 years
History of MAVE- prior to screening	yes, no	yes, no
Anti-C5 medication history- 6 months prior to randomization	eculizumab, ravulizumab	N/A
Duration of anti-C5 treatment	< 12 months, ≥ 12 months	N/A
Transfusion in last 6 months prior to randomization	yes, no	yes, no
No. of transfusions in last 6 months prior to starting study treatment	<2, ≥ 2	<2, ≥ 2

N/A = not applicable, NE= not evaluated
[1] SCE-specific analyses, all other analyses are included in the respective CSRs.
2 Countries are classified into regions as follows: America (Brazil, USA), Asia (Japan, South Korea, Taiwan), Europe (Czech Republic, France, Germany, Hungary, Netherlands, Italy, Spain, UK).



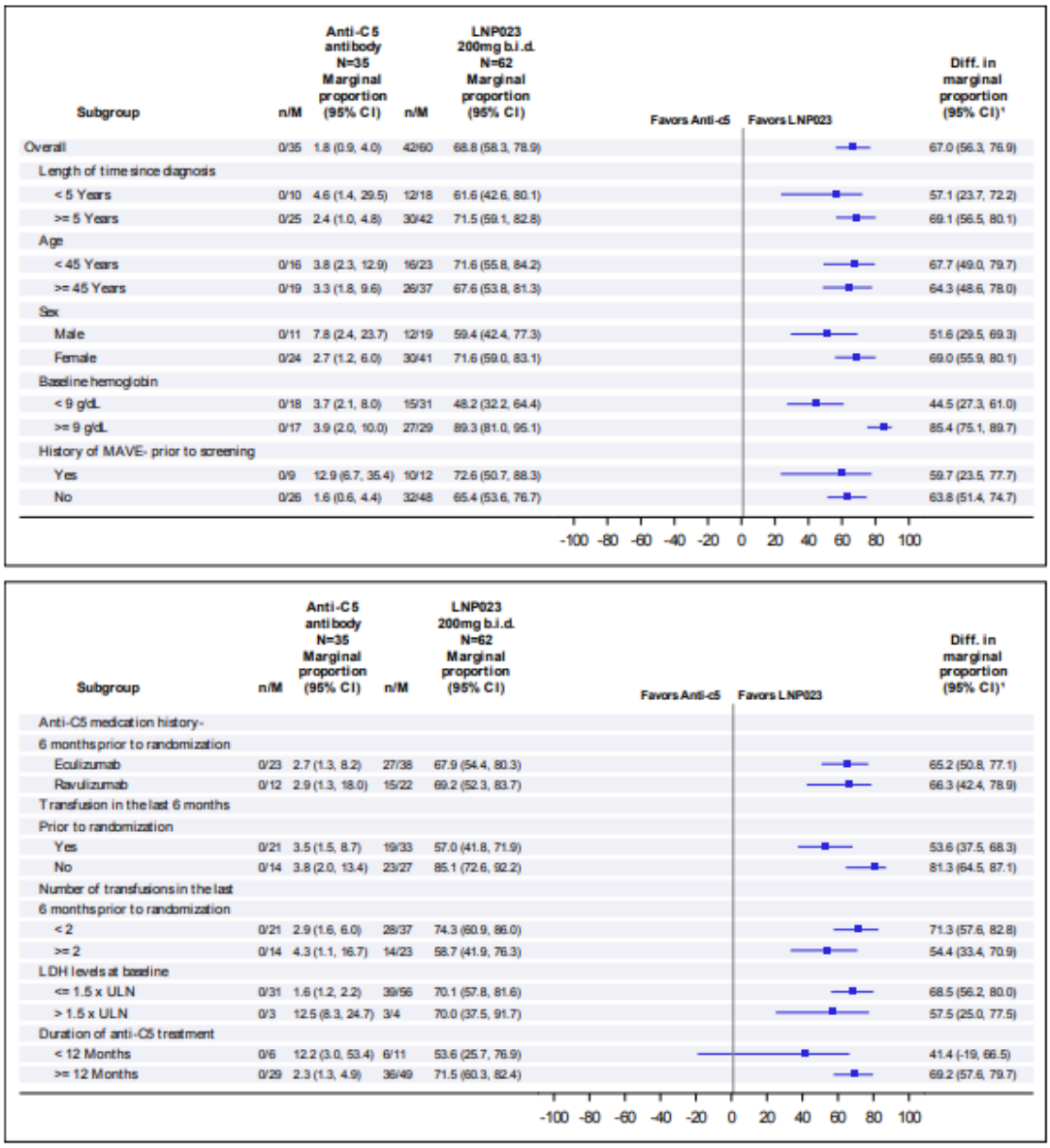
N = The total number of patients in the treatment group included in the model (without missing covariates).

n = The number of patients who responded before the occurrence of any intercurrent event.

M = The number of patients in the treatment group with response variable defined and not imputed as per the intercurrent event handling strategy.

1 Logistic regression model using Firth correction with common intercept and randomization strata, sex, indicator variable of age >= 45 years, indicator variable of baseline hemoglobin >= 9 g/dL as factors. The 95% CI is computed using bootstrap.

Figure 49: Forest plot of subgroup analysis of response based on change from baseline in haemoglobin ≥2 g/dL between Day 126 and Day 168 in the absence of requirement of red blood cell transfusions between Day 14 and Day 168 (Full Analysis Set) - APPLY-PNH



N = The total number of patients in the treatment group included in the model (without missing covariates).
n = The number of patients who responded before the occurrence of any intercurrent event.
M = The number of patients in the treatment group with response variable defined and not imputed as per the intercurrent event handling strategy.

Figure 50: Forest plot of subgroup analysis of response based on haemoglobin absolute level ≥12 g/dL between Day 126 and Day 168 in the absence of requirement of red blood cell transfusions between Day 14 and Day 168 (Full Analysis Set) - APPLY-PNH

Secondary endpoints

Iptacopan monotherapy was statistically significantly superior to anti-C5 for the following secondary endpoints based on the testing strategy:

1. Transfusion avoidance (absence of administration of RBC transfusions) between day 14 and day 168,
2. Change from baseline in Hb (g/dL) as mean of visits between Day 126 and Day 168,

3. Change from baseline in patient-reported FACIT-Fatigue scores as mean of visits between Day 126 and Day 168,
4. Change from baseline in ARC (10^9/L) as mean of visits between Day 126 and Day 168,
5. Occurrences of clinical BTH reported between Day 1 and Day 168.

Iptacopan did not show a statistically significant difference to anti-C5 for the following secondary endpoints based on the testing strategy:

- Percent change from baseline in LDH levels as mean of visits between Day126 and Day 168
- Occurrences of MAVEs between Day 1 and Day 168.

Transfusion avoidance

Iptacopan monotherapy was statistically significantly superior to anti-C5 treatment for transfusion avoidance with an estimated treatment difference of 70.3% (95% CI 52.6, 84.9), (unadjusted two-sided p-value<0.0001). Based on evaluable/non missing data, 60 out of 62 patients in the iptacopan arm were transfusion-avoidant vs 14 out of 35 patients in the anti-C5 arm.

Table 37: Analysis of transfusion avoidance between Day 14 and Day 168 (Full Analysis Set) – Treatment policy estimand - APPLY-PNH

					Unadjusted for multiplicity	
Responder Criterion Treatment	**n/M**	**Marginal proportion (95% CI)[1]**	**Diff. in marginal proportion (95% CI)[1]**	**Ratio of marginal proportion (95% CI)[1]**	**OR (95% CI)[2]**	**p-value[2]**
Transfusion avoidance (#)						
LNP023 200mg b.i.d. N=62	60/62	96.4 (90.7, 100.0)	**70.3** (52.6, 84.9)	3.72 (2.24, 7.83)	133.53 (19.78, 901.44)	**<0.0001**
Anti-C5 antibody N=35	14/35	26.1 (12.4, 42.7)				

N = The total number of patients in the treatment group included in the model (without missing covariates).
n = The number of patients who did not receive transfusions nor meet protocol defined criteria between Day 14 and Day 168 per CRF page 'Transfusion during the study'
M = The number of patients in the treatment group with response variable defined based on non-missing data (evaluable patients)
1 Logistic regression model with common intercept and randomisation strata, sex, indicator variable of age >= 45 years, indicator variable of baseline haemoglobin >= 9 g/dL as factors. The 95% CI is computed using bootstrap.
2 Conditional logistic regression model with randomisation strata, sex, indicator variable of age >= 45 years, indicator variable of baseline haemoglobin >= 9 g/dL as factors.
between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria.

The primary endpoint also incorporated a component for transfusion avoidance and the same methods to handle missing data were applied. Similar sensitivity analyses were carried out for the primary endpoints and these yielded identical results to the results already provided in the table above.

Change from baseline in haemoglobin levels

Mean (SD) Hb at baseline was 8.933 (0.7026) g/dL in iptacopan arm and 8.853 (0.8975) g/dL in anti-C5 arm. Iptacopan monotherapy was statistically significantly superior to anti-C5 antibody treatment for change from baseline in Hb with an adjusted mean difference of +3.63 g/dL (95% CI 3.18, 4.08)

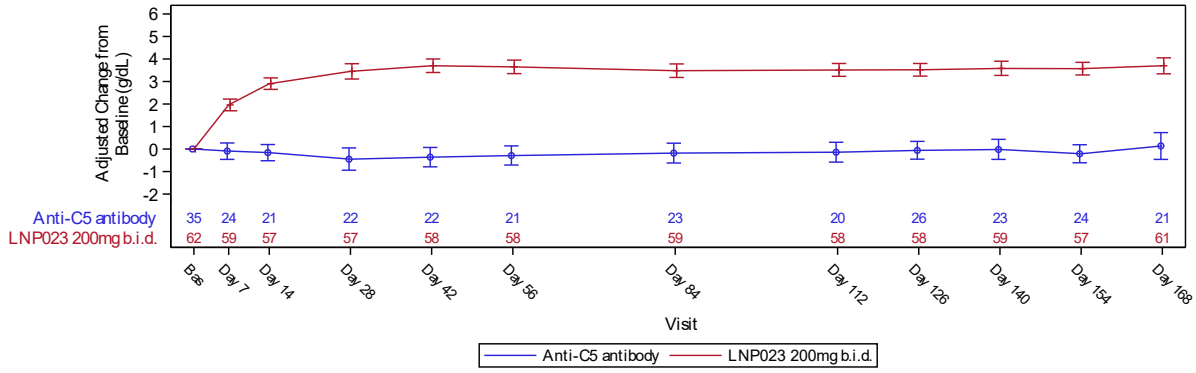
(unadjusted two-sided p-value <0.0001). The adjusted mean Hb change from baseline was +3.59 g/dL (95% CI 3.32, 3.86) in the iptacopan arm vs. −0.04 g/dL (95% CI −0.42, 0.35) in the anti-C5 arm.

In patients treated with iptacopan, increases in Hb levels were seen early in the study with an adjusted mean change from baseline of 1.96 g/dL (95% CI 1.70, 2.22) by Day 7, and further increase to adjusted mean change from baseline > 3 g/dL from Day 28 onwards (versus close to 0g/dL in the anti-C5 group). At day 168 mean haemoglobin was 12.61 g/dL (SD 1.432) in the iptacopan group and 9.15g/dL (1.407) in the anti-C5 group.

Table 38: Repeated measures analysis of change from baseline in haemoglobin levels (g/dL) – randomised treatment period in APPLY-PNH (FAS) – direct efficacy estimand

				LNP023 200mg b.i.d. vs. Anti-C5 antibody	
Visit	**Treatment**	**n**	**Adjusted mean (95% CI)**	**Adjusted mean diff. (95% CI)**	**p-value**
Day 126 - Day 168	LNP023 200mg b.i.d. N=62	62	3.59 (3.32, 3.86)	**3.63** (3.18, 4.08)	**<0.0001**
	Anti-C5 antibody N=35	30	-0.04 (-0.42, 0.35)		

N = number of all patients included in the analysis (with no missing baseline or covariates).
n = number of patients with values non-missing/not imputed as per the intercurrent event handling strategy.
Change from baseline is analyzed using a Mixed Model of Repeated Measures (MMRM) which includes randomization strata, age indicator variable of age >= 45 years, sex, treatment, visit, baseline hemoglobin, timepoint as fixed effects, treatment*timepoint and timepoint*baseline hemoglobin as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Note: for this analysis, in order to factor out the effect of transfusions, if a patient had a transfusion during the randomized treatment period, then the hemoglobin values 30 days following the transfusion were excluded and hemoglobin data were imputed.



Bas: baseline
Change from baseline is analysed using a Mixed Model of Repeated Measures (MMRM) which includes randomisation strata, age indicator variable of age >= 45 years, sex, treatment, visit, baseline haemoglobin, timepoint as fixed effects, treatment*timepoint and timepoint*baseline haemoglobin as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Error bars represent 95% confidence intervals.

Figure 51: Least squares mean of change from baseline in Hb – randomised treatment period (Full Analysis Set) – Direct efficacy estimand - APPLY-PNH

Change from baseline in FACIT-F score

The FACIT-F questionnaire is a validated 13-item questionnaire that assesses patient self-reported fatigue and its impact on daily activities and function. Mean (SD) FACIT-F score at baseline was 34.7

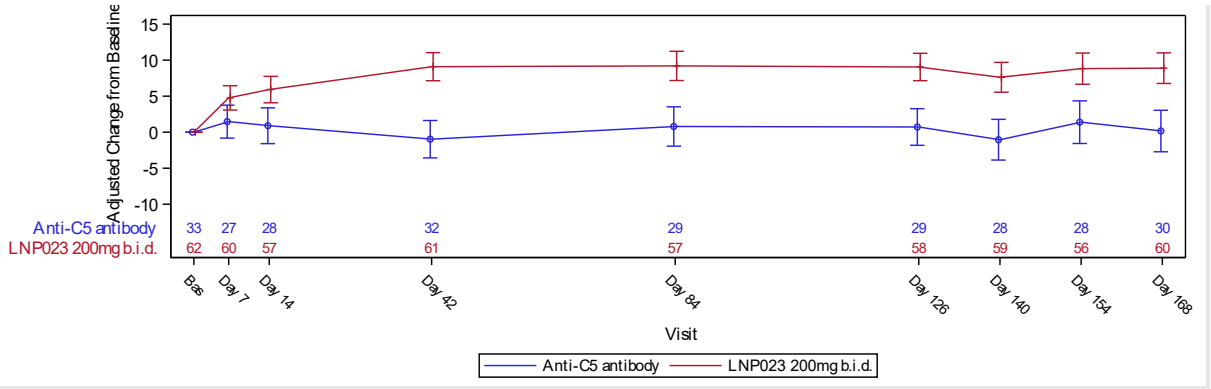
(9.82) in the iptacopan arm and 30.8 (11.45) in the anti-C5 arm. Iptacopan monotherapy was statistically significantly superior to anti-C5 treatment for change from baseline in FACIT-F score with an adjusted mean difference of +8.29 (95% CI 5.28, 11.29) (unadjusted two-sided p-value <0.0001).

The adjusted mean FACIT-F score change from baseline was +8.59 (95% CI 6.72, 10.47) for iptacopan vs. +0.31 (95% CI −2.20, 2.81) for anti-C5. In patients treated with iptacopan, increases in FACIT-F score were seen early in the study with an adjusted mean change from baseline of ≥ 5 points by day 14 and further increases up to day 42, maintained throughout the RTP.

Table 39: Repeated measures analysis of change from baseline in FACIT-Fatigue scores – randomised treatment period (Full Analysis Set) – Including-transfusion estimand - APPLY-PNH

				LNP023 200mg b.i.d. vs. Anti-C5 antibody	
Visit	**Treatment**	**n**	**Adjusted mean (95% CI)**	**Adjusted mean diff. (95% CI)**	**p-value**
Day 126 - Day 168	LNP023 200mg b.i.d. N=62	62	8.59 (6.72, 10.47)	8.29 (5.28, 11.29)	<0.0001
	Anti-C5 antibody N=33	31	0.31 (-2.20, 2.81)		

N = number of all patients included in the analysis (with no missing baseline or covariates).
n = number of patients with values non-missing and not imputed as per the missing data handling strategy.
Change from baseline is analysed using a Mixed Model of Repeated Measures (MMRM) which includes randomisation strata, age indicator variable of age >= 45 years, sex, treatment, visit, baseline FACIT-Fatigue score, timepoint as fixed effects, treatment*timepoint and timepoint*baseline FACIT-Fatigue score as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.



Bas: baselineChange from baseline is analysed using a Mixed Model of Repeated Measures (MMRM) which includes randomisation strata, age indicator variable of age >= 45 years, sex, treatment, visit, baseline FACIT-Fatigue score, timepoint as fixed effects, treatment*timepoint and timepoint*baseline FACIT-Fatigue score as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Error bars represent 95% confidence intervals

Figure 52: Least squares means of change from baseline in FACIT-Fatigue scores – randomised treatment period (Full Analysis Set) – Including- transfusion estimand - APPLY-PNH

Response analysis

A response analysis was performed, based on within-patient improvement of 9 points. This showed that a higher proportion of patients on iptacopan than on anti-C5 treatment had a meaningful improvement in symptoms (difference in marginal proportions of 39% for the transfusion estimand).

Table 40: Response analysis: average of proportions, difference and ratio for visits Day 126 – Day 168, applying a threshold of 9 points in APPLY-PNH

Estimand	Treatment	Averaged Proportions	Difference	Ratio
Direct efficacy	Anti-C5	0.10 (0.04,0.19)		
	LNP023 200 mg	0.51 (0.42,0.58)	0.40 (0.31, 0.49)	5.20 (2.77, 10.90)
Including transfusions	Anti-C5	0.11 (0.05,0.19)		
	LNP023 200 mg	0.51 (0.43,0.59)	0.39 (0.31, 0.49)	4.47 (2.75, 10.07)

- The number of imputations excluded from estimation were 41 and 43 respectively.

Other assessment of QoL

EORTC-QLQ-C30PRO

Patients in the iptacopan group experienced significant improvements in physical functioning, role functioning, fatigue and dyspnoea, as measured by the EORTC QLQ-C30 questionnaire, supporting the positive patient experience with iptacopan:

- Clear treatment benefit of iptacopan vs. anti-C5 treatment was seen in key subscales of the EORTC QLQ C-30 when comparing differences between groups in score change from baseline averaged over Days 126, Day 140, Day 154, and Day 168. Iptacopan showed greater increases in score from baseline with respect to functioning (physical and role functioning subscales), and greater decreases in scores from baseline for the symptom subscales of fatigue and dyspnoea.
- Response analyses, using internally derived thresholds, for the EORTC QLQ-C30 subscale fatigue and for disease impact/symptoms indirectly measuring fatigue were in line with the FACIT-Fatigue response analyses.

Table 41: Overview of key patient reported outcome results in APPLY-PNH – including transfusion estimand

PRO measure	Summary measure	
FACIT-Fatigue		
Change from baseline in FACIT-Fatigue scores (secondary endpoint)[1, 2]	Difference in adjusted mean (95% CI)	+8.29 (5.28, 11.29)
Response analysis using 9-point threshold [3]	Difference in marginal proportions (95% CI) [4]	39% (31, 49)
EORTC-QLQ-C30		
Change from baseline in subscales [3]	Estimated average difference [5] (95% CI)	
Physical functioning		+14.7 (9.9, 19.4)
Role functioning		+17.4 (10.4, 24.5)
Global health index		+13.8 (9.0, 18.7))
Fatigue		-16.8 (-23.0, -10.7)
Pain		-7.4 (-13.7, -1.2)
Dyspnea		-22.4 (-29.4, -15.3)
Insomnia		-0.9 (-8.0, 6.2)

[1] Assessed between Day 126 and Day 168
[2] Based on FAS
[3] Based on PRO evaluable set
[4] Proportions are mean of Day 126, Day 140, Day 154, and Day 168
[5] Average is mean of the difference between LS means at visits Day 126, Day 140, Day 154, and Day 168. Estimates from a longitudinal model including baseline, visit, sex, age group, history of transfusions, and treatment group, and the interactions between visit and baseline, and visit and treatment group
Increase of function subscales and GHI, and decrease of symptom subscales are improvements

PNH signs and symptoms

The summary of PNH signs and symptoms as assessed by investigator was presented. Overall, 39/62 (62.9%) patients in the iptacopan group and 24/35 (68.6%) patients the in anti-C5 group were reported with PNH signs and symptoms at baseline. At the end of the randomised treatment period, 15/62 (24.2%) in the iptacopan group and 20/35 (57.1%) in anti-C5 group were reported with at least one PNH related sign and symptom. Feeling weak was the most frequently reported event with 48.4% of patients reported as none, 29% as mild, 19.4% as moderate and 3.2% as severe in iptacopan group vs 31.4% of patients reported as none, 34.3% as mild, 25.7% as moderate and 5.7% as severe in anti-C5 group at baseline. At Day 168 this changed to 80.6% of patients reported as none, 14.5% as mild, 4.8% as moderate and 0 patients as severe in iptacopan group vs 45.7% of patients reported as none, 31.4% as mild, 17.1% as moderate and 5.7% as severe in anti-C5 group. At baseline, haemoglobinuria was reported for 83.9% of patients as none, 11.3% as mild, 4.8% as moderate in the iptacopan group vs 85.7% of patients reported as none, 8.6% as moderate and as 2.9% severe in the anti-C5 group. At Day 168, this changed to 100% reported as none in the iptacopan group vs 85.7% reporting as none, 8.6% as mild and 5.7% as moderate in the anti-C5 group. At baseline, shortness of breath was reported as none for 71% of patients, as mild for 14.5%, as moderate for 12.9% and as severe for 1.6% patients in the iptacopan group whereas the same was reported as none for 62.9% of patients, as mild for 20%, as moderate for 11.4% and as severe for 2.9% patients in the anti-C5 group. This changed at Day 168 with 93.5% of patients reported as none, 4.8% as mild, and 1.6% as moderate in the iptacopan group whereas it was reported for 71.4% of patients as none, as mild for 5.7%, as moderate for 17.1% and as severe for 5.7% patients in the anti-C5 group.

While at baseline 90.3% of patients reported no dysphagia at baseline compared to 80% in the anti-C5 arm, at day 168 these proportions increased to 93.5% in the iptacopan arm and decreased to 71.4 % in the anti-C5 arm, moderate dysphagia was reported by 1.6% of patients in the iptacopan arm and

5.7% of patients in the anti-C5 arm at baseline; at day 168 the respective proportions were 1.6% and 17.1%.

For severe dysphagia at baseline there were no patients in the iptacopan arm and 2.9% in the anti-C5 arm; the respective proportions were 0% and 5.7% at day 168, respectively.

Patient interviews

Patient interviews were conducted in a subset of patients; results were correlated with FACIT-Fatigue and PGIS with the aim to further support the meaningfulness of changes in the FACIT score to patients. The patient experience data confirmed a positive perception of treatment with iptacopan in terms of improvement in disease and showed agreement with PGIS and FACIT. All patients considered that at least some of the concepts measured by the FACIT-Fatigue were relevant to their experience, and responses indicated all important and relevant aspect of the disease experience were likely covered by FACIT-Fatigue.

Change from baseline in absolute reticulocyte count (ARC)

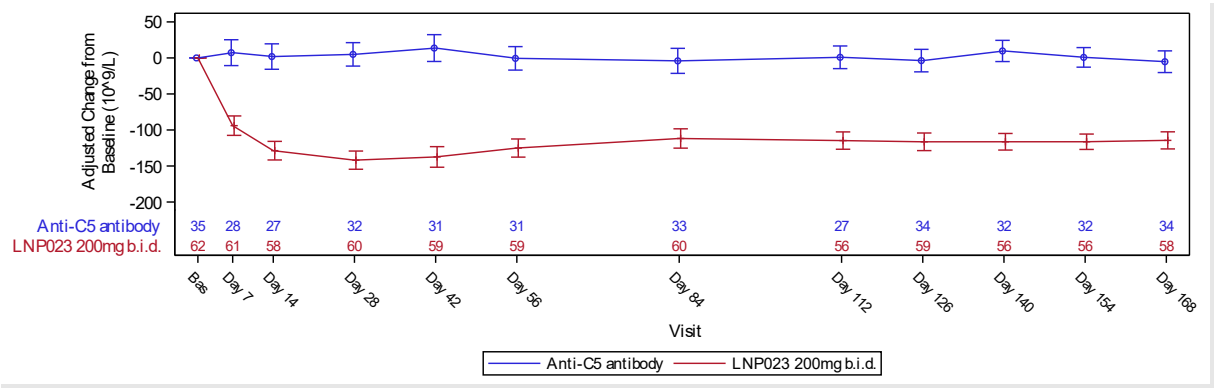
Baseline mean (SD) absolute reticulocyte count (ARC) was 193.22 (83.637) x 10^9/L in the iptacopan arm and 190.59 (80.922) x 10^9/L in the anti-C5 arm. The upper limit of normal (ULN) for ARC is 124 x 10^9/L (central laboratory). Iptacopan monotherapy was statistically significantly superior to anti-C5 antibody treatment for change from baseline in ARC with adjusted mean difference of -116.26 (95% CI -132.17, -100.36) x 10^9/L, (unadjusted two-sided p-value <0.0001).

The adjusted mean change from baseline in ARC was -115.89× 10^9/L (95% CI -126.49, -105.30) x 10^9/L for iptacopan vs. 0.37 × 10^9/L (95% CI -13.03, 13.77) for the anti-C5 arm. In patients treated with iptacopan, decreases in ARC score were seen early in the study with an adjusted mean change from baseline of -94.01 × 10^9/L (95% CI -107.50, -80.52) already by day 7 and further decreases to day 28 maintained throughout the RTP.

Table 42: Repeated measures analysis of change from baseline in absolute reticulocyte counts (x 10^9/L) – randomised treatment period (Full Analysis Set) – Including-transfusion estimand - APPLY-PNH

				LNP023 200mg b.i.d. vs. Anti-C5 antibody	
Visit	**Treatment**	**n**	**Adjusted mean (95% CI)**	**Adjusted mean diff. (95% CI)**	**p-value**
Day 126 - Day 168	LNP023 200mg b.i.d. N=62	62	-115.89 (-126.49, -105.30)	-116.26 (-132.17, -100.36)	<0.0001
	Anti-C5 antibody N=35	35	0.37 (-13.03, 13.77)		

N = number of all patients included in the analysis (with no missing baseline or covariates).
n = number of patients with values non-missing and not imputed as per the missing data handling strategy.
Change from baseline is analysed using a Mixed Model of Repeated Measures (MMRM) which includes randomisation strata, age indicator variable of age >= 45 years, sex, treatment, visit, baseline reticulocyte counts, timepoint as fixed effects, treatment*timepoint and timepoint*baseline reticulocyte counts as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.



Bas: baseline
Change from baseline is analysed using a Mixed Model of Repeated Measures (MMRM) which includes randomisation strata, age indicator variable of age >= 45 years, sex, treatment, visit, baseline reticulocyte counts, timepoint as fixed effects, treatment*timepoint and timepoint*baseline reticulocyte counts as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
Error bars represent 95% confidence intervals.

Figure 53: Least squares means of change from baseline in absolute reticulocyte counts – randomised treatment period (Full Analysis Set) – Including-transfusion estimand - APPLY-PNH

Rate of clinical breakthrough haemolysis

Clinical breakthrough haemolysis (BTH) was defined in the protocol as meeting either of the two clinical criteria given in the table below, in the presence of laboratory evidence of IVH (LDH level).

Table 43: Clinical breakthrough haemolysis definition per protocol - APPLY-PNH

Clinical criteria		**Laboratory criteria**
Haemoglobin level	**Signs or symptoms**	**LDH level**
Decrease ≥ 2 g/dL (compared to the latest assessment, or within 15 days)	Gross haemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms	> 1.5-times ULN and increased as compared to the last 2 assessments

Iptacopan monotherapy was statistically significantly superior to anti-C5 antibody treatment for adjusted annualised rate, with a rate ratio of 0.10 (95% CI 0.02, 0.61) (unadjusted two-sided p-value 0.0118), demonstrating that iptacopan-treated patients had a significantly lower rate of clinical BTH.

The adjusted annualised rate (%) of clinical BTH was 0.07 (95% CI 0.02, 0.31) in the iptacopan arm vs. 0.67 (95% CI 0.26, 1.72) in the anti-C5 arm. Clinical BTH was reported for 2 out of 62 patients in the iptacopan arm vs 6 out of 35 patients in the anti-C5 arm.

Table 44: Number (%) of patients with clinical breakthrough haemolysis events by treatment – randomised treatment period (Full Analysis Set) – Including-transfusion estimand - APPLY-PNH

Breakthrough haemolysis event	LNP023 200mg b.i.d. N=62 n (%)	Anti-C5 antibody N=35 n (%)	Adjusted annual BTH rate (95% CI) LNP023 200mg b.i.d.	Adjusted annual BTH rate (95% CI) Anti-C5 antibody	LNP023 200mg b.i.d. vs. Anti-C5 antibody Rate diff. (95% CI)	LNP023 200mg b.i.d. vs. Anti-C5 antibody Rate ratio (95% CI)	p-value
Number of patients with at least one event	2 (3.2)	6 (17.1)	0.07 (0.02, 0.31)	0.67 (0.26, 1.72)	-0.60 (-1.24, 0.04)	**0.10** (0.02, 0.61)	**0.01183**

A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.
Adjusted annual rates of clinical Breakthrough haemolysis events are from negative binomial model.
The model includes randomisation strata (prior anti-C5 treatment, transfusion history), sex, age (indicator of age >= 45 years), indicator variable of baseline haemoglobin >= 9 g/dL as factors, and log (Day 1 till minimum (end of study, end of randomised treatment period) in years) as offset.

Rate of major adverse vascular events (MAVEs)

One iptacopan-treated patient had a MAVE (transient ischemic attack, considered unrelated to iptacopan by the investigator; iptacopan treatment was ongoing) which translated into an adjusted annualised rate of 0.03 (95% CI 0.00, 0.25) in the iptacopan arm vs. zero in the anti-C5 arm.

Ratio to baseline in LDH

Baseline mean (SD) LDH, a marker for IVH, was 269.1 (70.14) U/L in the iptacopan arm and 272.7 (84.8) U/L in the anti-C5 arm. The ULN for LDH was 250 U/L (central laboratory). At baseline very few patients had significant residual IVH (LDH > 1.5×ULN).

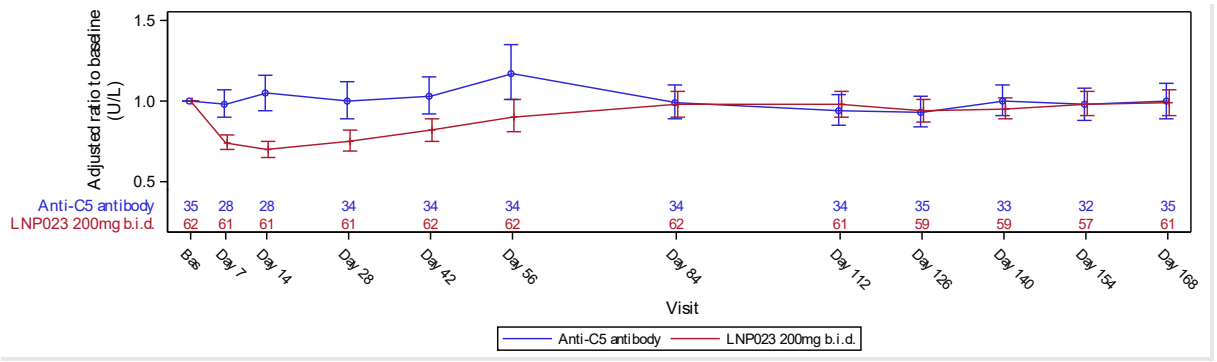
The adjusted reduction in LDH in the iptacopan arm, relative to anti-C5 was 1.15% (95% CI -10.18, 11.32), unadjusted two-sided p=0.8345. The results are not statistically significant. The ratio to baseline in log-transformed LDH was 0.96 (95% CI 0.90, 1.03) in the iptacopan arm vs. 0.98 (95% CI 0.89, 1.07) in the anti-C5 arm, corresponding to respective reduction from baseline of 4% and 2%.

In patients treated with iptacopan, there was an initial decrease of up to 30% from baseline. From Day 84 until the end of the RTP, geometric means of LDH ratio to baseline over time in the two treatment arms were superimposed, showing no difference between treatment arms.

Table 45: Repeated measures analysis of log-transformed LDH ratio to baseline – randomised treatment period (Full Analysis Set) – Including-transfusion estimand - APPLY-PNH

				LNP023 200mg b.i.d. vs. Anti-C5 antibody		
Visit	**Treatment**	**n**	**Geometric adjusted mean (95% CI)**	**Geometric mean ratio (95% CI)**	**% Reduction (95% CI)**	**p-value**
Day 126 - Day 168	LNP023 200mg b.i.d. N=62	62	0.96 (0.90, 1.03)	0.99 (0.89, 1.10)	1.15 (-10.18, 11.32)	0.8345
	Anti-C5 antibody N=35	35	0.98 (0.89, 1.07)			

N = number of all patients included in the analysis (with no missing baseline or covariates).
n = number of patients with values non-missing and not imputed as per the missing data handling strategy.
log transformed ratio to baseline is analysed using a Mixed Model of Repeated Measures (MMRM) which is stratified by randomisation strata, and includes age indicator variable of age >=45 years, sex, treatment, visit, log-transformed baseline LDH level, timepoint as fixed effects, treatment*timepoint and timepoint*log-transformed baseline LDH level as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
The log transformation used refers to the natural log (base of e). Results are back-transformed and expressed as geometric means.



log transformed ratio to baseline is analysed using a Mixed Model of Repeated Measures (MMRM) which is stratified by randomisation strata, and includes age indicator variable of age >=45 years, sex, treatment, visit, log-transformed baseline LDH level, timepoint as fixed effects, treatment*timepoint and timepoint*log-transformed baseline LDH level as interaction terms. The correlations between visits within patients were modelled using an unstructured covariance matrix.
The log transformation used refers to the natural log (base of e). Results are back-transformed and expressed as geometric means. Error bars represent 95% confidence intervals.

Figure 54: Least squares geometric means of LDH ratio to baseline – randomised treatment period (Full Analysis Set) – Including-transfusion estimand - APPLY-PNH

Haptoglobin over time

The plot below is based on the safety analysis set.

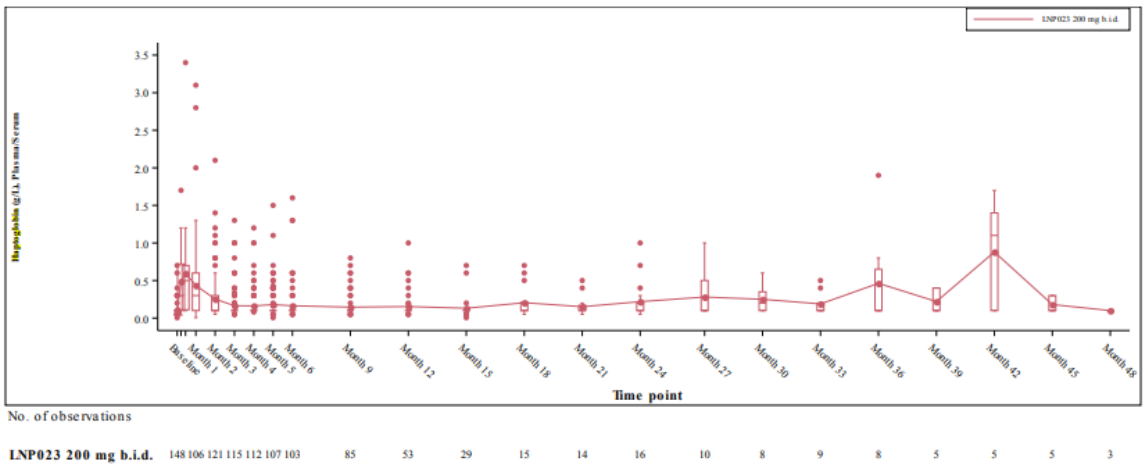


Figure 55: Box plot of haematological parameters by visit – PNH studies (200 mg b.i.d. Safety Set)

RBC (erythrocytes)

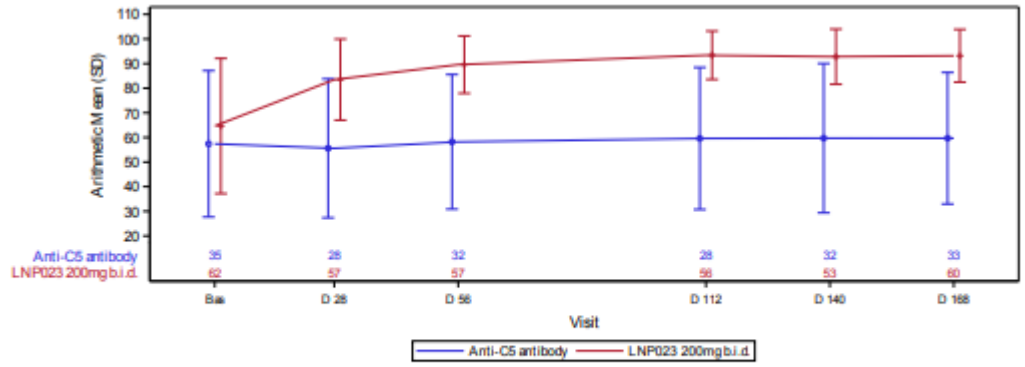
Baseline mean erythrocyte count was comparable between the iptacopan (2.50 (SD: 0.344)) × 1012/L) and the anti-C5 group (2.43 (SD: 0.408) × 1012/L), and were below the LLN (normal reference range for males: 4.1 to 5.9 × 1012/L and for females: 3.8 to 5.5 x 1012/L). Consistent with haemoglobin improvements, in the iptacopan group mean erythrocyte count increased early on, from Day 7 till Day 42 and was then maintained through to Day 168 (3.72 (SD: 0.501) × 1012/L). In contrast, in the anti-C5 group, mean erythrocyte count remained consistently low through to Day 168.

Bilirubin

Mean total bilirubin at baseline was comparable and above the ULN of 21 µmol/L in both treatment groups (iptacopan: 31.6 µmol/L (SD: 30.51); anti-C5 group: 31.8 µmol/L (SD: 20.33)). In the iptacopan group, a reduction in the mean total bilirubin was observed as early as Day 7. Thereafter the mean was maintained within the normal reference range through to Day 168 (12.5 µmol/L (SD: 9.83)). In the anti-C5 group, mean total bilirubin remained consistently high until Day 168 (31.4 µmol/L (SD: 30.97)). Consistent results were seen for indirect bilirubin.

Clone size

Mean (SD) total PNH RBC clone size at baseline was slightly higher in the iptacopan group (64.65% (27.454)) compared to anti-C5 group (57.39% (29.726)). In the iptacopan group, an increase in mean (SD) total PNH RBC clone size was observed from Day 28 (83.48% (16.470)) to Day 112 (93.39% (9.822)) with the mean (SD) thereafter stable till Day 168 (93.17% (10.718)). In the anti-C5 group, mean (SD) total PNH RBC clone size was stable from baseline (57.39% (29.73)) till Day 168 (59.68% (26.710)).



Bas: Baseline
SD: standard deviation.
- At each visit-window, only patients with a value at both Baseline and that visit-window are included.

Figure 56: Arithmetic mean (SD) profiles of total PNH clone size over time – randomised treatment period Full Analysis Set - APPLY-PNH

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 46: Summary of Efficacy for trial CLNP023C12302 APPLY-PNH

Title: A randomised, multicentre, 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		
Study identifier	Protocol number: CLNP023C12302 EudraCT number: 2019-004665-40	
Design	A randomised, multicentre, active-comparator controlled, open-label Phase III trial. The study comprised a screening period, a 24-week randomised controlled treatment period and a 24-week open-label iptacopan extension period. The randomised treatment period was defined from day 1 to day 168 and was used for the primary efficacy analyses.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24-week Not applicable 24-week
Hypothesis	Superiority	
Treatments groups	LNP023	200 mg b.i.d. oral use 62 patients randomised
	Anti-C5 antibody	Eculizumab i.v. or Ravulizumab i.v. 35 patients randomised

Endpoints and definitions	Primary endpoint	Increase from baseline Haemoglobin (Hb) levels ≥ 2 g/dL (assessed between Day 126 and Day 168) in the absence of Red Blood Cell (RBC) transfusion between Day 14 and Day 168.	The primary objective was to demonstrate superiority of iptacopan compared to anti-C5 antibody treatment in the proportion of patients achieving haematological response. The criterion for haematological response was assessed over the last 6 weeks of the 24-week randomised treatment period with serial assessments.
	Primary endpoint	Hb levels ≥ 12 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.	The primary objective was to demonstrate superiority of iptacopan compared to anti-C5 antibody treatment in the proportion of patients achieving haematological response. The criterion for haematological response was assessed over the last 6 weeks of the 24-week randomised treatment period with serial assessments.
	Key Secondary Endpoint	Absence of administration of packed-red blood cell transfusions between Day 14 and Day 168	To demonstrate superiority of iptacopa compared to anti-C5 antibody treatment in transfusion avoidance as the proportion of patients who remain free from transfusions (meaning patients not receiving a transfusion or not meeting protocol-defined criteria for transfusion between Day 14 and Day 168)
	Key Secondary Endpoint	Change from baseline in haemoglobin (g/dL) as mean of visits between Day 126 and Day 168	To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in average change in haemoglobin over the last 6 weeks of the 24-week randomised treatment period with serial assessments.
	Key Secondary Endpoint	Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168	To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in improving fatigue, using the FACIT-Fatigue questionnaire. Fatigue was assessed over the last 6 weeks of the 24-week randomised treatment period with serial assessments.
	Key Secondary Endpoint	Change from baseline in reticulocyte count (109/L) as mean of visits between Day 126 and Day 168	To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in average change in reticulocyte counts over the last 6 weeks of the 24-week randomised treatment period with serial assessments.
	Key Secondary Endpoint	Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168	To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in average percent change in LDH over the last 6 weeks of the 24-week randomised treatment period with serial assessments.

	Key Secondary Endpoint	Occurrences of breakthrough haemolysis (BTH)reported between Day 1 and Day 168	To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in the rate of BTH
	Key Secondary Endpoint	Occurrences of MAVEs occurring between Day 1 and Day 168	To assess the rates of Major Adverse Vascular Events (MAVEs incl. thrombosis) of iptacopan, compared to anti-C5 antibody treatment
Database lock	26-Sep-2022 (Primary endpoint completion date)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS): all randomised patients. Time point: Between Weeks 16 to 24 except for BTH and MAVE (from Day 1 to Week 24)		

Descriptive statistics and estimate variability	Treatment group	LNP023	Anti-C5 antibody
	Number of subjects	62	35
	Primary endpoint: Increase from baseline Haemoglobin (Hb) levels ≥ 2 g/dL (assessed between Day 126 and Day 168) in the absence of Red Blood Cell (RBC) transfusion between Day 14 and Day 168. Marginal proportion (95% CI)	82.3 (73.4, 90.2)	2.0 (1.1, 4.1)
	Primary endpoint: Hb levels ≥ 12 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168. Marginal proportion (95% CI)	68.8 (58.3, 78.9)	1.8 (0.9, 4.0)
	Absence of administration of packed-red blood cell transfusions between Day 14 and Day 168 Marginal proportion (95% CI)	96.4 (90.7, 100.0)	26.1 (12.4, 42.7)
	Change from baseline in haemoglobin (g/dL) as mean of visits between Day 126 and Day 168 Least square (LS) mean (95% CI)	3.59 (3.32, 3.86)	-0.04 (-0.42, 0.35)

	Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168 Least square (LS) mean (95% CI)	8.59 (6.72, 10.47)	0.31 (-2.20, 2.81)
	Change from baseline in reticulocyte count (10^9/L) as mean of visits between Day 126 and Day 168 Least square (LS) mean (95% CI)	-115.89 (-126.49, -105.30)	0.37 (-13.03, 13.77)
	Ratio to baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168 Geometric adjusted mean ratio (95% CI)	0.96 (0.90, 1.03)	0.98 (0.89, 1.07)
	Occurrences of breakthrough haemolysis (BTH) reported between Day 1 and Day 168 Adjusted annualised rate (95% CI)	0.07 (0.02, 0.31)	0.67 (0.26, 1.72)
	Occurrences of MAVEs occurring between Day 1 and Day 168 Adjusted annualised rate (95% CI)	0.03 (0.00, 0.25)	0.00 (0.00, 0.00)

Effect estimate per comparison	**Primary endpoint**: Increase from baseline Haemoglobin (Hb) levels ≥ 2 g/dL (assessed between Day 126 and Day 168) in the absence of Red Blood Cell (RBC) transfusion between Day 14 and Day 168.	Comparison groups	LNP023 vs Anti-C5 antibody
		difference in marginal proportions; logistic regression using Firth correction	80.3
		95% CI	(71.3, 87.6)
		Two-sided unadjusted P-value	<0.0001* (1)
	Primary endpoint: Hb levels ≥ 12 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.	Comparison groups	LNP023 vs Anti-C5 antibody
		difference in marginal proportions; logistic regression using Firth correction	67.0

		95% CI	(56.3, 76.9)
		Two-sided unadjusted P-value	<0.0001* (1)
	Key Secondary Endpoint: Absence of administration of packed-red blood cell transfusions between Day 14 and Day 168	Comparison groups	LNP023 vs Anti-C5 antibody
		difference in marginal proportions; logistic regression	70.3
		95% CI	(52.6, 84.9)
		Two-sided unadjusted P-value	<0.0001* (2)
	Key Secondary Endpoint: Change from baseline in haemoglobin (g/dL) as mean of visits between Day 126 and Day 168	Comparison groups	LNP023 vs Anti-C5 antibody
		Difference in Least square (LS) mean; Mixed Model for Repeated Measures (MMRM) (3)	3.63
		95% CI	(3.18, 4.08)
		Two-sided unadjusted P-value	<0.0001*
	Key Secondary Endpoint: Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168	Comparison groups	LNP023 vs Anti-C5 antibody
		Difference in Least square (LS) mean; Mixed Model for Repeated Measures (MMRM)	8.29
		95% CI	(5.28, 11.29)
		Two-sided unadjusted P-value	<0.0001*
	Key Secondary Endpoint: Change from baseline in reticulocyte count (10^9/L) as mean of visits between Day 126 and Day 168	Comparison groups	LNP023 vs Anti-C5 antibody
		Difference in Least square (LS) mean; Mixed Model for Repeated Measures (MMRM)	-116.26
		95% CI	(-132.17, -100.36)
		Two-sided unadjusted P-value	<0.0001*
	Key Secondary Endpoint: Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168	Comparison groups	LNP023 vs Anti-C5 antibody

		Geometric mean ratio; Mixed Model for Repeated Measures (MMRM)	0.99
		95% CI	(0.89, 1.10)
		Two-sided unadjusted P-value	0.8345
	Key Secondary Endpoint: Occurrences of breakthrough haemolysis (BTH) reported between Day 1 and Day 168	Comparison groups	LNP023 vs Anti-C5 antibody
		Annualised rate ratio; Negative binomial model	0.10
		95% CI	(0.02, 0.61)
		Two-sided unadjusted P-value	0.01183*
	Key Secondary Endpoint: Occurrences of MAVEs occurring between Day 1 and Day 168	Comparison groups	LNP023 vs Anti-C5 antibody
		Annualised rate difference; Poisson model	0.03
		95% CI	(-0.03, 0.10)
		Two-sided unadjusted P-value	0.31731
Notes	All primary and secondary endpoints were tested following the pre-defined scheme for multiplicity adjustment in order to control Type I error rate. Significant p-values as per this multiplicity adjustment scheme are marked with * (1) p-values are obtained from testing odds ratio (2) p-values are obtained from testing odds ratio from conditional logistic model (3) In order to account for the confounding effect of transfusion, data within 30 days after transfusion were not included in the analysis of change from baseline in haemoglobin		

APPOINT-study (CLNP023C12301)

Study design

Multicentre, phase III, single-arm, open-label trial in adult PNH patients who are naïve to complement inhibitor therapy, including anti-C5 antibody treatment (study ongoing).

This study enrolled PNH patients with haemolysis (LDH>1.5 ULN) and anaemia (haemoglobin <10 g/dL), who were naïve to complement inhibitor therapy, including anti-C5 antibody treatment with approximately 40% of all participants having received at least one (1) packed-RBC transfusion within 6 months prior to starting study treatment.

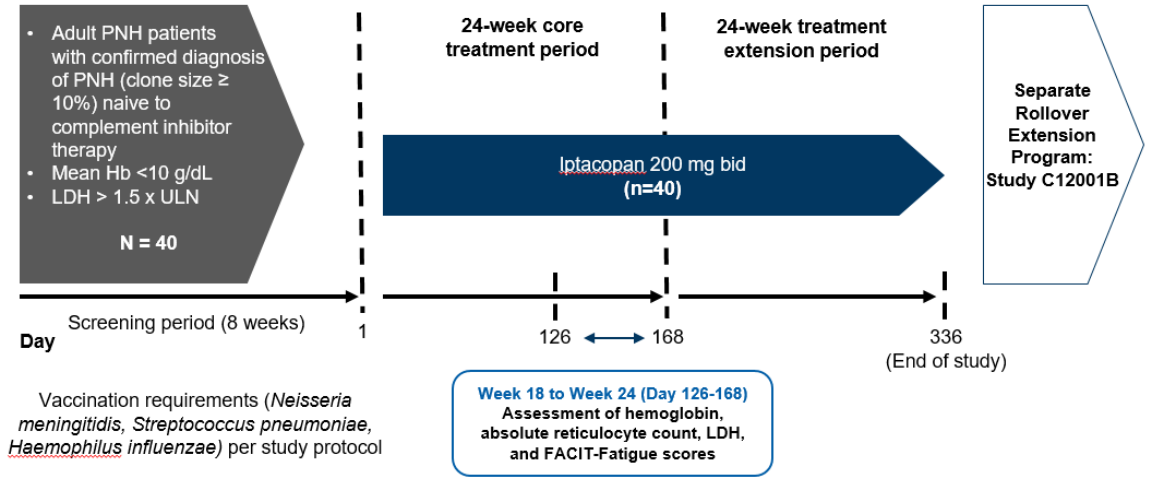


Figure 57: APPOINT-PNH (Study C12301) study design

Study Participants

Main inclusion criteria:

-Participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with RBCs and white blood cells (WBCs) (granulocyte/monocyte) clone size ≥ 10%.

- Mean haemoglobin level <10 g/dL confirmed by central laboratory assessment during screening and prior to starting study treatment: by two haemoglobin measurements (mean < 10 g/dL), two to eight weeks apart, for patients not receiving a RBC transfusion during screening, by one haemoglobin 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 two central laboratory measurements two to eight weeks apart during the screening period.

- Vaccination required against Neisseria meningitidis infection and vaccination against Streptococcus pneumoniae and Haemophilus influenzae recommended if available. Vaccine was to be given according to local regulations, at least 2 weeks prior to first dosing. If treatment had to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment was required to be initiated.

Main exclusion criteria:

- Prior treatment with a complement inhibitor, including anti-C5 antibody.

- 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 <0.5x109/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/1.73m2, dialysis), advanced cardiac disease (e.g., New York Heart Association (NYHA) class IV), severe pulmonary disease (e.g., severe pulmonary hypertension (World Health Organization (WHO) class IV)), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.

Rules for concomitant medication: Systemic corticosteroids were allowed to be used for haematological conditions if on stable dose (less than 0.5 mg/kg) at least 4 weeks before screening. During the study, the dose should not be changed during the core treatment period (up to Day 168 Visit). During the extension treatment period, the dose of systemic corticosteroids can be adjusted based on participant`s condition and local guidelines. Immunosuppressants and erythropoiesis stimulating drugs have to be stabilised for at least eight weeks before screening.

Study treatment

All patients received iptacopan 200mg orally b.i.d.

Rescue medication was allowed to treat serious complications such as thrombosis with anti-thrombotic treatment and management of this complication as per local guidelines and practice. For significant breakthrough haemolysis requiring rescue medication in the opinion of the investigator, rescue medication was allowed and was to be managed as per local guidelines and practice.

Outcomes and endpoints

Primary endpoint

A haematological responder endpoint was used for the primary efficacy analysis of the Core treatment period. A responder is defined as a participant achieving a haemoglobin increase from baseline ≥ 2 g/dL (assessed during the last 6 weeks of the 24 weeks Core treatment period) without the need of RBC transfusions from Day 14 to Day 168. Note that the primary endpoint was defined in the same way as the corresponding endpoint in APPLY-PNH.

Transfusion criteria was established to standardise administration criteria and was applied starting from Day 1 of the study.

Packed-RBC transfusions were administered to patients in the following cases:

• Hb level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and/or symptoms of sufficient severity to warrant a transfusion

• Hb of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms.

Symptoms typically associated with, or precipitating patient’s need for transfusion are listed below:

• Severe or worsening of fatigue

• Severe or worsening dyspnoea / shortness of breath

• Palpitation/angina (or worsening symptoms

• Change in mental status (syncope, light-headedness, confusion, stroke, transient ischemic attack).

Primary analysis and defined threshold for superiority

The primary analysis of the primary endpoint was the assessment of the proportion of patients reaching the status of a 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%.

Secondary endpoints

Secondary efficacy endpoints included proportion of participants achieving sustained haemoglobin levels ≥ 12 g/dL, transfusion avoidance, change from baseline Hb, clinical BTH, MAVE, a PRO measure for fatigue (FACIT-fatigue) as well as changes in reticulocytes and LDH.

Considering that some patients may present with very low haemoglobin levels (e. g.<7 g/dL), and thereby require a RBC transfusion during the first two weeks of the Core treatment period, transfusions administered during these first 2 weeks were not be considered for the transfusion avoidance definition.

Note that the secondary endpoints were defined in the same way as the corresponding endpoints in APPLY-PNH.

Patient disposition

All the 40 patients enrolled in the study completed the core treatment period. As of the data cut-off date (02-Nov-2022), of the 39 patients who entered the extension treatment period, 7 patients (17.5%) completed the extension treatment period and continued to receive open-label iptacopan therapy in the roll-over extension programme, while iptacopan extension treatment was ongoing for 32 patients (80.0%).

Table 47: Patient Disposition in APPOINT-PNH

	LNP023 200mg b.i.d. N=40
Disposition/Reason	**n (%)**
Core treatment period	
Completed treatment	40 (100)
Completed treatment period	40 (100)
Extension treatment period	
Treatment ongoing #	32 (80.0)
Completed treatment	7 (17.5)
Completed treatment period	7 (17.5)
Discontinued treatment period	0

N = number of patients in Full analysis set.
n is the number of non-missing observations in each row category.
One patient had the last visit in the core treatment period on the day of the data cut-off date and therefore did not enter the extension treatment period by the data cut-off date.
Percentages are based on no. of patients in Full analysis set.
Ongoing at the time of the data cut-off date 2022-11-02

Results

Baseline characteristics

Demographics

Table 48: Patient demographic summary (Full analysis set) - APPOINT-PNH

Characteristic Categories/Statistics	LNP023 200mg b.i.d. N=40
Age (years)	
N	40
Mean (SD)	42.1 (15.85)
Median (Min – Max)	38.5 (18 – 81)
Age category (years) - n (%)	
< 45 years	24 (60.0)
≥ 45 years	16 (40.0)
Age category (years) - n (%)	
18 - < 65 years	37 (92.5)
65 - < 85 years	3 (7.5)
Age category (years) - n (%)	
18 - < 65 years	37 (92.5)
65 - < 75 years	2 (5.0)
≥ 75 years	1 (2.5)
Gender - n (%)	
Male	23 (57.5)
Female	17 (42.5)
Race - n (%)	
White	12 (30.0)
Black or African American	1 (2.5)
Asian	27 (67.5)
Chinese	22 (55.0)
Korean	3 (7.5)
Other	2 (5.0)
Ethnicity - n (%)	
Hispanic/Latino	2 (5.0)
Not Hispanic/Latino	35 (87.5)
Not Reported	2 (5.0)
Unknown	1 (2.5)
Patient classification - n (%)	
Chinese	20 (50.0)
Non-Chinese	20 (50.0)

-SD = Standard Deviation, n is the number of non-missing observations in each row category.
- Percentages are based on no. of patients in Full analysis set.

Baseline disease characteristics

Table 49: Baseline disease characteristics (Full analysis set) - APPOINT-PNH

Characteristic Categories/Statistics	LNP023 200 mg b.i.d. N=40
Disease duration (years)[a]	
n	40
Mean (SD)	4.699 (5.5379)
Median (Min – Max)	3.625 (0.01 - 23.20)
Length of time since diagnosis - n (%)	
< 3 Years	18 (45.0)
≥ 3 Years	22 (55.0)
Baseline hemoglobin - n (%)	
< 8 g/dL	15 (37.5)
≥ 8 g/dL	25 (62.5)
Baseline hemoglobin - n (%)	
< 6 g/dL	2 (5.0)
≥ 6 g/dL	38 (95.0)
Baseline hemoglobin (g/dL)	
n	40
Mean (SD)	8.155 (1.0871)
Median (Min – Max)	8.050 (5.80 - 10.00)
Baseline LDH level (U/L)	
n	40
Mean (SD)	1698.8 (683.33)
Median (Min – Max)	1581.5 (522 – 3244)
Transfusion in the last 12 months prior to screening - n (%)	
Yes	27 (67.5)
No	13 (32.5)
Transfusion in the last 6 months prior to study treatment - n (%)	
Yes	28 (70.0)
No	12 (30.0)
Number of transfusions in the last 6 months prior to study treatment - n (%)	
< 2	19 (47.5)
≥ 2	21 (52.5)
Number of transfusions in the last 6 months prior to study treatment among patients who had a transfusion	
n	28
Mean (SD)	3.1 (2.09)
Median (Min – Max)	2.0 (1 – 8)
Platelets (10^9/L), Blood	
n	40
Mean (SD)	159.4 (61.09)
Median (Min – Max)	150.5 (35 – 316)
Absolute reticulocyte count (10^9/L), Blood	
n	40
Mean (SD)	154.33 (63.666)
Median (Min – Max)	139.20 (59.4 - 324.8)
Baseline FACIT - Fatigue total score	
n	40
Mean (SD)	32.78 (10.170)
Median (Min – Max)	34.25 (13.0 - 50.5)

Characteristic Categories/Statistics	LNP023 200mg b.i.d. N=40
Median	34.25
Min - Max	13.0 - 50.5
History of MAVE - n (%)	
Yes	5 (12.5)
No	35 (87.5)
History of aplastic anemia - n (%)	
Yes	16 (40.0)
No	24 (60.0)

- Percentages are based on no. of patients in Full analysis set and n is the number of non-missing observations in each row category. The baseline value is defined to be the last result obtained at or prior to start of study treatment (Day 1) but not for Hemoglobin. The baseline value of Hemoglobin is defined to be the mean of the two measurements taken during screening.
a. Disease duration is derived from the start date of PNH in Medical History page up to the date of screening.
Vaccination history is defined as any vaccination with a start date before Day 1.

History of MAVE

Table 50: History of MAVE – Full analysis set - APPOINT-PNH

Medical History Term	LNP023 200 mg b.i.d. N=40 n (%)
Number of patients with at least one MAVE	**5 (12.5)**
Cerebral arterial occlusion/cerebrovascular accident	2 (5.0)
Thrombophlebitis / deep vein thrombosis	1 (2.5)
Other	3 (7.5)

- Percentages are based on no. of patients in Full analysis set.
- A patient with multiple occurrences of a MAVE is counted only once in this MAVE category.

PNH clone size at baseline

The mean (range) PNH clone size was 42.71% (8.97 - 92.87) for total clone size in RBCs. The mean (range) proportion of C3d+ PNH RBCs (Type II and III) was 0.67% (0.106 - 1.919).

PNH related signs and symptoms at baseline

All the patients except one presented with at least one PNH related signs and symptoms at baseline. The most frequently reported PNH related signs and symptoms were reddish or cola coloured urine especially in the morning/or haemoglobinuria in 29/39 patients (74.4%) and feeling weak or tired in 28/39 patients (71.8%). The majority of patients had mild or moderate PNH related signs and symptoms. Erectile dysfunction (4 patients, 10.0%), and reddish or cola coloured urine especially in the morning/or haemoglobinuria (6 patients, 15.0%) were the only severe signs and symptoms reported in ≥10% of the patients.

Concomitant medication

Concomitant medications/ non-drug therapies and procedures were defined as any medication taken (excluding RBC transfusions and required/recommended vaccinations) at least once between first dose and last dose of study treatment (including those which were started prior to first dose and continued into the treatment period). During the core treatment period thirty-nine patients (97.5%) received at least one concomitant medication.

The most common concomitant medications included folic acid derivatives (32.5%), systemic glucocorticoids (30.0%), unspecified herbal and traditional medicine (27.5%), and proton pump inhibitors (25.0%). Twelve patients (12.5%) were receiving ciclosporin; one patient (2.5%) was receiving stable dose of mycophenolate mofetil for aplastic anaemia. One patient (2.5%) had received transdermal tacrolimus for 7 days for a TEAE of allergic dermatitis.

For brevity, only tables containing details on concomitantly immunosuppressant therapy are given.

Table 51: Prior/Concomitant/Post-treatment medications in the core treatment period by ATC class and preferred term – Safety Analysis Set - APPOINT-PNH

Medication type: Prior

ATC Class Preferred Term	LNP023 200mg b.i.d. N=40 n (%)
Number of patients with at least one medication in any ATC class	25 (62.5)
GLUCOCORTICOIDS	12 (30.0)
PREDNISONE ACETATE	6 (15.0)
METHYLPREDNISOLONE	5 (12.5)
DEXAMETHASONE	2 (5.0)
METHYLPREDNISOLONE SODIUM SUCCINATE	2 (5.0)
PREDNISONE	2 (5.0)
TRIAMCINOLONE	2 (5.0)

- Prior medications are defined as medications taken and stopped prior to first dose of study treatment. Concomitant medications were defined as any medication taken at least once between first dose and last dose of study treatment (including those which were started prior to first dose and continued into the treatment period). Post-treatment medications will be defined as any medication with start date after the end of treatment (any dose).
- Anatomical Therapeutic Chemical (ATC) classes are classified as per WHO drug dictionary version DDEBOct22
- ATC classes are presented in descending frequency; preferred terms are sorted within ATC class in descending frequency.
- A patient with multiple occurrences within an ATC class is counted only once in the total row.

Medication type: Prior

ATC Class Preferred Term	LNP023 200mg b.i.d. N=40 n (%)
DEXAMETHASONE PROPIONATE;DEXAMETHASONE SODIUM PHOSPHATE	1 (2.5)
ANDROSTAN DERIVATIVES	6 (15.0)
STANOZOLOL	5 (12.5)
DANAZOL	2 (5.0)
CALCINEURIN INHIBITORS	5 (12.5)
CICLOSPORIN	5 (12.5)
OTHER VIRAL VACCINES	5 (12.5)
TOZINAMERAN	5 (12.5)

- Prior medications are defined as medications taken and stopped prior to first dose of study treatment. Concomitant medications were defined as any medication taken at least once between first dose and last dose of study treatment (including those which were started prior to first dose and continued into the treatment period). Post-treatment medications will be defined as any medication with start date after the end of treatment (any dose).
- Anatomical Therapeutic Chemical (ATC) classes are classified as per WHO drug dictionary version DDEBOct22
- ATC classes are presented in descending frequency; preferred terms are sorted within ATC class in descending frequency.
- A patient with multiple occurrences within an ATC class is counted only once in the total row.

Results on primary and secondary endpoints

Iptacopan monotherapy resulted in a 92.2% (95% CI: 82.5%, 100.0%) marginal proportion of patients achieving clinically meaningful Hb increases of 2 g/dL or more in absence of transfusions. Lower bound of the two-sided 95% confidence interval was 82.5%, which was above the study protocol pre-specified threshold of 15%.

Analysis of secondary endpoints demonstrated consistent efficacy of iptacopan 200 mg b.i.d. including proportion of patients achieving sustained haemoglobin levels ≥ 12 g/dL in the absence of RBC transfusions, transfusion avoidance, changes from baseline in haemoglobin, absolute reticulocyte counts, FACIT-fatigue scores, and percentage change from baseline in LDH. There were no cases of MAVEs or clinical breakthrough haemolysis in the core treatment period.

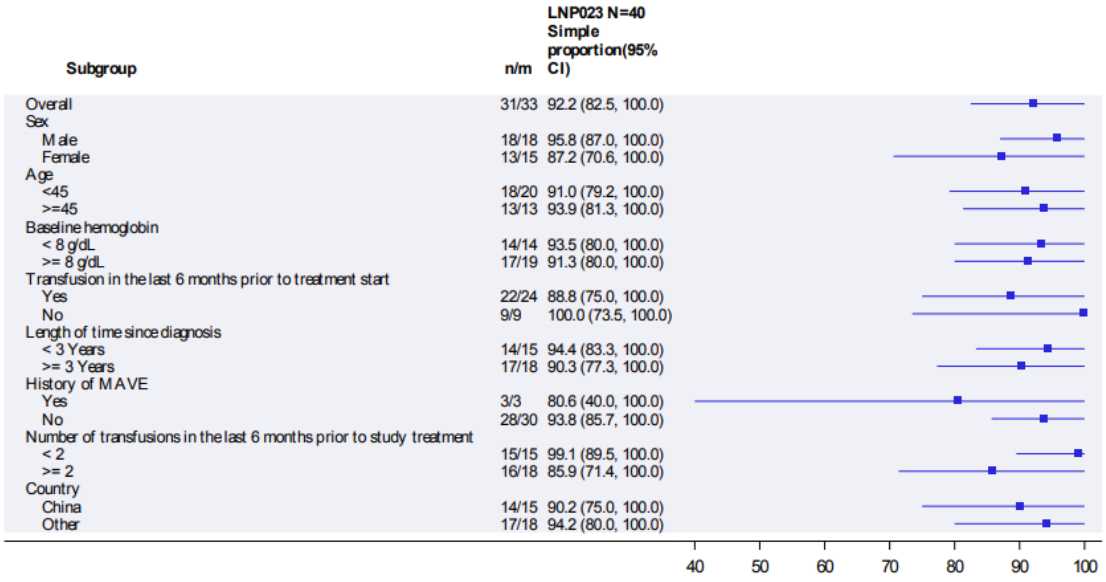
Key efficacy results are presented in the following table:

Table 52: Summary of APPOINT-PNH primary and secondary efficacy endpoints: core treatment period (FAS)

Endpoint (Estimand definition)	Summary measure	
Primary endpoint		
≥ 2 g/dL increase in Hb from baseline[1] in the absence of RBC transfusions [2]	Marginal proportion (95% CI)	92.2% (82.5, 100.0)
Secondary endpoints		
Hb ≥ 12 g/dL[1] in the absence of RBC transfusions	Marginal proportion (95% CI)	62.8% (47.5, 77.5)
Transfusion avoidance[2] (treatment policy estimand)	Marginal proportion (95% CI)	97.6% (92.5, 100.0)
Change from baseline in Hb levels (g/dL) [1] (direct efficacy estimand)	Adjusted mean (95% CI)	4.28 (3.87, 4.70)
Percentage change from baseline in LDH levels (U/L)[1]	Percentage change from baseline (%) (95% CI)	-83.55 (-84.90, -82.08)
Clinical BTH[3] (including transfusion estimand)	Adjusted annual BTH rate (95% CI)	0.00 (0.00,0.17)
Change from baseline in ARC (10^9/L)[1] (including transfusion estimand)	Adjusted mean (95% CI)	-82.48 (-89.33, -75.62)
Change from baseline in FACIT-Fatigue scores[1] (including transfusion estimand)	Adjusted mean (95% CI)	10.75 (8.66, 12.84)
Rates of MAVEs [3] (%) (including transfusion estimand)	Adjusted annual MAVE rate (95% CI)	0.00 (0.00,0.17)

[1] assessed between Day 126 and 168 (at least 3 out of 4 scheduled measurements).
[2] assessed between Day 14 and Day 168. Requiring RBC refers to any patient receiving transfusions or meeting protocol defined criteria or imputed hemoglobin values ≤9 g/dL (≤ 8 g/dL for Chinese population).
[3] between Day 1 and Day 168.

Subgroup analyses of the primary endpoint



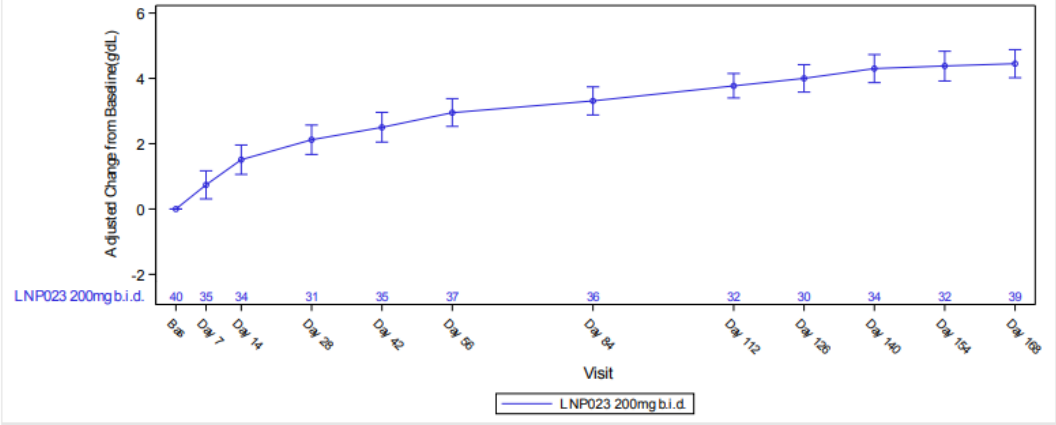
Response is defined as change from baseline in hemoglobin ≥ 2 g/dL on three out of four measurements from Day 126 to Day 168 in patients who didn't meet any protocol defined transfusion criteria or did not receive transfusions between Day 14 and Day 168.
N: Total number of patients included in the model (without missing covariates).

Figure 58: Forest plot of subgroup analysis of response based on change from baseline in haemoglobin (≥2 g/dL) between Day 126 and Day 168 in the absence of requirement of packed-red blood cell transfusions between Day 14 and Day 168 (Full Analysis Set) - APPOINT-PNH

Change from baseline in haemoglobin levels

Mean (SD) Hb at baseline was 8.16 (1.09) g/dL. The adjusted mean change from baseline in Hb as mean of visits between Day 126 and Day 168 was +4.28 g/dL (95% CI: 3.87, 4.70). In order to factor out the effect of transfusions in this analysis, if a patient had a transfusion during the core treatment period, the Hb values during the 30 days following the transfusion were excluded and Hb data were imputed.

In patients treated with iptacopan, the increases in Hb levels were seen early in the core treatment period with an adjusted mean change from baseline in Hb (95% CI) of 0.74 g/dL (0.31, 1.17) at Day 7. A further increase in Hb was observed at Day 14 with an adjusted mean change from baseline in Hb (95% CI) of 1.51 g/dL (1.06, 1.96). At each visit from Day 28 on up to Day 168, the adjusted mean change from baseline in Hb level was > 2 g/dL. The effect of iptacopan monotherapy on change from baseline in Hb was observed early as of Day 7 and continued to increase up to Day 140 and was sustained until Day 168.



Bas: Baseline

Intercurrent events were handled with treatment policy strategy, except for RBC transfusions which was handled as hypothetical strategy.

In addition, hemoglobin values at visits in 30 days following transfusions were considered as missing and were imputed. Treatment discontinuation for any reason was handled with a treatment policy strategy.

Change from baseline was analyzed using a Mixed Model of Repeated Measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline hemoglobin as fixed effects and the interaction between visit and baseline hemoglobin levels.

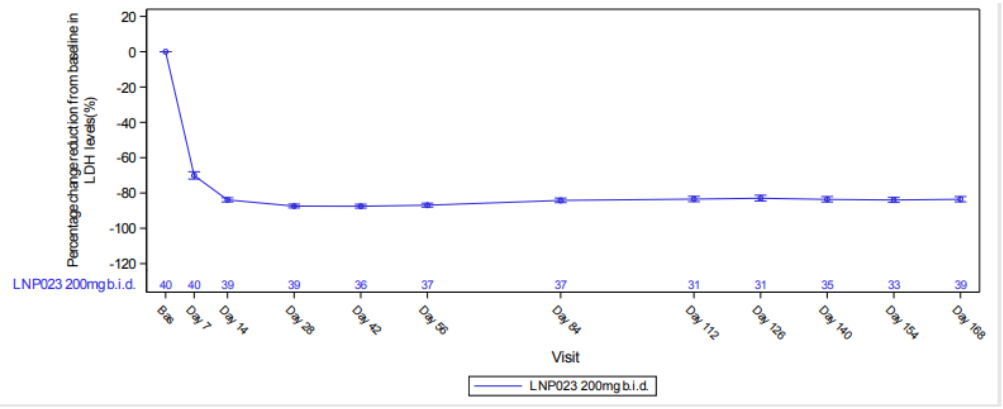
- Error bars represent 95% confidence intervals.

Figure 59: Least squares mean of change from baseline in haemoglobin in the core treatment period (Full Analysis Set) - APPOINT-PNH

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 – 3244 U/L). The ULN for LDH is 250 U/L (central laboratory).

Treatment with iptacopan resulted in an adjusted mean percent change from baseline in LDH levels as mean of visits 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) at Day 7 and greater than -83% (- 84.55, - 86.37) at any visit after Day 7 in the core treatment period.



Bas: Baseline

Intercurrent events are handled with treatment policy strategy.

The baseline LDH is derived following SAP definition.

Percentage change from baseline was analyzed using a Mixed Model of Repeated Measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline LDH as fixed effects and visit*baseline LDH as interaction.

The log transformation used refers to the natural log (base of e). Results were back-transformed and expressed as geometric means.

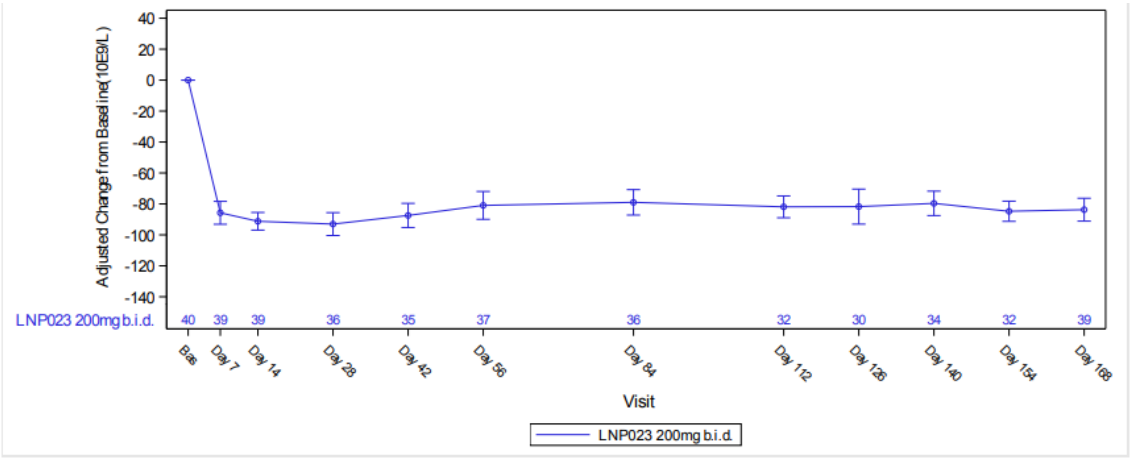
- Error bars represent 95% confidence intervals.

Figure 60: Least squares geometric means of percentage change from baseline in LDH levels (U/L) in the core treatment period - APPOINT-PNH

Change from baseline in absolute reticulocyte count

Baseline mean (SD) absolute reticulocyte count was 154.33 (63.666) x 10^9/L. The ULN for absolute reticulocyte count is 123 x 10^9/L (central laboratory).

The adjusted mean (95% CI) change from baseline in absolute reticulocyte count as mean of visits between Day 126 and Day 168 was -82.48 x 10^9/L (-89.33, -75.62). In patients treated with iptacopan, decreases in absolute reticulocytes 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 x 10^9/L (-93.16, -78.35). There was further decrease in absolute reticulocytes count on Day 14 with an adjusted mean change from baseline of -91.23 x 10^9/L (-96.94, -85.53). The maximum effect was at Day 28 with an adjusted mean (95% CI) change from baseline of - 93.04 x 10^9/L (-100.43, -85.65). At each visit from Day 42 onwards up to Day 168, the adjusted mean change from baseline in absolute reticulocytes count ranged between -78.99 x 10^9/L and < - 87.46 x 10^9/L.



Bas: Baseline

Intercurrent events were handled with treatment policy strategy.

- The baseline value of reticulocyte counts is defined to be the last result obtained at or prior to start of study treatment (Day 1).

Change from baseline was analyzed using a Mixed Model of Repeated Measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline reticulocyte counts as fixed effects and visit*baseline reticulocyte counts as interaction.

- Error bars represent 95% confidence intervals.

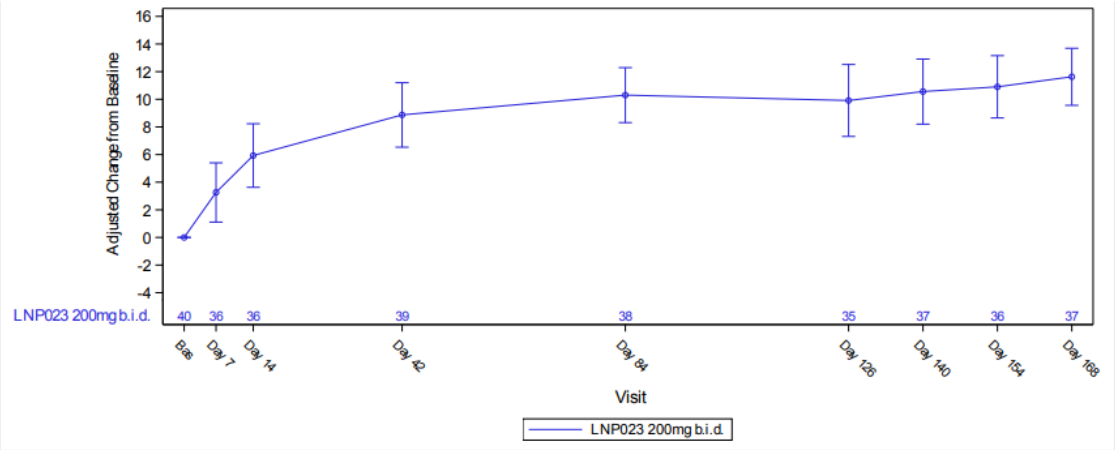
Figure 61: Least squares means of change from baseline in absolute reticulocyte counts (10^9/L) in the core treatment period (Full Analysis Set) - APPOINT-PNH

Change from baseline in FACIT-Fatigue score

The FACIT-Fatigue is a 13-item questionnaire with support for its validity and reliability in PNH that assesses patient self-reported fatigue and its impact on daily activities and function (Yellen 1997, Webster 2003). All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best.

The mean (SD) FACIT-F score at baseline was 32.78 points (10.170). The adjusted mean (95% CI) FACIT-Fatigue score change from baseline between Day 126 and Day 168 was +10.75 points (8.66, 12.84). At Day 168 the mean (SD) FACIT-F 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 onwards up to Day 168, the adjusted mean change from baseline in FACIT-Fatigue score was ≥ 9.91 points.



Bas: Baseline

Intercurrent events are handled with treatment policy strategy.

The baseline score of fatigue using the FACIT-Fatigue questionnaire was defined as the mean of first assessment prior to Day 1 and the Day 1 value.

Change from baseline was analyzed using a Mixed Model of Repeated Measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline FACIT-Fatigue score, visit as fixed effects and visit*baseline FACIT-Fatigue score as interaction terms.

- Error bars represent 95% confidence intervals.

Figure 62: Least squares means of change from baseline in FACIT-Fatigue score in the core treatment period (Full Analysis Set) - APPOINT-PNH

Results on exploratory endpoints

RBCs

At baseline, the mean (SD) erythrocyte count was 2.6 x 10^{12}/L (0.60) and the median (range) erythrocyte count was 2.5 x10^{12}/L (1.50 – 3.80) below the lower limit of normal (normal reference range for males: 4.1 to 5.9 x 10^{12}/L and for females: 3.8 to 5.5 x 10^{12}/L). A consistent increase in the mean (SD) erythrocyte count was observed between Day 7 (2.96 x 10^{12}/L (SD: 0.49) until Day 84 (4.06 x10^{12}/L (SD: 0.60)). From Day 112 until Day 168, the mean erythrocyte count was stable.

Total bilirubin

Mean (SD) total bilirubin at baseline was 28.7 µmol/L (14.92). Both mean and median total bilirubin values at the baseline were above the ULN (normal reference range: ≤21 µmol/L). A reduction in the mean (SD) total bilirubin values was observed on Day 7 (mean: 8.9 µmol/L (SD: 4.48). Total bilirubin mean values remained within the normal range from Day 7 through the end of core treatment period. At Day 168, mean total bilirubin was 10.7 µmol/L (SD: 4.96)

Biomarkers

As expected for a treatment-naïve study population, there was negligible C3 fragment deposition on PNH RBCs at baseline but importantly this remained negligible through to Day 168. This shows that the mechanism of action of iptacopan inhibited C3 deposition on PNH RBCs also in complement-naïve patient, preventing C3 opsonisation and subsequent EVH. The good control of haemolysis with iptacopan is further substantiated by an early and marked increase in mean PNH RBC total clone size from 42.71% at baseline to 87.06% at Day 168 approaching the size of the mean PNH WBC clone. It also indicates prolonged survival of PNH RBCs towards a close to normal life span.

PNH related signs and symptoms

Overall, 39 (97.5%) of patients had PNH signs and symptoms at baseline. At the end of core treatment period, 14 patients (35.0%) reported at least one PNH related sign and symptom. Feeling weak or

tired was the most frequently reported symptom with only 30.0% of patients without this symptom (none) and, 37.5% reported as mild, 27.5% as moderate and 5.0% as severe weakness and tiredness at baseline. At Day 168, this changed to 80.0% patients reported as none, 17.5% as mild, 2.5% as moderate and none of patients reported with severe weakness or tiredness. At baseline, only 27.5% of patients had no haemoglobinuria (none), 37.5% reported as mild, 20.0% as moderate, and 15.0% as severe. At Day 168, this changed to 100% of patients reported as none. At baseline, shortness of breath was reported for 70.0% of patients as none, 17.5% were reported as mild, 12.5% as moderate and none of patients was reported with severe shortness of breath. At Day 168, this changed to 90.0% reported as none, 10.0% as mild, and 0% of patients with moderate and severe shortness of breath.

Table 53: Summary of efficacy for trial CLNP023C12301 APPOINT-PNH

Title: A multicentre, single-arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who are naïve to complement inhibitor therapy			
Study identifier	Protocol number: CLNP023C12301 EudraCT number: 2020-003172-41		
Design	A multicentre, single-arm, open-label Phase III trial. The study comprised a screening period, a 24-week core treatment period and a 24-week extension period. The core treatment period was defined from day 1 to day 168 and was used for the primary efficacy analyses.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24-week Not applicable 24-week
Hypothesis			
Treatments groups	LNP023		200 mg b.i.d. 40 patients enrolled
Endpoints and definitions	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.	The primary objective was to assess the effect of iptacopan in the proportion of patients achieving haematological response. The criterion for haematological response was assessed over the last 6 weeks of the 24-week core treatment period with serial assessments.

	Secondary endpoint	Response defined as having Hb levels ≥ 12 g/dL between Day 126 and Day 168 in absence of RBC transfusion between Day 14 and Day 168	To assess the effect of iptacopan in the proportion of patients achieving haematological response. The criterion for haematological response was assessed over the last 6 weeks of the 24-week core treatment period with serial assessments.
	Secondary Endpoint	Absence of administration of RBC transfusions between Day 14 and Day 168	To assess the effect of iptacopan in transfusion avoidance as the proportion of patients who remain free from transfusions (meaning patients not receiving a transfusion or not meeting protocol-defined criteria for transfusion between Day 14 and Day 168)
	Secondary Endpoint	Change from baseline in haemoglobin (g/dL) as mean of visits between Day 126 and Day 168	To assess the effect of iptacopan in average change in haemoglobin over the last 6 weeks of the 24-week core treatment period with serial assessments.
	Secondary endpoint	Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168	To assess the effect of iptacopan in average percent change in LDH over the last 6 weeks of the 24-week core treatment period with serial assessments.
	Secondary Endpoint	Occurrences of BTH reported between Day 1 and Day 168	To assess the effect of iptacopan on the rate of BTH
	Secondary Endpoint	Change from baseline in reticulocyte count (109/L) as mean of visits between Day 126 and Day 168	To assess the effect of iptacopan in average change in reticulocyte counts over the last 6 weeks of the 24-week core treatment period with serial assessments.

	Secondary Endpoint	Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168	To assess the effect of iptacopan in improving fatigue, using the FACIT-Fatigue questionnaire. Fatigue was assessed over the last 6 weeks of the 24-week core treatment period with serial assessments.
	Secondary Endpoint	Occurrences of MAVEs occurring between Day 1 and Day 168	To assess the rates of MAVEs incl. thrombosis
Database lock	02-Nov-2022 (Primary endpoint completion date)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS): all enrolled patients. Time point: Between Weeks 16 to 24 except for BTH and MAVE (from Day 1 to Week 24)		

Descriptive statistics and estimate variability	Treatment group	LNP023		
	Number of subjects	40		
	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. Marginal proportion (95% CI)[#]	92.2 (82.5, 100.0)		
	Response defined as having Hb levels ≥ 12 g/dL between Day 126 and Day 168 in absence of RBC transfusion between Day 14 and Day 168 Marginal proportion (95% CI)	62.8 (47.5, 77.5)		
	Absence of administration of RBC transfusions between Day 14 and Day 168 Marginal proportion (95% CI)	97.6 (92.5, 100.0)		

	Change from baseline in haemoglobin (g/dL) as mean of visits between Day 126 and Day 168 Least square (LS) mean (95% CI)	4.28 (3.87, 4.70)		
	Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168 Percentage change from baseline (%) (95% CI)	-83.55 (-84.90, -82.08)		
	Occurrences of BTH reported between Day 1 and Day 168 Adjusted annualised rate (95% CI)	0.00 (0.00,0.17)		
	Change from baseline in reticulocyte count (10^9/L) as mean of visits between Day 126 and Day 168 Least square (LS) mean (95% CI)	-82.48 (-89.33, -75.62)		
	Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168 Least square (LS) mean (95% CI)	10.75 (8.66, 12.84)		
	Occurrences of MAVEs occurring between Day 1 and Day 168 Adjusted annualised rate (95% CI)	0.00 (0.00,0.17)		

Notes	The lower bound of the two-sided 95% CI of the haemoglobin response endpoint obtained from the primary analysis was compared to a threshold of 15% for the study to meet success criterion. The 15% threshold was chosen to be above the estimated haemoglobin response derived from two studies with eculizumab (ALXN1210-PNH-301 and TRIUMPH). Exceeding this threshold was deemed sufficient to demonstrate the effectiveness of iptacopan in complement inhibitor-naïve patients with PNH with haemolysis and anaemia. In order to account for the confounding effect of transfusion, data within 30 days after transfusion were not included in the analysis of change from baseline in haemoglobin

2.6.5.3. Clinical studies in special populations

Table 54 Numbers of patients by age group across efficacy studies for iptacopan in PNH

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled trials			
CLNP023C12302 (APPLY-PNH)	19/97 (LNP023: 12/62 Anti-C5: 7/35)	7/97 (LNP023: 6/62 Anti-C5: 1/35)	0/97 (LNP023: 0/62 Anti-C5: 0/97)
Non-controlled trials			
CLNP023C12301 (APPOINT-PNH)	2/40	1/40	0/40
CLNP023X2204 (Ph2)	0/13	0/13	0/13
CLNP023X2201 (Ph2)	0/16	1/16	0/16

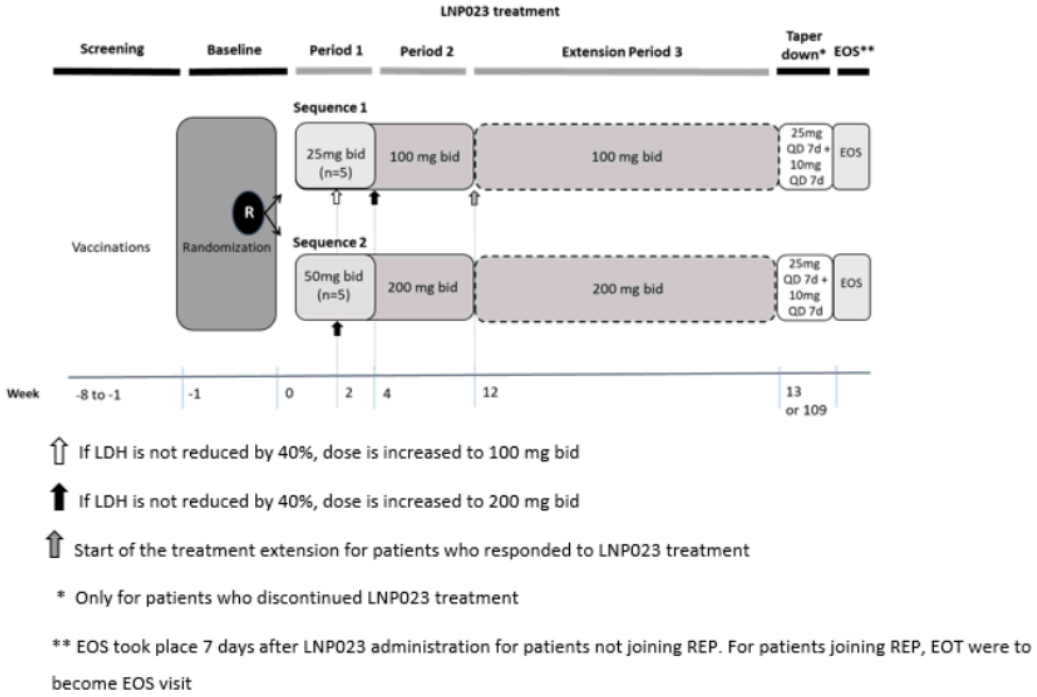
2.6.5.4. Supportive studies

Phase II Study X2204

Study X2204 was a multicentre, open-label, randomised study assessing the efficacy, safety, PK and PD of iptacopan in anti-C5 treatment-naïve PNH patients with active haemolysis (LDH (≥1.5 × ULN and Hb < 10.5 g/dL at baseline), without concomitant complement inhibition (e.g. eculizumab). Two dosing schemes were tested. Cohort 1: 25 mg of iptacopan b.i.d. for 4 weeks, followed by 100 mg b.i.d. for 8 weeks (n=7); Cohort 2: 50 mg iptacopan b.i.d. for 4 weeks, followed by 200 mg b.i.d. for 8 weeks (n=6). Treatment Extension period: up to ~ 2 years.

Study design

This study investigated efficacy, safety, pharmacokinetic and pharmacodynamics assessing four iptacopan doses in adult PNH patients with active haemolysis who were not on eculizumab or any other complement inhibitor less than 3 months prior to first iptacopan dose. Active haemolysis was defined by an LDH value ≥ 1.5 × ULN. At least 3 pre-treatment LDH measurements each separated by at least a week over a maximum of 8 weeks prior to Day 1 of the study had to be ≥ 1.5 × ULN, to include the patients in the study.



Patients were randomized to Sequence 1 or Sequence 2 in a 1:1 ratio.

Figure 63: Study design - Study X2204

Study objectives

The primary objective was to assess the effect of iptacopan on the reduction of PNH associated haemolysis, based on the percentage of patients with 60% reduction in LDH or LDH below ULN after 12 weeks of treatment. The primary variable was treatment response. A responder was defined as a patient with at least 60% reduction in LDH compared to baseline or LDH below the ULN at any time up to and including Week 12 for that patient, whether or not early escalation from the first dose level occurred. A non-responder was defined as any patient who did not meet either of the responder criteria.

The secondary variables of this study were haemoglobin and RBC count, markers of intravascular and extravascular haemolysis: including but not restricted to total and free haemoglobin, carboxyhaemoglobin, reticulocytes, C3 fragment deposition, haptoglobin, bilirubin, RBC count, platelet counts, ferritin, PNH type III RBCs and PNH clone size.

Study population

The study enrolled 13 adult patients (7 in Cohort 1 and 6 in Cohort 2). Twelve patients were assessed for the primary endpoint, as one patient in Cohort 2 discontinued on study Day 2 due to a non-severe AE of headache. All but the patient who discontinued on Day 2 were anti-C5 inhibitor treatment-naïve.

At baseline, all patients had signs of active haemolysis with median serum LDH levels of 1686 U/L (range: 1008.0-3761.0), and clinically significant anaemia with median Hb levels of 86.5 g/L (range: 68.0-107.0). Eleven of the 13 patients were transfusion-dependent 1 year prior to study entry (~85%).

Key inclusion criteria

- Male and female patients at least 18 years old at baseline

- Diagnosis of active PNH based on documented clone size of ≥ 10% by RBCs and/or granulocytes, measured by GPI-deficiency on flow cytometry (screening or medical history data acceptable)

- LDH values ≥ 1.5 × ULN for at least 3 measurements over a maximum of 8 weeks prior to Day 1 (screening, baseline, or medical history data acceptable)

- Haemoglobin level < 10.5 g/dL at baseline

- For Period 3 of the study, patients who as per judgment of the Investigator benefitted from iptacopan treatment based on reduced haemolytic parameters as compared to screening and baseline

- Vaccinations against N. meningitidis, S. pneumoniae, and H. influenzae were required at least 4 weeks prior to first dosing with iptacopan (existing vaccinations were to provide effective titres at the time of iptacopan treatment start). If iptacopan treatment were to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment was initiated.

Key exclusion criteria

- Patients treated with eculizumab or any other complement inhibitor less than 3 months prior to Study Day 1

- History of currently active primary or secondary immunodeficiency, splenectomy

- History of bone marrow/hematopoietic stem cell or solid organ transplants (e.g. heart, lung, kidney, liver)

- Patients with laboratory evidence of bone marrow failure (reticulocytes < 60 × 109 /L, or platelets < 50 × 109 /L, or neutrophils < 1 × 109 /L) verified both at screening and baseline.

- Patients on immunosuppressive agents such, as but not limited to, cyclosporine, tacrolimus, mycophenolate or mycophenolic acid, cyclophosphamide, methotrexate or IV immunoglobulins, less than 8 weeks prior to first treatment with iptacopan, unless on a stable regimen for at least 3 months prior to first iptacopan dose.

- Systemic corticosteroids unless on a stable dose for at least 4 weeks before randomisation.

Disposition

Thirteen patients were enrolled from 5 centres in the following 4 countries (Republic of Korea, Malaysia, Singapore, and Taiwan). All 13 patients with PNH (7 in Cohort 1 and 6 in Cohort 2) completed the screening phase and were randomised to either Cohort 1 (n=7) or Cohort 2 (n=6).

Table 55: Patient disposition (All patients) - Study X2204

Subcategory for disposition event	LNP023 Cohort 1 25 mg/100 mg bid n (%)	LNP023 Cohort 2 50 mg/200 mg bid n (%)	Total n (%)
Screening phase	**N=7**	**N=6**	**N=13**
Patients			
Completed	7 (100.0)	6 (100.0)	13 (100.0)
Randomized	7 (100.0)	6 (100.0)	13 (100.0)
End of study			
Patients			
Completed	4 (57.1)	4 (66.7)	8 (61.5)
Discontinued	3 (42.9)	2 (33.3)	5 (38.5)
Primary reason for discontinuation			
Patient/guardian decision[1]	1 (14.3)	1 (16.7)	2 (15.4)
Adverse event	0	1 (16.7)	1 (7.7)
Physician decision	1 (14.3)	0	1 (7.7)
Technical problems[1]	1 (14.3)	0	1 (7.7)

N=Number of patients entered the subcategory for disposition event.
[1]The reasons for discontinuing study were recorded in the Clinical Database as 'patient decision' for patients X2204-3001-002 and X2204-1001-001 and 'technical problems' for patient X2204-2001-001 although these 3 patients completed the study treatment on Days 762, 771, and 772, respectively.

Two patients discontinued due to adverse event (non-severe headache) and physician decision (patients had history of MDS).

Baseline characteristics

Demographics

Table 56: Demographics (FAS*)* - *Study X2204*

	LNP023 Cohort 1 25 mg bid/100 mg bid N=7	LNP023 Cohort 2 50 mg bid/200 mg bid N=6	Total N=13
Age (years)			
n	7	6	13
Mean (SD)	34.4 (15.27)	42.5 (11.98)	38.2 (13.93)
Median	30.0	35.5	35.0
Range	20 - 55	34 - 62	20 - 62
Sex n (%)			
Male	5 (71)	1 (17)	6 (46)
Female	2 (29)	5 (83)	7 (54)
Race n (%)			
Asian	7 (100)	6 (100)	13 (100)
Ethnicity n (%)			
Not Hispanic or Latino	5 (71)	5 (83)	10 (77)
Unknown	2 (29)	1 (17)	3 (23)
Weight (kg)			
n	7	6	13
Mean (SD)	60.6 (14.55)	59.7 (16.77)	60.2 (14.94)
Median	57.2	61.8	57.2
Range	46 - 83	35 - 81	35 - 83
Height (cm)			
n	7	6	13
Mean (SD)	166.5 (7.36)	159.4 (11.79)	163.2 (9.93)
Median	165.5	161.4	164.5
Range	154 - 175	138 - 170	138 - 175
Body mass index (kg/m^2)			
n	7	6	13
Mean (SD)	21.7 (4.14)	23.1 (4.49)	22.4 (4.19)
Median	21.6	23.1	21.8
Range	16 - 27	18 - 29	16 - 29

For weight (kg), height (cm) and body mass index (kg/m^2) the Baseline visit is presented.

Disease

At baseline, all patients had signs of active haemolysis with median serum LDH levels of 1686 U/L (range: 1008.0-3761.0), and clinically significant anaemia with median haemoglobin levels of 86.5 g/L (range: 68.0-107.0)). Median reticulocytes were 209 ×109 /L (range: 30.0 - 352.0), urine blood dipstick was positive for 9 patients (69.2%). The median PNH type II+type III RBC clone size was 39.8% (range: 3.4-85.1).

Table 57: Baseline characteristics (FAS) - Study X2204

	LNP023 Cohort 1 25 mg/100 mg bid N=7 n (%)	LNP023 Cohort 2 50 mg/200 mg bid N=6 n (%)	Total N=13 n (%)
Serum LDH (U/L)			
n	7	6	13
Mean (SD)	2228.00 (1104.755)	1946.00 (690.347)	2097.85 (911.168)
Median	1686.00	1736.50	1686.00
Range	1008.0 - 3761.0	1212.0 - 2832.0	1008.0 - 3761.0
Hemoglobin (g/L)			
n	7	5	12
Mean (SD)	90.29 (13.149)	79.40 (11.675)	85.75 (13.240)
Median	93.00	73.00	86.50
Range	70.0 - 107.0	68.0 - 96.0	68.0 - 107.0
Free hemoglobin (mg/dL)			
n	4	4	8
Mean (SD)	45.83 (24.526)	24.28 (9.567)	35.05 (20.729)
Median	34.60	25.15	32.45
Range	31.6 - 82.5	14.2 - 32.6	14.2 - 82.5
Total bilirubin (µmol/L)			
n	7	6	13
Mean (SD)	32.43 (9.880)	32.33 (11.343)	32.38 (10.120)
Median	27.00	29.00	27.00
Range	24.0 - 48.0	20.0 - 51.0	20.0 - 51.0
Reticulocytes ($\times 10^9$/L)			
n	7	6	13
Mean (SD)	205.43 (60.108)	200.83 (110.173)	203.31 (82.884)
Median	177.00	214.50	209.00
Range	136.0 - 284.0	30.0 - 352.0	30.0 - 352.0

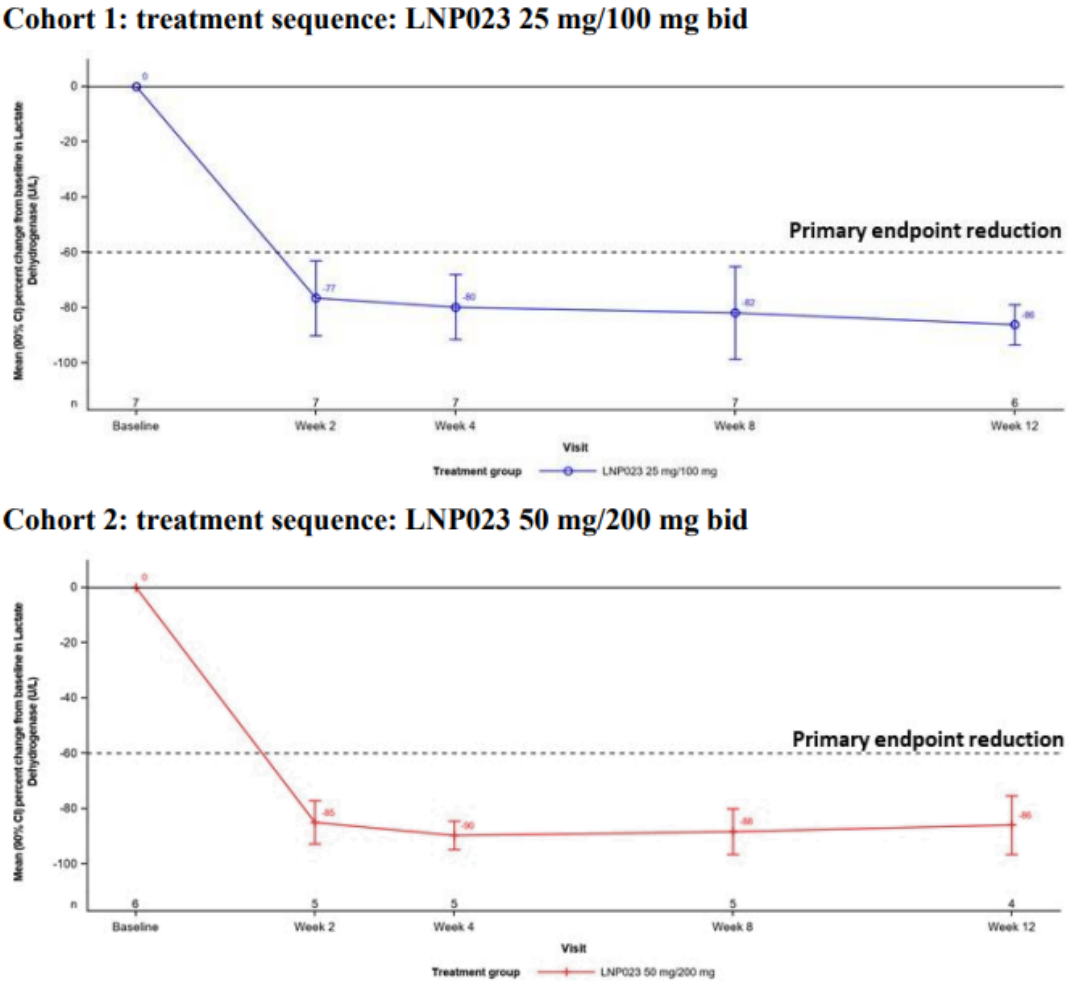
	LNP023 Cohort 1 25 mg/100 mg bid N=7 n (%)	LNP023 Cohort 2 50 mg/200 mg bid N=6 n (%)	Total N=13 n (%)
Urine blood dipstick			
+1	3 (43)	1 (17)	4 (31)
+2	2 (29)	2 (33)	4 (31)
+3	0	1 (17)	1 (8)
Negative	2 (29)	2 (33)	4 (31)
Red cell count (×10^{12}/L)			
n	7	6	13
Mean (SD)	3.14 (0.458)	2.63 (0.656)	2.91 (0.595)
Median	3.10	2.45	3.10
Range	2.4 - 3.8	1.9 - 3.7	1.9 - 3.8
Reticulocytes/Erythrocytes (%)			
n	7	6	13
Mean (SD)	6.70 (2.110)	8.35 (6.008)	7.46 (4.242)
Median	6.50	7.10	6.50
Range	4.2 - 10.0	1.2 - 18.9	1.2 - 18.9
Clone size (type II+type III RBC, PNH RBC) (%)			
n	6	6	12
Mean (SD)	33.63 (18.149)	49.13 (29.701)	41.38 (24.824)
Median	26.55	55.16	39.80
Range	17.7 - 57.3	3.4 - 85.1	3.4 - 85.1
Number of blood transfusions in the previous year			
n	7	6	13
Mean (SD)	6.6 (8.30)	4.8 (4.88)	5.8 (6.72)
Median	2.0	3.5	3.0
Range	0 - 19	0 - 13	0 - 19
Number of units of blood transfusions in the previous year			
n	6	5	11
Mean (SD)	7.2 (8.82)	15.6 (21.28)	11.0 (15.47)
Median	2.0	8.0	2.0
Range	0 - 19	0 - 52	0 - 52

The Baseline visit is presented.
Lab normal ranges, LDH [U/L]: 53-234, Hb [g/L]: Male 130-175 & Female 116-162, Reticulocytes [10E9/L]: ULN 123, Bilirubin (umol/L): 3-21, Free hemoglobin (g/L): 0-4.9. Source: Table 14.1-3.2, Table 14.1-3.1

Results

Primary endpoint

The primary endpoint was met in both cohorts. Of the 13 patients enrolled, all 12 patients assessed for efficacy (7 in Cohort 1 and 5 in Cohort 2) achieved the primary endpoint of reduction in serum LDH levels by ≥ 60% by Week 12 compared to baseline or LDH levels below ULN up to 12 weeks of treatment. Of note, 9 out of 12 patients had LDH levels below ULN at any time up to 12 weeks of treatment. None of the patients in either cohort required an unscheduled up-titration of the iptacopan dose due to a lack of LDH reduction by ≥ 40% from baseline.



Baseline LDH was calculated as the average of the last three screening values prior to randomization.

Figure 64: Percent mean (90% CI) change from baseline in LDH levels at Weeks 2, 4, 8 and 12 (Pharmacodynamic analysis set) - Study X2204

Results on selected secondary endpoints

Most patients achieved an improvement in haemoglobin levels (baseline Hb 8.58g/dl). Cohort 1: Treatment with iptacopan resulted in an improvement in haemoglobin levels, with a mean improvement from 8.86 g/dl at baseline (n=7) to 9.55 g/dL at Week 4 (n=6) and 11.52 g/dL at Week 12 (n=6). The mean increase in haemoglobin levels from baseline was 0.96 g/dL at Week 4 and 2.34 g/dL at Week 12. Cohort 2: Treatment with iptacopan resulted in an improvement in haemoglobin levels from 7.68 g/dL at baseline (n=5) to 10.90 g/dL at Week 4 (n=4) and 10.90 g/dL at Week 12 (n=3). On average, the improvement in haemoglobin levels was higher in Cohort 2 (50 mg/200 mg bid dose) with an increase of 3.71 g/dL at Week 12 as compared to an increase of 2.34 g/dL in Cohort 1 (25 mg/100 mg bid dose).

These benefits were associated with improvements in other markers of haemolysis including free haemoglobin, bilirubin and ARC as well as erythrocyte count in both Cohorts. As a result of haemolysis control, overall, there was an early and marked increase in PNH RBC clone size which was sustained over time, demonstrating prolonged survival of PNH RBCs.

Other markers of intravascular and extravascular haemolysis showed consistent improvements, among other things, a reduction in bilirubin and reticulocytes were observed in both cohorts.

Phase II Study X2201

Design and objectives

Study X2201 was an open-label, single arm, multiple dose phase II study designed to assess the efficacy, safety, PK and PD of iptacopan administered in addition to anti-C5 treatment (eculizumab) in PNH patients with signs of active haemolysis despite ≥ 3 months of stable treatment with a complement inhibitor (eculizumab) (LDH ≥1.5 × and ≥1.25 × ULN for Cohorts 1 and 2 respectively, and Hb < 10.5 g/dL at screening). Two dose regimens were tested (cohort 1: 200mg iptacopan bid; cohort 2: 50 mg iptacopan bid, both on top of eculizumab).

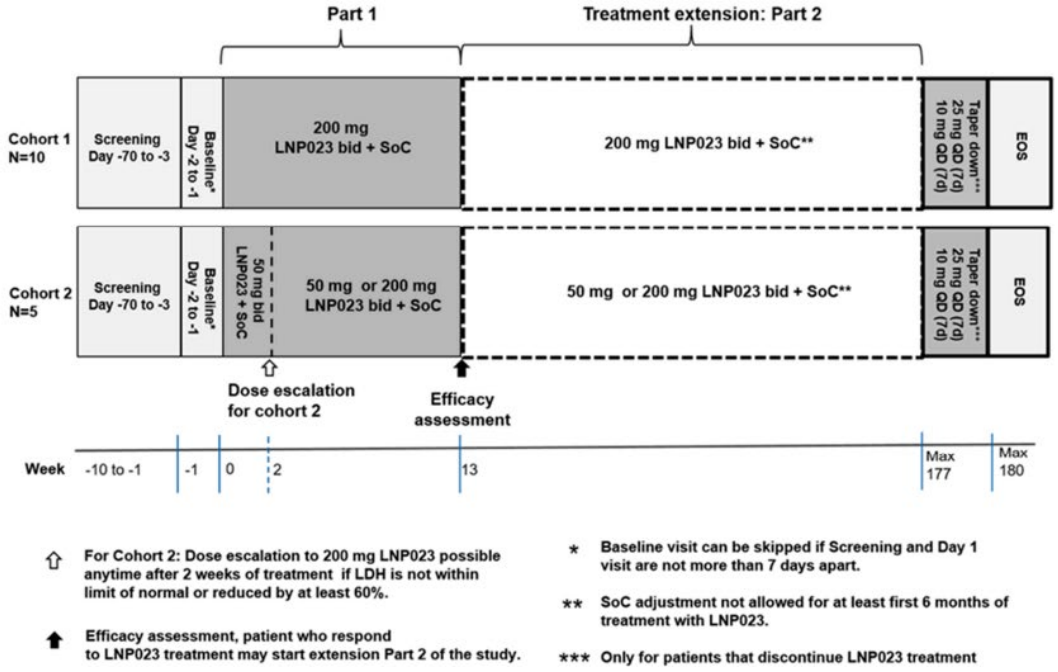


Figure 65: Study design - Study X2201

Table 58: Key elements of Study X2201

Study design	
Treatment Dosing and Duration	*Primary efficacy analysis (Part 1) – 13 weeks* Cohort 1: 200 mg iptacopan b.i.d. on top of SOC eculizumab** (n=10) Cohort 2: 50 mg iptacopan b.i.d.* on top of SoC eculizumab** (n=6) *Treatment Extension (Part 2) - up to approx. 3 years* Cohort 1: 200 mg iptacopan b.i.d. on top of SoC eculizumab** Cohort 2: 50 mg iptacopan b.i.d.* on top of SoC eculizumab** *Dose escalation to 200 mg b.i.d. iptacopan was possible any time after 2 wks of treatment if LDH was not within limit of normal or was not reduced from baseline by at least 60% **Dose adjustment or discontinuation of eculizumab possible after > 6 months of treatment with iptacopan
Primary Objective/Endpoint	*Primary Objective:* To assess the effect of iptacopan on the reduction of chronic hemolysis as assessed by LDH level at 13 weeks in PNH patients when administered in addition to SoC (monoclonal antibody with anti C5 activity)
Secondary Objectives	*Secondary objectives include:* Safety and tolerability of iptacopan, pharmacokinetics of iptacopan, and effects of iptacopan on markers of intra- and extravascular hemolysis (including hemoglobin) in PNH patients.

Patient population

The study enrolled 16 adult patients who all completed Part 1 (13 weeks). Thirteen (81.3%) patients also completed Part 2 (up to 176 weeks). Patients had incomplete haematological response to eculizumab, based on baseline LDH (mean (SD) 492.1 (221.10) U/L) and Hb levels (mean (SD) 94.6 (10.77) g/L) and percentage of patients that were transfusion dependent in the year prior to study entry (88%).

All 10 patients in Cohort 1 received 200 mg iptacopan b.i.d. from study start. Five out of 6 patients in Cohort 2 underwent dose escalation to iptacopan 200 mg; These 15 patients received iptacopan 200 mg b.i.d. monotherapy for a duration ranging from 18 weeks to 136 weeks, with 14 patients receiving iptacopan for at least 1 year.

Baseline characteristics

Overall, the mean age was 47.1 years (range: 24-78), 63% of patients were male. All 16 patients were enrolled in Europe and the majority of patients were White (94%).

At baseline, patients had clinically significant anaemia with mean haemoglobin 9.46 g/dL (range: 7.4 – 12.3). Median LDH was 424.0 U/L (range: 259 – 1169) and mean ARC was 206.06 10^9/L. (range: 79.6 - 416.1). The mean (SD) Day 1 (pre-dose) PNH RBC (Type II + III) clone size was 51.87% (31.316). Fourteen out of 16 patients (87.5%) required packed RBC transfusions in the previous year; the mean number of packed RBC transfusions in previous year was 6.9 (range 0 - 27); and the mean number of packed RBC units transfused in the previous year was 11.7 (range 0 - 40).

Key results

The primary efficacy results showed a reduction of LDH. There was a rapid and sustained reduction from baseline in LDH on both cohorts at Week 13. The mean percentage reduction from baseline for both Cohorts was 43.6% with a greater reduction in Cohort 1 The key secondary efficacy results showed a clinically meaningful increase in mean haemoglobin from baseline of +3.20 g/dL to 12.66

g/dL at Week 13. The vast majority of patients (87.5%) were transfusion-free up to week 13. These benefits were associated with improvement in other markers of haemolysis including ARC and bilirubin.

Table 59: Primary and secondary efficacy results - Study X2201

Primary efficacy results	Secondary efficacy results
• The primary efficacy results demonstrated that at Day 92, iptacopan treatment (as an add-on treatment in addition to SoC) resulted in a rapid, sustained, and clinically meaningful reduction in LDH levels, that was robust and durable following discontinuation of SoC up to Day 92. • In patients with chronic residual intravascular hemolysis (IVH) despite SoC treatment (baseline mean LDH of 492.06 U/L), iptacopan resulted in rapid and sustained reduction of LDH (mean LDH of 245.21 U/L; decrease by mean −251.43 U/L at the primary endpoint analysis at Day 92 (Week 13).	• A trend towards transfusion-free hemoglobin normalization which was sustained and durable up to 176 weeks of treatment. Iptacopan led to a rapid and sustained increase in hemoglobin (mean hemoglobin increased by 32.04 g/L from baseline to 126.60 g/L at Day 92 with a durable and sustained increase in hemoglobin of 33.08 g/L from baseline to Day 1233). Overall, 9 patients achieved fully normal hemoglobin levels at Day 92 (in addition to 9 patients at Day 393; and 8 patients at Day 729). The majority of patients were transfusion independent, with the exception of 1 patient requiring an RBC transfusion on Day 1 in Cohort 1 and 1 patient on Day 2 in Cohort 2 (both transfusions were required before iptacopan steady state and full complement inhibition was achieved), all other patients in both cohorts were transfusion-free at Day 92.

Primary efficacy results	Secondary efficacy results
• By Day 92, 6 out of a total of 10 patients in Cohort 1 and 1 out of a total of 6 patients in Cohort 2 showed complete normalization of LDH levels (<250 U/L). Overall, there was a numerically greater and more marked reduction in LDH levels in Cohort 1 (iptacopan 200 mg b.i.d. dose). • Efficacy was sustained on iptacopan monotherapy even after patients discontinued SoC background therapy; iptacopan is more efficacious in PNH control compared to SoC anti-C5 therapy. • The effects and clinical benefits described were fully maintained and durable over up to 176 weeks of iptacopan treatment.	• Control of extravascular hemolysis (EVH) associated with the reduction of reticulocytes, reduction in bilirubin, and increase in haptoglobin, indicating a sustained and durable effect over a longer duration of treatment. • C3 fragment deposition on PNH RBCs rapidly decreased upon iptacopan treatment leading to sustained control of EVH and an overall marked and sustained increase in PNH clone size on RBC at Day 92, which correlated with observations for Type III RBCs, thus demonstrating prolonged survival and suggesting a normal lifespan of PNH-type RBCs. • Iptacopan inhibited not only IVH but also EVH, by blockage of C3 deposition. The PNH clone size and Type III cells plateaued towards the EoS, indicating the sustained increase was robust and durable over a longer duration of treatment. • Markers of IVH (haptoglobin, free hemoglobin) and of EVH (reticulocytes, bilirubin) improved at the primary endpoint analysis at Day 92; the effect was rapid, sustained and durable.

The primary objective was to assess the effect of iptacopan on the reduction of chronic haemolysis in PNH patients when administered in addition to SoC; the primary endpoint was LDH level at Day 92 (Week 13). All patients showed a dose-dependent, early and clinically meaningful reduction of their LDH levels; by Day 92, 6 out of a total of 10 patients in Cohort 1 and 1 out of a total of 6 patients in Cohort 2 achieved complete normalisation of LDH levels (< 250 U/L).

At Day 92, the least square means of LDH level (95% CI) for Cohort 1 was 189 (−15.8, 394.7) U/L, compared to 391 (106.4, 674.8) U/L in Cohort 2 -1). The graphical summary of the estimated mean treatment estimates over time for LDH level is depicted in the following figure:

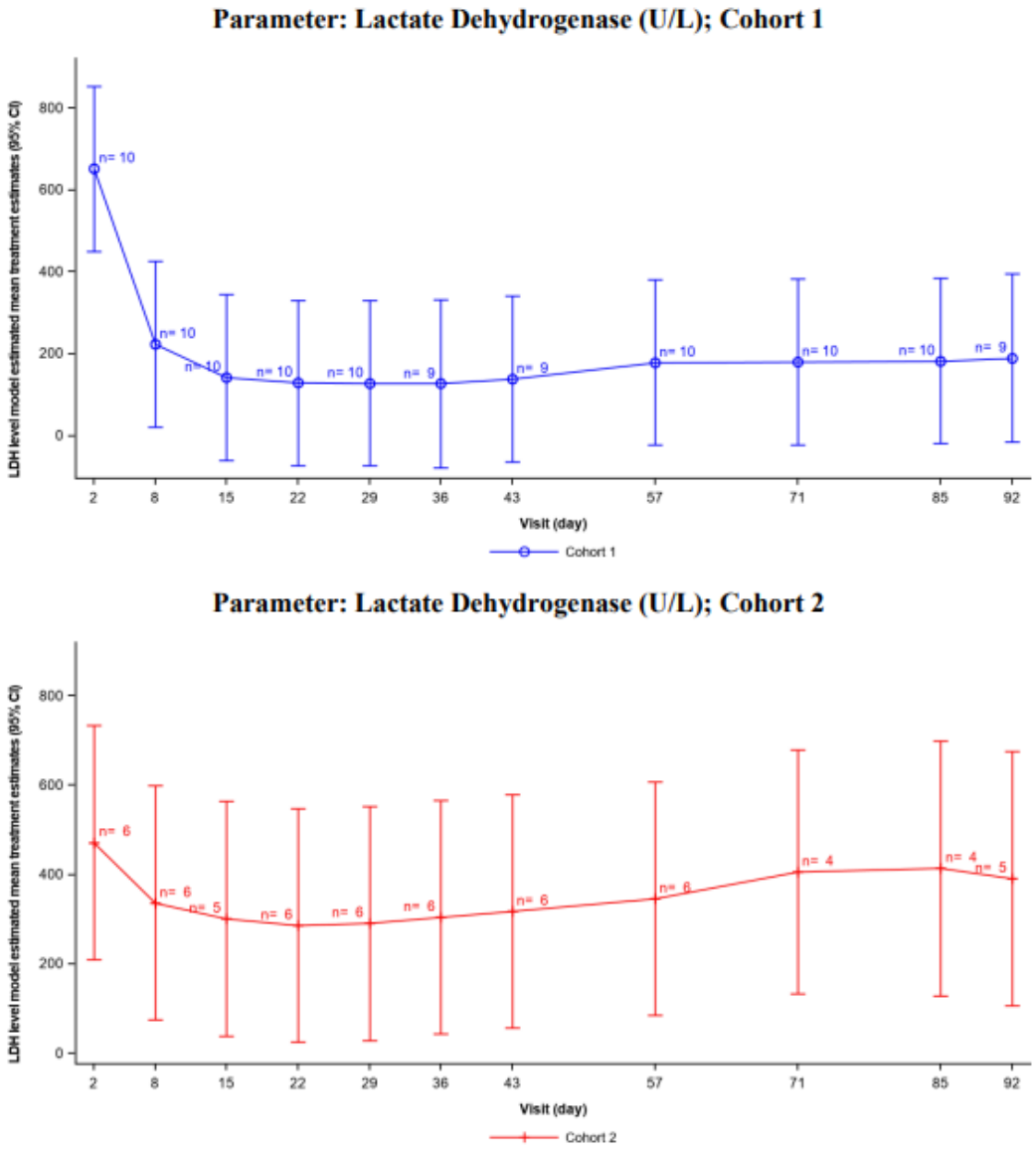


Figure 66: Model estimated mean treatment estimates (95% CI) plot for LDH level up to Day 92 (PD analysis set) - Study X2201

Haemoglobin at week 92 (week 13)

Overall, a trend towards the normalisation of haemoglobin (LLN haemoglobin values: for females >116 g/L; and for males >130 g/L Listing 16.2.8-2.1) at Day 92 (Week 13) was observed. Overall, 9 (9/15) patients had normal haemoglobin values at Day 92 (5 males and 4 females); 9 (9/13) patients had normal haemoglobin values at Day 393 (5 males and 4 females); and 8 (8/12) patients had normal haemoglobin values at Day 729 (5 males and 3 females)

For Cohort 1, the mean (90% CI) haemoglobin value at baseline was in the anaemic range with 97.65 (91.57, 103.73) g/L, but increased to 129.50 (118.89, 140.11) g/L at Day 92.

For Cohort 2, the mean (90% CI) haemoglobin value at baseline was even lower with 89.39 (81.21, 97.57) g/L, but similarly increased to 120.80 (107.38, 134.22) g/L at Day 92.

At Day 92, the mean percentage change from baseline (90% CI) in haemoglobin (g/L) in Cohort 1 was 32.87% (23.55, 42.19) compared to 37.82% (20.19, 55.45) in Cohort 2.

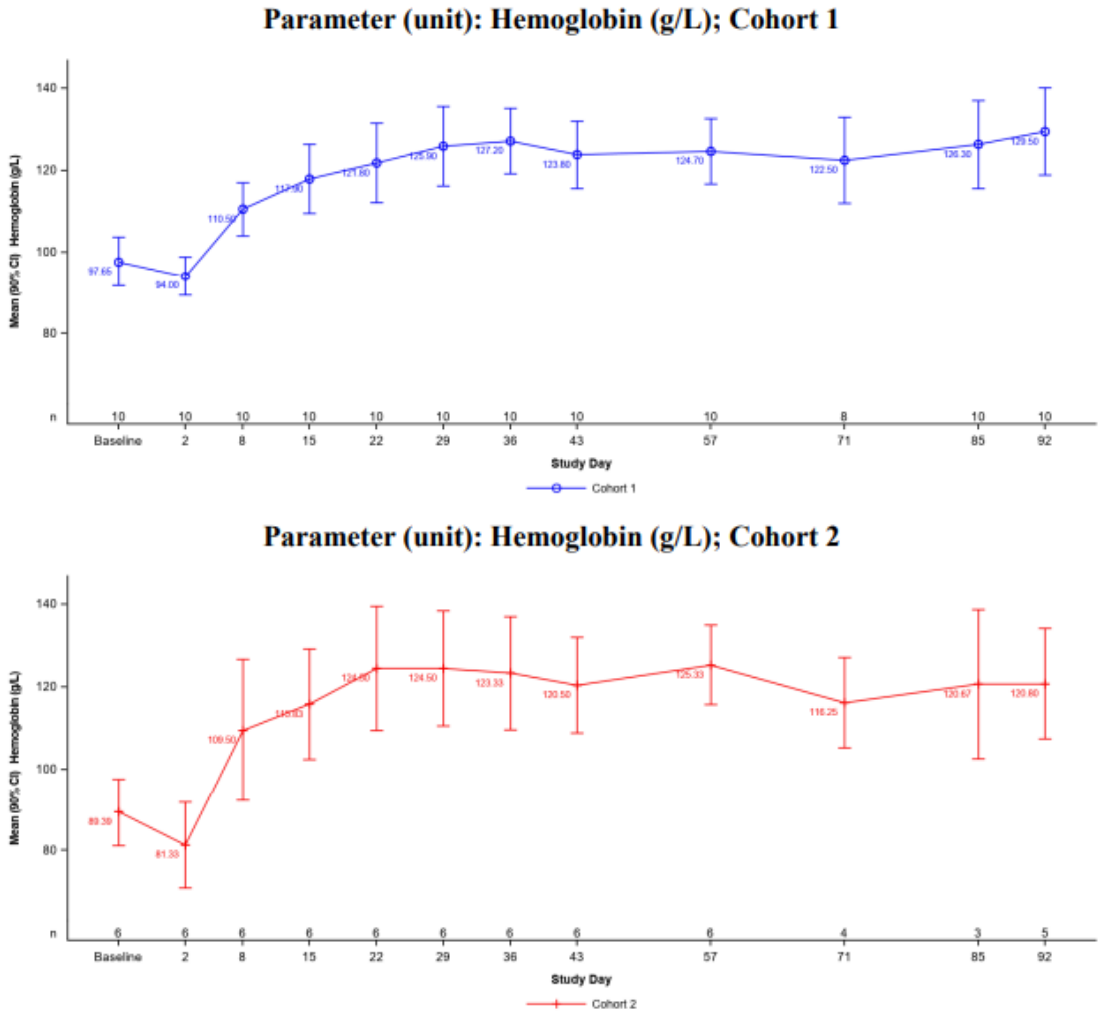


Figure 67: Mean (90% CI) of markers of disease activity – haemoglobin up to Day 92 (PD analysis set) - Study X2201

Markers of EVH

Control of EVH was associated with the reduction of reticulocytes. In the overall population, the mean (90% CI) of reticulocytes (10^9/L) at baseline was 206.06 (168.77, 243.35) which decreased at Day 92 to 87.97 (73.61, 102.34) and at Day 1233 to 91.36 (37.33, 145.39).

Control of EVH was further shown by a reduction in bilirubin. In the overall population, the mean (90% CI) of bilirubin (µmol/L) was 37.15 (28.56, 45.74) at baseline, which decreased at Day 92 to 13.87 (11.34, 16.40) and at Day 1233 to 14.60 (5.82, 23.38).

2.6.6. Discussion on clinical efficacy

The iptacopan PNH development program included a total of 170 PNH patients. Efficacy data supporting the PNH indication are mainly provided by a pivotal active-controlled phase 3 study (APPLY-PNH) and a supportive single arm phase 3 study (APPOINT-PNH).

Rationale for the dose studied

The iptacopan 200 mg b.i.d. dosing was selected for the phase 3 studies based on the available PK/PD, efficacy and safety data from the Phase I first-in-human study and the Phase II studies in patients with PNH, Studies X2204 and X2201.

Baseline factor B levels were evaluated in three studies: X2201, X2202 and X2203. Patients with PNH had higher factor B levels (420-460 µg/mL) than healthy subjects (200-300 µg/mL). Assuming a baseline factor B concentration >420 µg/mL, the 200 mg b.i.d. dose reached an approximately equimolar concentration with factor B in the intravascular compartment over the 12-hour dosing interval. In contrast, doses lower than 200 mg b.i.d. were insufficient to fully inhibit factor B, especially in the setting of increased factor B levels as seen in patients with PNH.

Multiple doses of iptacopan from 25 to 200 mg b.i.d. led to rapid and near complete (>87%) inhibition of the alternative pathway (as measured by the Wieslab assay) 2 h after the first dose. However, a sustained >60% inhibition throughout a 14-day period was only observed for the 100 and 200 b.i.d. cohorts. The inhibition was maximal and with a low standard deviation for the 200 b.i.d. cohort. Alternative pathway inhibition was on a trajectory returning towards baseline 12 h post-dose on day 14 for all cohorts except the 200 mg b.i.d. cohort. For the 200 mg b.i.d. cohort, there continued to be near complete inhibition 12 h after the last dose and 67% inhibition 24 h after the last dose. This is consistent with the 200 mg b.i.d. dose providing more substantial and sustained inhibition over the entire steady-state dosing interval compared to lower doses or less frequent administration.

A PK/PD model developed with data from the first in-human study in healthy volunteers (Study X2101) predicted that a dose of 200 mg b.i.d. was needed to achieve near complete alternative pathway inhibition in most subjects. This model has since been updated using more complete data from Phase II patients and confirms the initial finding, with >90% inhibition of the alternative pathway in 67% of patients with PNH.

Results from the phase 2 studies X2204 and X2201, both showing a dose-related improvement of LDH reduction when comparing 200 mg bid regimens with lower dosages, further support iptacopan 200 mg bid dosing.

Design and conduct of clinical studies

APPLY-PNH is a randomised, open-label, active-comparator trial which enrolled 97 adult PNH patients with residual anaemia (Hb <10 g/dL) despite receiving a stable regimen of anti-C5 antibody therapy (eculizumab or ravulizumab) for at least 6 months prior to randomisation. Patients received iptacopan monotherapy 200 mg b.i.d. (n=62) or continued their anti-C5 regimen (n=35) for 24 weeks (randomised treatment period, RTP). Anti-C5 therapy with the monoclonal antibodies eculizumab or ravulizumab is considered standard of care for haemolytic PNH and were the only approved PNH therapy at time of study initiation.

The timing of the first iptacopan administration (= day 1 of the RTP) provided a seamless switch from prior anti-C5 antibody treatment to iptacopan, allowing for some overlap of exposure to anti-C5 antibody treatment to limit the potential risk of breakthrough haemolysis while iptacopan exposure built up. The first iptacopan dose administration for patients on prior eculizumab regimen was to occur

at days 7 to 8 after last infusion. The first iptacopan dose administration for patients on prior ravulizumab regimen was to occur at days 41 to 43 after the last infusion.

Following completion of the RTP at week 24, 94 out of 97patients entered the 24 week treatment extension period during which all patients received iptacopan monotherapy 200 mg b.i.d.

Albeit it was recommended against open-label conduction in a SA (EMEA/H/SA/3968/3/2019/III), the open-label design seems acceptable, as Hb as an important component of the primary endpoint was objectively measured; in addition criteria for transfusion were pre-defined in the protocol and were in line with Guideline recommendations (Carson *et al*. JAMA 2016), which alleviated potential bias in the decision to transfuse. However, results of patient reported outcome measures have to be seen in the light of the patients` awareness of treatment assignment.

APPOINT-PNH is a phase 3, single-arm, open-label trial in 40 adult treatment-naïve PNH patients. The study comprised an 8-week screening period, 24-week core treatment period and 24-week extension treatment period.

Study Population

APPLY-PNH

The target population consisted of 97 adult patients diagnosed with PNH who were treated with a stable regimen of anti-C5 antibody (eculizumab,64.9% or ravulizumab, 35.1%) for at least 6 months prior to randomisation, but still presenting with residual anaemia (i.e., Hb < 10 g/dL). The diagnosis of PNH had to be confirmed by high-sensitivity flow cytometry with RBCs and WBCs granulocyte/monocyte clone size ≥ 10%. Patients were randomised from Europe (74.2%), Asia (13.4%), the US (8.2%) and South America (4.1%). Overall, the mean baseline haemoglobin level was 8.9 g/dL, and the majority (57.7%) of patients had received RBC transfusions in the 6 months prior to randomisation. Only 7.2% had LDH levels >1.5×ULN, indicating significant residual IVH. The mean LDH at baseline was 270.4 (75.34). Normal LDH, reflecting control of intravascular haemolysis, was expectable in patients on stable anti-C5 therapy. Total clone size at baseline was 62.03% (9.82-99.88). A history of aplastic anaemia was reported in 14.4% of patients at baseline.

The majority of patients (64.9%) presented with at least one PNH related symptom at baseline. The most commonly reported symptom at baseline was 'feeling weak or tired' reported in 32/62 patients (51.6%) in iptacopan group vs 23/35 patients (65.7%) in anti-C5 group, followed by shortness of breath/dyspnoea in 18/62 patients (29.0%) in iptacopan group vs 12/35 patients (34.3%) in anti-C5 group.

APPOINT-PNH

This study enrolled 40 PNH patients with haemolysis (LDH > 1.5 ULN) and anaemia (haemoglobin <10 g/dL), who were naïve to complement inhibitor therapy. Patients were enrolled from Asia (65.0%) and Europe (35.0%). Overall, 67.5% (27 patients) of patients were Asian, 30% (12 patients) were White and 2.5% (one patient) was Black or African American. Mean baseline haemoglobin level was 8.16 g/dL. The mean LDH at baseline was 1698.8 U/L (683.33). The mean (range) PNH clone size was 42.71% (–.97 - 92.87) for total clone size in RBCs.

The majority (70.0%) of patients having received at least one RBC transfusion in the 6 months prior to study treatment and 21 patients (52.5%) having received ≥ 2 transfusions. The mean (SD) platelet count was 159.4 (61.09) $x10^9$/L and the mean (SD) absolute reticulocyte count was 154.33 (63.666) $x10^9$/L. A history of aplastic anaemia was reported in 40.0% of patients at baseline. The higher proportion of patients with a history of AA reflects the about three times higher incidence of AA in Asia compared to the US/Europe.

All the patients except one presented with at least one PNH related sign or symptom at baseline. The most frequently reported PNH related signs and symptoms were reddish or cola coloured urine especially in the morning/or haemoglobinuria in 29/39 patients (74.4%) and feeling weak or tired in 28/39 patients (71.8%).

Endpoints

APPLY-PNH

The primary efficacy analysis was based on two haematological responder endpoints:

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

A patient was a responder, meeting the criterion for the two primary endpoints, if they:

- Achieved a sustained haematological response, defined as 3 out of 4 assessments between Day 126 and Day 168.
- Did not receive a transfusion or met one of the following pre-defined criteria for transfusion: 1) Hb between >7 and ≤ 9g/dL with signs/symptoms of sufficient severity to warrant a transfusion or 2) Hb ≤7g/dL regardless of presence of clinical signs and/or symptoms.

The primary endpoint is accepted. An increase of 2 g/dL in Hb level is clinically meaningful, corresponding approximately to the increase achieved by administration of two RBC packs. Achieving Hb levels ≥12 g/dL corresponds approximately to normalisation of Hb, which is one of the key treatment goals for PNH patients. Criteria to transfuse align with Guideline recommendations and a priori definition ameliorated bias in this decision-based endpoint component.

Important secondary efficacy endpoints were transfusion avoidance between Day 14 and Day 168, average change in Hb (g/dL) from baseline as mean of visits between Day 126 and Day 168, improvement in fatigue from baseline, using the FACIT-Fatigue questionnaire as mean of visits between Day 126 and Day 168. Average change in absolute reticulocyte counts (ARC) from baseline as mean of visits between Day 126 and Day 168 was a measure of EVH; average percent change in LDH levels from baseline as mean of visits between Day 126 and Day 168 reflected IVH.

Analysis of the primary endpoint was predefined in subgroups separated, among others, by age categories (<45 years, ≥45 years, <65 years, ≥65years), baseline haemoglobin (<9 g/dL, ≥9 g/dL), anti-C5 medication history, and LDH levels at baseline (≤1.5 x ULN, >1.5 x ULN). The secondary endpoints are acceptable as they capture iptacopan's effect on IVH, EVH and the patients' key symptoms.

APPOINT-PNH

A haematological responder endpoint was used for the primary efficacy analysis. A responder was defined as a participant achieving a haemoglobin increase from baseline ≥ 2 g/dL (assessed during the last 6 weeks of the 24 weeks Core treatment period) without the need of RBC transfusions from Day 14 to Day 168. 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%, which was chosen based on the haemoglobin response in previous studies with eculizumab (Hillmen *et al.* 2006; Dmytrijuk *et al.* 2008; Brodsky *et al.* 2021). The magnitude of the threshold is not further discussed as the results of the responder analysis exceeded 15% five-fold, rendering any discussion irrelevant.

Transfusions were administered to patients in the following pre-defined cases:

• Hb level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and/or symptoms of sufficient severity to warrant a transfusion,

• Hb of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms.

Secondary endpoints were well in line with those defined for APPLY-PNH.

Concomitant medication

APPLY-PNH

Few patients in APPLY-PNH received concomitant immunosuppressive medication: two patients (3.2%) in the iptacopan group and one patient (2.9%) in the anti-C5 group were treated with cyclosporin. One patient (2.9%) in the anti-C5 group was receiving tacrolimus and azathioprine. Nine patients (14.5%) in the iptacopan group and two patients (5.7%) in the anti-C5 group were receiving glucocorticoids (prednisolone, methylprednisolone prednisone and dexamethasone in the iptacopan group and prednisone in the anti-C5 group). The imbalance in glucocorticoid administration (14.5% in the iptacopan group vs. 5.5% in the anti-C5 group) might have favoured the intervention arm. The impact is considered moderate, given the low percentage of glucocorticoid users and the large between-treatment differences.

APPOINT-PNH

Considerable proportions of the study population received immunosuppressive agents: systemic glucocorticoids (27.5%) cyclosporin (12.5%), mycophenolate mofetil (2.5%). Due to the single-arm design the potential effect of concomitant medication on haematological response cannot be separated from the intervention effect. A meta-analysis identified the presence of PNH clones in patients with AA as a predictor for a good haematological response to immunosuppressive therapy (first-line SOC: anti-thymocyte globulin and cyclosporine A; Tu *et al.* 2021). APPOINT-PNH included 40% of patients with a history of aplastic anaemia, which may have benefitted from immunosuppression. As such, the applicant had been asked to explore the impact of concomitant immunosuppressive therapy on the primary outcome taking into account the nature, start and duration of concomitant immunosuppression, the clone size, and the presence or absence of AA. These analyses showed that concomitant immunosuppression had little impact on the primary outcome. Immunosuppressive therapy had largely been stabilised before inclusion and there were no dose increases during the core treatment period. In addition, the study population foremostly had "classical PNH" and no signs of bone marrow failure which deceases the likelihood that these patients had benefitted from immunosuppressive drugs.

Conduct of the studies

Both, in APPLY-PNH and APPOINT-PNH, all patients completed the core treatment periods (and nearly all on study drug), which is considered reassuring. COVID 19 impact summaries were submitted which showed little impact of the pandemic on efficacy results in APPLY and APPOINT.

Statistical aspects

For the primary endpoints, superiority was assessed based on the odds ratio and by comparing the marginal probability of haemoglobin response to iptacopan to the respective marginal probability of haemoglobin response on anti- C5 antibody treatment.

The term 'marginal proportion' can be interpreted as the population average probability of meeting the criteria for response for each treatment. These values include adjustment for baseline covariates and missing data has also been taken into account. Hence these values are not identical to the observed proportions. The term marginal proportion can also be thought of as "response rate" for the response

analyses, or as "transfusion avoidance rate" in the context of the transfusion avoidance endpoint, for simplicity.

Estimands/intercurrent events

Intercurrent events due to administration of RBC transfusions or meeting the protocol defined criteria for RBC transfusions was handled using a composite strategy for both primary endpoints. All other intercurrent events (discontinuation of treatment, breakthrough haemolysis events and MAVEs) were handled with a treatment policy strategy. This is accepted.

For most secondary analyses an "including transfusion" strategy was used, meaning that receiving a transfusion was ignored and values after transfusion was used in the analysis. Since more transfusions were given in the comparator arm, this approach is expected to be conservative for the treatment comparison and hence accepted. The only exception being the analysis of mean change from baseline in haemoglobin levels where a "direct efficacy" approach was used. In this analysis data collected within 30 days after transfusion were discarded and imputed under MAR assumptions using the haemoglobin data not impacted by transfusion. The hypothetical strategy not using haemoglobin data after transfusion is agreed, however imputing data under MAR assumptions using the haemoglobin data not impacted by transfusion is questionable. This analysis is not expected to estimate the efficacy *in the absence of transfusion* but rather the efficacy *had transfusion not been required*. It might be more reasonable to assume values after transfusion would have been worse, had transfusion not been given. However, since more transfusions were given in the control arm, this analysis is expected to be conservative for the treatment comparison and hence accepted.

The Full Analysis Set (FAS) was the data set used for analysis of all efficacy endpoints in the randomised treatment period. The FAS included all randomised subjects.

For each of the two primary endpoints, the test of hypothesis was initially implemented by fitting a conditional logistic regression model. However, these analysis models did not converge due to zero responders in the anti-C5 arm. As per-protocol cases of non-convergence due to sparsity of events were handled by fitting a logistic regression model with a penalised likelihood (Firth) approach. This is considered acceptable.

Several sensitivity and supplementary analyses for the primary endpoints were planned and performed with similar or identical results as the primary analysis.

To adjust for multiplicity of the simultaneous test of two primary endpoints, a weighted permutation test with equal weights to each of the two endpoints was applied. For secondary endpoints a graphical procedure following principles described in Bretz *et al* (Bretz *et al*, 2009, Bretz *et al*, 2011) was used.

Efficacy data and additional analyses

Pivotal phase 3 study: APPLY-PNH, results of the 24-week randomised study period

Iptacopan monotherapy 200 mg bid was statistically significantly superior to anti-C5, with an estimated treatment difference (95% CI) in the primary endpoint of:

1. 80.3 (80.2)[1]% (71.3 (71.2)[1], 87.6) for Hb increase ≥ 2 g/dL from baseline in the absence of transfusion (unadjusted two-sided p-value <0.0001),
2. 67.0% (56.3 (56.4)[1], 76.9) for Hb ≥12 g/dL in the absence of transfusion (unadjusted two-sided p-value <0.0001).

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

Hence, iptacopan monotherapy resulted in clinically meaningful increases in Hb, with 68.8% of patients achieving Hb levels >12g/dl, corresponding to near normalisation at week 24.

The treatment benefit of iptacopan monotherapy over anti-C5 therapy was consistent across all subgroups, including age, sex, baseline haemoglobin, previous anti-C5 treatment (eculizumab or ravulizumab), the need for transfusion in the last 6 months, number of transfusions in the last 6 months, LDH level at baseline, and duration of previous anti-C5 treatment and history of MAVE.

Treatment benefit was confirmed by the results in secondary endpoints with statistically significant differences vs anti-C5 therapy as regards transfusion avoidance (estimated treatment difference of 70.3% (68.9%)[1], unadjusted two-sided p<0.0001; 60 (59)[1] of 62 patients in the iptacopan group and 14 of 35 patients in the anti-C5 group did not require RBC transfusions between day 14 and day 168. During the six months prior to randomisation 57.7% of patients had received RBC transfusions. This went along with an increase in Hb levels from baseline, with a treatment difference in adjusted mean change from baseline in Hb of +3.63 (3.66)[1] g/dL (unadjusted two-sided p<0.0001). The effect size on Hb change from BL was of the same order of magnitude as the effect seen with pegcetacoplan (Hillmen *et al.* 2021).

ARC was reduced with iptacopan to a clinically meaningfully greater extent as compared to anti-C5 therapy, with a treatment difference in adjusted mean change from baseline of - 116.26 (-116.15)[1]$\times 10^9$/L (unadjusted two-sided p<0.0001). The majority of patients presented with reticulocytosis at baseline as a result of anaemia due to C3-mediated EVH and compensatory erythropoiesis. Iptacopan countered EVH.

Baseline mean (SD) LDH, a marker for IVH, was 269.1 (70.14) U/L in the iptacopan arm and 272.7 (84.8) U/L in the anti-C5 arm. The ULN for LDH is 250 U/L (central laboratory). As expected in anti-C5 pre-treated patients, at baseline very few (7.2%) patients had significant residual IVH (LDH > 1.5×ULN). The adjusted reduction in LDH in the iptacopan arm, relative to anti-C5 was 1.15 (1.14)[1]% (95% CI -10.18 (-10.19)[1], 11.32 (11.31)[1]), unadjusted two-sided p=0.8345 (0.8361)[1]. The results were not statistically significant. The ratio to baseline in log-transformed LDH was 0.96 (95% CI 0.90, 1.03) in the iptacopan arm vs. 0.98 (95% CI 0.89, 1.07) in the anti-C5 arm, corresponding to respective reductions from baseline of 4% and 2%. The proportion of patients with LDH levels ≤1.5×ULN was very high and similar at baseline (93.5% in the iptacopan group; 91.4% in the anti-C5 group), and at Day 168 (iptacopan group: 93.5%; anti-C5 group: 85.7%).

Fatigue is one of the most debilitating symptoms reported by PNH patients (Hill *et al.* 2007). Patient-reported fatigue improved with iptacopan, with a treatment difference in adjusted mean change from baseline in FACIT-F score of 8.29 points (unadjusted two-sided p<0.0001). The latter was greater than the protocol pre-specified 5-point change. Although the patients' awareness of treatment group assignment may have influenced score ratings in favour of iptacopan, the order of magnitude of the score difference in the FACIT-fatigue score suggests a true beneficial effect on fatigue. This is physiologically plausible as this went along with significant Hb increases. Patient interviews concerned the relevance of the concepts measured by the FACIT-fatigue score, advantages and disadvantages of study treatment and changes in PNH disease experience. Patients found that the concepts captured by the FACIT-fatigue score adequately reflected their disease experience. Further, treatment with iptacopan was perceived as advantageous. Thereby, the patient interviews supported a positive patient reported outcome associated with iptacopan.

Impact of prior anti-C5 therapy on study results

In the light of the long half-lives of prior anti-C5 therapy (for eculizumab 11 days, SmPC Soliris; for ravulizumab 33.5 days with a sub-therapeutic dose of 800 mg, EPAR Ultomiris), a potential carry-over of prior anti-C5 therapy had been issued as MO. Simulations taking into account the half-lives and the

minimally pharmacodynamic active plasma concentrations of anti-C5 therapy showed carry-over of anti-C5 into the APPLY-PNH randomised study period. However, the clinical relevance of this finding is limited. Among others, this is due to the inferior effect size of anti-C5 therapy as regards Hb improvement as shown in the APPLY-PNH control group (eculizumab or ravulizumab), where there was no improvement, but merely stabilisation of Hb.

Likewise, additional data weakened the notion that there was clinically relevant dual complement inhibition during the randomised study period of APPLY-PNH:

- analyses displaying changes from baseline in haemoglobin, LDH, ARC, and haptoglobin by treatment group split by type of anti-C5 treatment (eculizumab, ravulizumab). No separation of the effect between iptacopan-treated patients pre-treated with eculizumab versus iptacopan-treated patients pre-treated with ravulizumab became discernible for haemoglobin, LDH, ARC, and haptoglobin. This is supportive of no relevant initial carry-over, which would have caused greater and more durable effects in the ravulizumab treated patients due to its longer half-life.
- 48-week results of APPLY-PNH showed that the efficacy in the iptacopan group is durable with stable mean haemoglobin values up to Day 336 of the study, supporting the notion that the efficacy of iptacopan in the randomised controlled period of APPLY-PNH is mainly the result of iptacopan, and not of dual complement inhibition.
- the graphical depiction of time to BTH events showed that BTH events occurred throughout the 48 week study duration, which is inconsistent with a potential carry-over (which would have prevented events through dual inhibition at earlier time points in the study). In addition, none of the 40 complement-inhibitor naïve patients in APPOINT-PNH experienced a breakthrough haemolysis event in the core treatment period (initial 24 weeks) and two of 40 (5.0%) patients experienced a breakthrough haemolysis in the extension period (second 24 weeks).

Supportive phase 3 study in treatment naïve patients: APPOINT-PNH

In complement inhibitor naïve patients, Iptacopan resulted in a 92.2% (95% CI: 82.5%, 100.0%) marginal proportion of patients achieving clinically meaningful Hb increases of 2 g/dL or more in the absence of transfusions. The lower bound of the two-sided 95% confidence interval was 82.5%, which was clearly above the study protocol pre-specified threshold of 15%.

Subgroup analyses of the primary endpoint showed consistent results irrespective of transfusion history in the six months prior to starting study treatment, baseline haemoglobin value and country (China/other).

Results of secondary endpoints supported the anti-haemolytic benefit: mean Hb at baseline was 8.16 (1.09) g/dL. The adjusted mean change from baseline in Hb as mean of visits between Day 126 and Day 168 was +4.28 g/dL (95% CI: 3.87, 4.70). In order to factor out the effect of transfusions in this analysis, if a patient had a transfusion during the core treatment period, the Hb values during the 30 days following the transfusion were excluded and Hb data were imputed.

In patients treated with iptacopan, the increases in Hb levels were seen early in the core treatment period with an adjusted mean change from baseline in Hb (95% CI) of 0.74 g/dL (0.31, 1.17) at day 7. A further increase in Hb was observed at Day 14 with an adjusted mean change from baseline in Hb (95% CI) of 1.51 g/dL (1.06, 1.96). At each visit from Day 28 on up to Day 168, the adjusted mean change from baseline in Hb level was > 2 g/dL; Hb continued to increase up to Day 140 and was sustained until Day 168.

Baseline mean LDH was 1698.8 (683.33) U/L and the median (range) LDH was 1581.5 U/L (522 – 3244 U/L). The ULN for LDH is 250 U/L. Treatment with iptacopan resulted in an adjusted mean percent change from baseline in LDH levels as mean of visits 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) at Day 7 and greater than -83% (- 84.55, - 86.37) at any visit after day 7 in the core treatment period. At day 168 of the core treatment period, mean LDH was 261.3 U/L, which was close to the ULN of 250 U/L.

Baseline mean (SD) absolute reticulocyte count was 154.33 (63.666) x 10^9/L. The ULN for absolute reticulocyte count is 123 x 10^9/L (central laboratory).

The adjusted mean (95% CI) change from baseline in absolute reticulocyte count as mean of visits between Day 126 and Day 168 was -82.48 x 10^9/L (-89.33, -75.62). In patients treated with iptacopan, decreases in absolute reticulocytes 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 x 10^9/L (-93.16, -78.35). There was further decrease in absolute reticulocytes count on Day 14 with an adjusted mean change from baseline of -91.23 x 10^9/L (-96.94, -85.53). The maximum effect was at Day 28 with an adjusted mean (95% CI) change from baseline of – 93.04 x 10^9/L (-100.43, -85.65). At each visit from Day 42 onwards up to Day 168, the adjusted mean change from baseline in absolute reticulocytes count ranged between -78.99 x 10^9/L and < - 87.46 x 10^9/L.

Interestingly, C3 fragment disposition on PNH RBCs were negligible during the core treatment period; absence of anti-C5 treatment seemed to prevent "iatrogenic opsonisation".

The mean (SD) FACIT-F score at baseline was 32.78 points (10.170). The adjusted mean (95% CI) FACIT-Fatigue score change from baseline between Day 126 and Day 168 was +10.75 points (8.66, 12.84). At Day 168 the mean (SD) FACIT-F 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 onwards up to Day 168, the adjusted mean change from baseline in FACIT-Fatigue score was ≥ 9.91 points.

Overall, the APPOINT study added information in patients who were not pre-treated with anti-C5 therapy. Effect sizes are considered large and clinically relevant. These patients had pronounced IVH at baseline, as reflected by baseline LDH of 1699 U/L, and somewhat less pronounced EVH at baseline compared to the APPLY study (192,3 x10^9/L versus 154,33x10^9/L). Increased IVH was expectable in treatment naïve patients. Somewhat more pronounced EVH at baseline may have been due to more opsonisation of RBCs with C3 fragments by anti-C5 therapy.

Limitations of APPOINT-PNH as regards the representativeness of the mainly Asian target population for the EU context has been issued as an MO. This was solved as patients from Asia also suffered from "classical PNH" albeit a larger percentage had AA at baseline, the influence of concomitantly applied immunosuppressive agents appeared to be limited, and subgroup analyses did not show distinct anti-haemolytic efficacy in European vs Asian patients.

The study results showed that treatment naïve patients with PNH can be effectively treated with iptacopan monotherapy. APPOINT-PNH supports an unrestricted monotherapy indication.

Sustainability of action (APPLY and APPOINT)

PNH requires life-long therapy. Results from the extension periods of APPLY-PNH and APPOINT-PNH showed durability of response:

-APPLY_PNH: of the 96 patients who completed the 24-week randomised treatment period, 95 entered the 24-week extension period. At Week 48, patients in both groups achieved similar mean haemoglobin. In patients randomised to iptacopan (who continued to receive iptacopan in the extension period), mean (SD) haemoglobin was 8.93 (0.70) g/dL at baseline, 12.61 (1.43) g/dL at Day

168 (24 weeks) and 12.19 (1.57) g/dL at Day 336 (48 weeks). In patients randomised to anti-C5 who switched to iptacopan 200 mg b.i.d. in the extension period, mean (SD) haemoglobin was 8.85 (0.90) g/dL at baseline, 9.15 (1.41) g/dL at Day 168 (24 weeks) (last assessment before switch) and 12.12 (1.41) g/dL at Day 336 (48 weeks).

-APPOINT-PNH: all 40 patients who were enrolled completed the 24-week core treatment period and completed the 24-week extension period. The increase in mean haemoglobin achieved in the core treatment period (up to Day 168; 24 weeks) was maintained throughout the extension period (i.e., to Day 336; 48 weeks). At baseline, patients had a mean (SD) haemoglobin level of 8.16 (1.087) g/dL, 12.56 (1.486) g/dL at Day 168 and 13.24 g/dL (1.798) at Day 336, resulting in a mean increase from baseline of 5.09 (2.010) g/dL.

2.6.7. Conclusions on the clinical efficacy

The APPLY results demonstrated superiority of iptacopan monotherapy over anti-C5 therapy across a broad spectrum of clinically relevant endpoints in haemolytic PNH over the 24-week RTP in terms of clinically meaningful increases in haemoglobin levels, significant reduction of the need for RBC transfusions and meaningful improvements of patient-reported fatigue. These treatment benefits of iptacopan were achieved by maintaining IVH control and inhibiting EVH. Results of the uncontrolled APPOINT study support iptacopan use in treatment naïve patients. Overall, APPLY-PNH and APPOINT-PNH demonstrated that Iptacopan as monotherapy is efficacious in patients with haemolytic anaemia in both pre-treated and untreated patients.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

A total of 223 patients (170 patients with PNH and 53 patients from studies in renal indications) received at least one dose of 200 mg b.i.d., comprising the Safety set. In APPLY-PNH RTP, the median duration of exposure to study treatment was the same for both the treatment groups; 5.6 months (range: 4.6 to 5.6) for the iptacopan group and 5.6 months (range: 5.5 to 6.2) for the anti-C5 treatment group. Similarly, the median duration of exposure to iptacopan 200 mg b.i.d. in the APPOINT-PNH core treatment period was 5.55 months (range: 5.5 to 5.8) or 169.0 days (165 to 175); see table below.

Table 60: Duration of exposure to study treatment, pooled PNH studies and pooled renal studies (200 mg b.i.d. Safety set)

	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

2.6.8.2. Adverse events

The following table provides an overview of AE frequency (i.e. number and percentage of patients suffering at least one AE) in various data sets, the controlled period of the APPLY study, the uncontrolled APPOINT study, pooled PNH studies (uncontrolled data) and pooled renal studies (uncontrolled data). In the controlled study period, the percentage of patients suffering at least any AE was similar between iptacopan and comparator anti-C5. The percentage of patients suffering SAEs was numerically higher with anti-C5, but the absolute number was low.

Table 61: Overview of TEAEs in APPLY-PNH RTP, APPOINT-PNH core treatment period, pooled PNH studies and pooled renal studies (Controlled study and 200 mg b.i.d. Safety Set)

	APPLY-PNH RTP		**APPOINT-PNH core treatment**	**Pooled PNH studies**	**Pooled renal studies**
Adverse events	**LNP023 200mg b.i.d. N=62 n (%)**	**Anti-C5 N=35 n (%)**	**LNP023 200mg b.i.d. N=40 n (%)**	**LNP023 200mg b.i.d. N=170 n (%)**	**LNP023 200mg b.i.d. N=53 n (%)**
Any TEAE	**51 (82.3)**	**28 (80.0)**	**37 (92.5)**	**144 (84.7)**	**38 (71.7)**
AEs leading to discontinuation of study treatment	0	0	0	1 (0.6)	1 (1.9)
AEs leading to study treatment interruption	0	0	0	2 (1.2)	5 (9.4)
SAEs	6 (9.7)	5 (14.3)	4 (10.0)	29 (17.1)	6 (11.3)
Deaths resulting from TEAEs*	0	0	0	2 (1.2)	1 (1.9)

n: number of patients with at least one event
* One additional death was reported; it was not a TEAE. One patient in the pooled PNH studies died due to general physical health deterioration on Day 867 after last dose of iptacopan on Day 779

The AEs are listed according to Preferred Terms (PTs) in the table below, observed in the randomised period of the APPLY-study (Study C12302) and in the pooled uncontrolled extension period of the PNH studies. In the controlled randomised period, salient numerical differences between iptacopan and anti-C5 therapy, disfavouring iptacopan, were observed for headache, diarrhoea and nausea. For less frequently occurring PTs, it is less clear whether the observed numerical difference is true, but some of them may be related to nausea and diarrhoea such as abdominal pain and upper abdominal pain. Similarly, dizziness and insomnia, together with headache, may indicate that iptacopan somehow affects the CNS. Notably, the system organ class (SOC) "nervous system disorders" was markedly more frequent in the iptacopan vs. the anti-C5 group (25.8% vs. 2.9%, see respective table further below).

Other noteworthy findings were a slightly higher percentage of LDH increase in the anti-C5 group and a higher percentage of patients having reported hypertension. Although the number of patients was low, which precludes firm conclusions, the laboratory finding of increased diastolic blood pressure (see respective section below) is in line with this observation.

Breakthrough haemolysis (BTH), an important undesired effect of PNH therapy, occurred much more frequently in the anti-C5 than in the iptacopan group during the controlled study period. In the uncontrolled period, the percentage of patients suffering BTH slightly increased under iptacopan therapy but remained far lower than observed with anti-C5.

Table 62: Treatment emergent adverse events, by preferred terms - PNH studies (Controlled study and 200 mg b.i.d. Safety Set)

	C12302			Pooled PNH studies	
Preferred terms	LNP023 200mg b.i.d. N=62 n (%)	Total exp=28.6 PY m (OccR) 95% CI	Anti-C5 N=35 n (%)	LNP023 200mg b.i.d. N=170 n (%)	Total exp=185.5 PY m (OccR) 95% CI
Number of subjects with at least one event	51 (82.3)	270 (944.7) (602.8, 1480.6)	28 (80.0)	144 (84.7)	850 (458.2) (369.4, 568.3)
Headache	10 (16.1)	17 (59.5) (28.4, 124.4)	1 (2.9)	29 (17.1)	41 (22.1) (14.6, 33.5)
Diarrhoea	9 (14.5)	10 (35.0) (18.5, 66.1)	2 (5.7)	19 (11.2)	24 (12.9) (8.2, 20.5)
Nasopharyngitis	7 (11.3)	7 (24.5) (12.1, 49.5)	2 (5.7)	15 (8.8)	15 (8.1) (5.0, 13.1)
Nausea	6 (9.7)	8 (28.0) (12.4, 63.4)	1 (2.9)	12 (7.1)	14 (7.5) (4.2, 13.5)
COVID-19	5 (8.1)	5 (17.5) (7.5, 40.8)	9 (25.7)	40 (23.5)	42 (22.6) (16.8, 30.6)
Arthralgia	5 (8.1)	7 (24.5) (9.1, 65.7)	1 (2.9)	10 (5.9)	14 (7.5) (3.7, 15.6)
Urinary tract infection	5 (8.1)	5 (17.5) (7.5, 40.8)	1 (2.9)	7 (4.1)	7 (3.8) (1.8, 7.8)
Abdominal pain	4 (6.5)	5 (17.5) (6.3, 48.3)	1 (2.9)	10 (5.9)	11 (5.9) (3.1, 11.2)
Blood lactate dehydrogenase increased	4 (6.5)	4 (14.0) (5.4, 36.4)	3 (8.6)	6 (3.5)	7 (3.8) (1.6, 8.7)
Dizziness	4 (6.5)	5 (17.5) (6.3, 48.3)	0	6 (3.5)	7 (3.8) (1.7, 8.6)
Thrombocytopenia	3 (4.8)	4 (14.0) (4.3, 45.7)	0	9 (5.3)	10 (5.4) (2.8, 10.4)
Hypertension	3 (4.8)	3 (10.5) (3.4, 31.9)	0	8 (4.7)	8 (4.3) (2.2, 8.6)
Insomnia	3 (4.8)	3 (10.5) (3.4, 31.9)	0	8 (4.7)	9 (4.9) (2.4, 9.8)
Back pain	3 (4.8)	3 (10.5) (3.4, 31.9)	2 (5.7)	6 (3.5)	6 (3.2) (1.5, 7.0)
Abdominal pain upper	3 (4.8)	4 (14.0) (4.3, 45.7)	0	5 (2.9)	7 (3.8) (1.5, 9.4)
Alanine aminotransferase increased	3 (4.8)	3 (10.5) (3.4, 31.9)	1 (2.9)	4 (2.4)	4 (2.2) (0.8, 5.7)
Oedema peripheral	3 (4.8)	3 (10.5) (3.4, 31.9)	1 (2.9)	4 (2.4)	4 (2.2) (0.8, 5.6)
Toothache	3 (4.8)	3 (10.5) (3.4, 31.9)	0	4 (2.4)	4 (2.2) (0.8, 5.7)
Bronchitis	3 (4.8)	3 (10.5) (3.4, 31.9)	0	3 (1.8)	4 (2.2) (0.7, 7.1)
Pyrexia	2 (3.2)	3 (10.5) (2.5, 44.8)	3 (8.6)	11 (6.5)	15 (8.1) (4.4, 14.8)
Vomiting	2 (3.2)	2 (7.0) (1.8, 27.7)	1 (2.9)	10 (5.9)	10 (5.4) (2.9, 9.9)
Breakthrough haemolysis	2 (3.2)	2 (7.0) (1.8, 27.7)	6 (17.1)	8 (4.7)	11 (5.9) (2.9, 12.3)
Upper respiratory tract infection	2 (3.2)	3 (10.5) (2.5, 44.8)	3 (8.6)	8 (4.7)	13 (7.0) (3.4, 14.4)

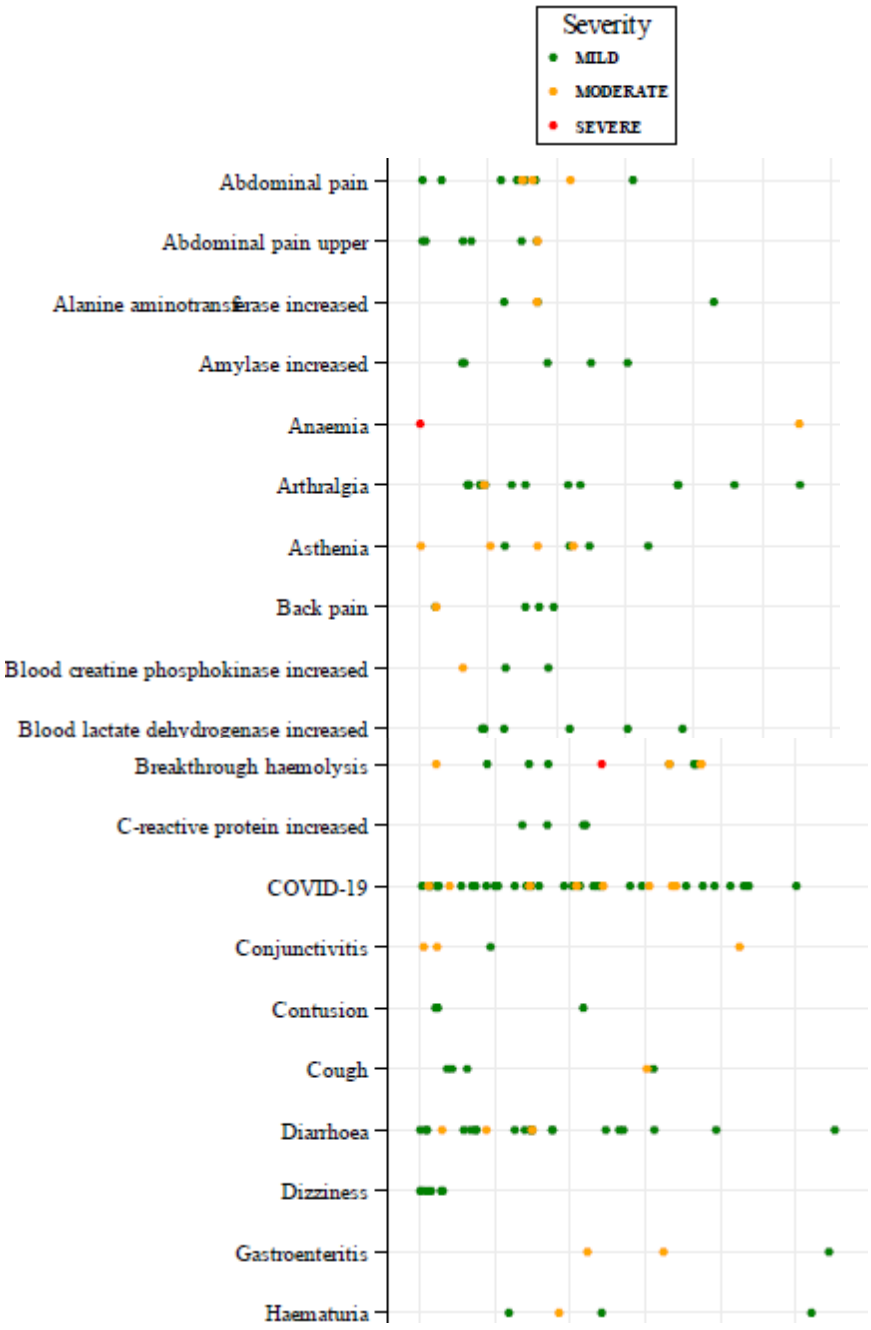
When regarding AEs by system organ class (SOC), see following table, the most prominent difference between iptacopan and anti-C5, disfavouring iptacopan, was observed for nervous system disorders.

Table 63: Treatment emergent adverse events, by system organ class - PNH studies (Controlled study and 200 mg b.i.d. Safety Set)

	C12302			Pooled PNH studies	
System organ class	LNP023 200mg b.i.d. N=62 n (%)	Total exp=28.6 PY m (OccR) 95% CI	Anti-C5 N=35 n (%)	LNP023 200mg b.i.d. N=170 n (%)	Total exp=185.5 PY m (OccR) 95% CI
Number of subjects with at least one event	51 (82.3)	270 (944.7) (602.8,	28 (80.0)	144 (84.7)	850 (458.2) (369.4,
		1480.6)			568.3)
Infections and infestations	24 (38.7)	38 (133.0) (91.8, 192.5)	17 (48.6)	86 (50.6)	157 (84.6) (69.5, 103.0)
Gastrointestinal disorders	20 (32.3)	42 (147.0) (93.7, 230.4)	7 (20.0)	57 (33.5)	105 (56.6) (42.1, 76.0)
Nervous system disorders	16 (25.8)	35 (122.5) (71.0, 211.2)	1 (2.9)	42 (24.7)	72 (38.8) (27.6, 54.6)
Investigations	13 (21.0)	33 (115.5) (38.9, 342.3)	5 (14.3)	36 (21.2)	84 (45.3) (26.1, 78.4)
Musculoskeletal and connective tissue disorders	11 (17.7)	18 (63.0) (29.3, 135.6)	5 (14.3)	33 (19.4)	50 (27.0) (17.4, 41.6)
General disorders and administration site conditions	9 (14.5)	26 (91.0) (25.0, 331.2)	4 (11.4)	37 (21.8)	67 (36.1) (20.3, 64.4)

Whereas headache was a prominent AE in the iptacopan group of the PNH study, headache was much less frequent in the iptacopan than in the placebo group in the population of patients with renal disease. Otherwise, the renal studies provide very limited safety information due to the low number of patients and events.

Overall, most AEs were mild in severity. There were a few serious events. One case of anaemia shortly after treatment initiation which presumably was related to the underlying disease; one case of breakthrough haemolysis after around 30 weeks; one case of decreased platelet count after around 60 days of treatment which also could be related to the underlying disease; one case of pneumonia and one case of urinary tract infection. Time of occurrence and severity of AEs with iptacopan is graphically shown in the following figure. No comparator data are included in the figure.


Severity
MILD
MODERATE
SEVERE
Abdominal pain
Abdominal pain upper
Alanine aminotransferase increased
Amylase increased
Anaemia
Arthralgia
Asthenia
Back pain
Blood creatine phosphokinase increased
Blood lactate dehydrogenase increased
Breakthrough haemolysis
C-reactive protein increased
COVID-19
Conjunctivitis
Contusion
Cough
Diarrhoea
Dizziness
Gastroenteritis
Haematuria

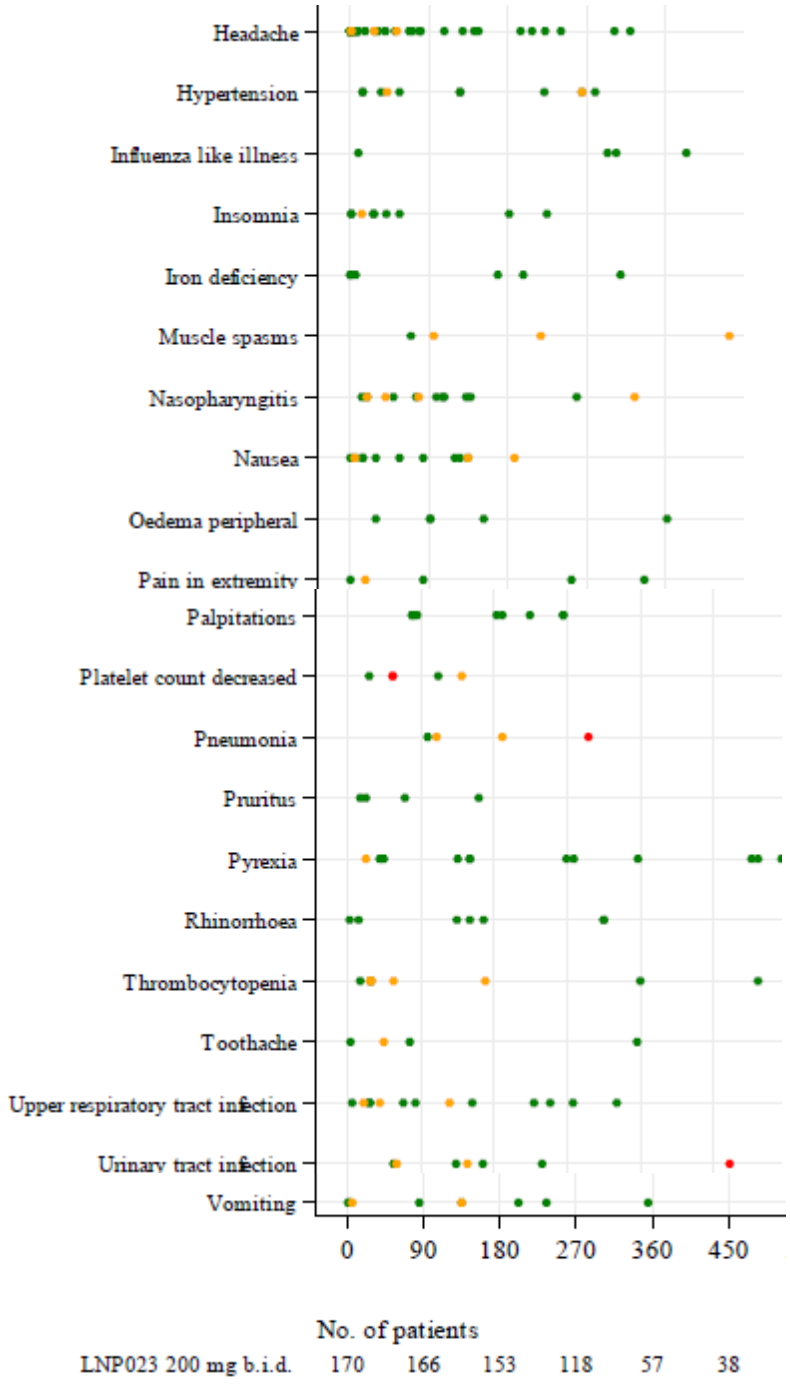


Figure 68: Most frequent (>=2%) treatment emergent adverse events by PT dot plot by severity - PNH pooled studies (200 mg b.i.d. Safety Set), x-axis: Start Day.

Note: The figure is truncated at Day 450 because thereafter the number of patients becomes very low which precludes meaningful conclusions.

Although the information provided by the above figure is limited by the lack of comparator data, the safety profile of iptacopan overall appears acceptable even when assuming the worst case that all AEs were due to iptacopan. Reassuringly, nearly all events were mild or moderate in severity. However, it has to be taken into consideration that AE reports from the extension periods of the iptacopan studies can be biased. Since the patients could decide whether entering the extension period or not, it can be

assumed that patients poorly tolerating iptacopan were not willing to enter the extension period and thereby did not contribute to the safety profile beyond the controlled phase.

Aes of special interest (AESIs)

Adverse events of special interest (AESIs) were identified by the applicant based on the mechanism of action of iptacopan, class effects associated with complement inhibition and available non-clinical and clinical data. AESI were identified by pre-defined MedDRA grouping.

The following table provides an overview of the AESI findings. Except for the topics haemolysis/thrombosis and decreased platelets, the percentage of patients suffering an AESI was low. For haemolysis/thrombosis, the incidence during the controlled study period was higher in the comparator (anti-C5) group. Decreased platelets were only observed in the iptacopan group (controlled and uncontrolled period).

Table 64: AESIs in APPLY-PNH RTP, pooled PNH studies, and pooled renal studies (Controlled study and 200 mg b.i.d. Safety Set) and APPOINTPNH core treatment period (Safety Analysis Set)

	APPLY-PNH RTP		APPOINT-PNH core	Pooled PNH studies	Pooled renal studies
AESI	**LNP023 200mg b.i.d. N=62 n (%)**	**Anti-C5 N=35 n (%)**	**LNP023 200mg b.i.d. N=40 n (%)**	**LNP023 200mg b.i.d. N=170 n (%)**	**LNP023 200mg b.i.d. N=53 n (%)**
Infections caused by encapsulated bacteria	1 (1.6)	0	1 (2.5)	7 (4.1)	2 (3.8)
Haemolysis and thrombosis*	10 (16.1)	10 (28.6)	1 (2.5)	19 (11.2)	NA
Decreased platelets	4 (6.5)	0	0	13 (7.6)	0
Testicular effects**	0	0	1 (2.5)	1 (0.6)	0
Thyroid changes	1 (1.6)	0	1 (2.5)	2 (1.2)	0

* The topic of haemolysis and thrombosis are specific to PNH patients and were not examined for the pooled renal studies.
** The topic of testicular effects is specific to male patients
n: number of patients with at least one event
NA: not applicable for renal indications

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Across the pooled PNH and pooled renal studies up to the respective cut-off dates, there were four patients who died. There were no deaths in the APPLY-PNH RTP or the APPOINT-PNH core treatment period. Three patients in the PNH pool and one patient in the renal pool died. All four patients had medical histories and/or confounding factors for the event leading to death.

Three patients in the PNH pool died, all from Cohort 1 in study X2201, representing 3/16 subjects in this study. Overall, there was a longer duration of exposure for patients in X2201 compared to APPLY-PNH RTP. In comparison to the APPLY-study, all patients received eculizumab not only prior to, but also during iptacopan treatment.

SAEs

Across the PNH studies, 29/170 (17.1%) patients had SAEs. In the APPLY-PNH RTP, SAEs were less frequent in the iptacopan treatment group (6/62, 9.7%) vs. the anti-C5 group (5/35, 14.3%), see table below. SAEs in the APPOINT-PNH core treatment period were reported with similar frequency (4/40, 10%) as in the iptacopan group of the APPLY-PNH RTP. In the renal studies, 6/53 (11.3%) patients had an SAE.

Table 65: SAEs by SOC and PT in APPLY-PNH RTP and pooled PNH studies (Controlled study and 200 mg b.i.d. Safety Set)

	APPLY-PNH RTP		Pooled PNH studies
Primary system organ class Preferred term	**LNP023 200mg b.i.d. N=62 n (%)**	**Anti-C5 N=35 n (%)**	**LNP023 200mg b.i.d. N=170 n (%)**
Any SAE	6 (9.7)	5 (14.3)	29 (17.1)
Infections and infestations	2 (3.2)	3 (8.6)	11 (6.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (3.2)	0	7 (4.1)

The following individual SAEs were suspected to be related to iptacopan by the investigator:

- infectious pneumonia
- platelet count decreased
- blood creatine phosphokinase increased
- lymphoproliferative disorder

Due to the low number of patients and the short duration of the controlled study period, it is difficult to draw firm conclusions on SAEs related to iptacopan treatment, even if the investigator has suspected a relationship. In the uncontrolled extension period, the lack of comparator treatment makes establishing a relationship to iptacopan difficult.

2.6.8.4. Laboratory findings

Haematology/coagulation

The changes were mostly related to the desired effect of iptacopan, i.e. decreasing haemolysis and increasing red blood cell count. In detail, the following changes were observed:

- increase in erythrocyte count, haemoglobin and haematocrit;
- transient increase in haptoglobin;
- decrease in reticulocyte count, most pronounced one month after treatment start.

Clinical chemistry

The following changes were observed:

- increase in total cholesterol and LDL-cholesterol; HDL-cholesterol remained unchanged;
- decrease in LDH, most pronounced one month after start of treatment;
- decrease in bilirubin (total, direct and indirect).

The decrease in bilirubin is most likely related to the desired effect of reducing haemolysis; the same is true for LDH. The increase in cholesterol is most likely independent from haemolysis and could be an off-target effect of iptacopan. The cholesterol changes over time are shown in the figures below.

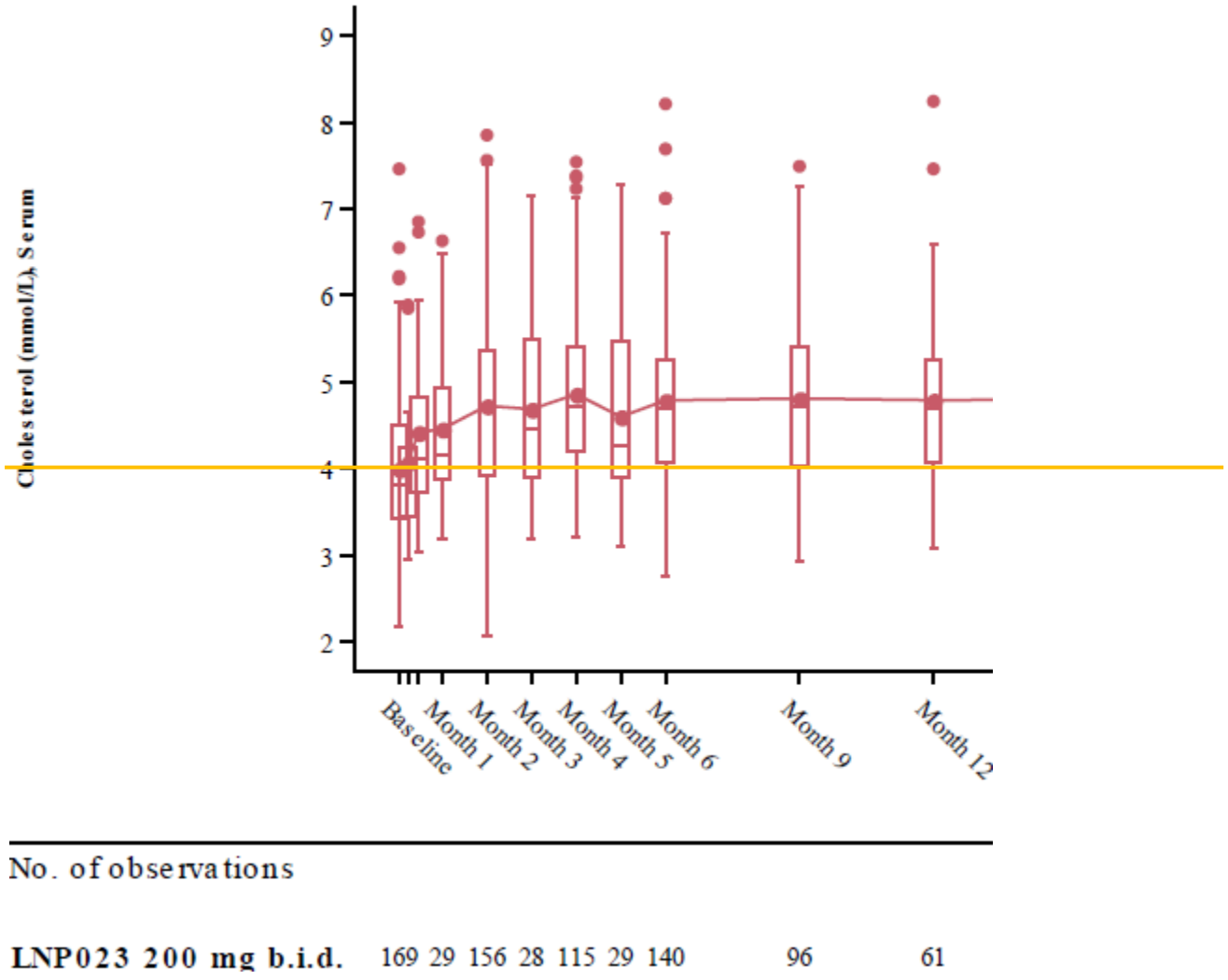


Figure 69: for Total cholesterol changes over time

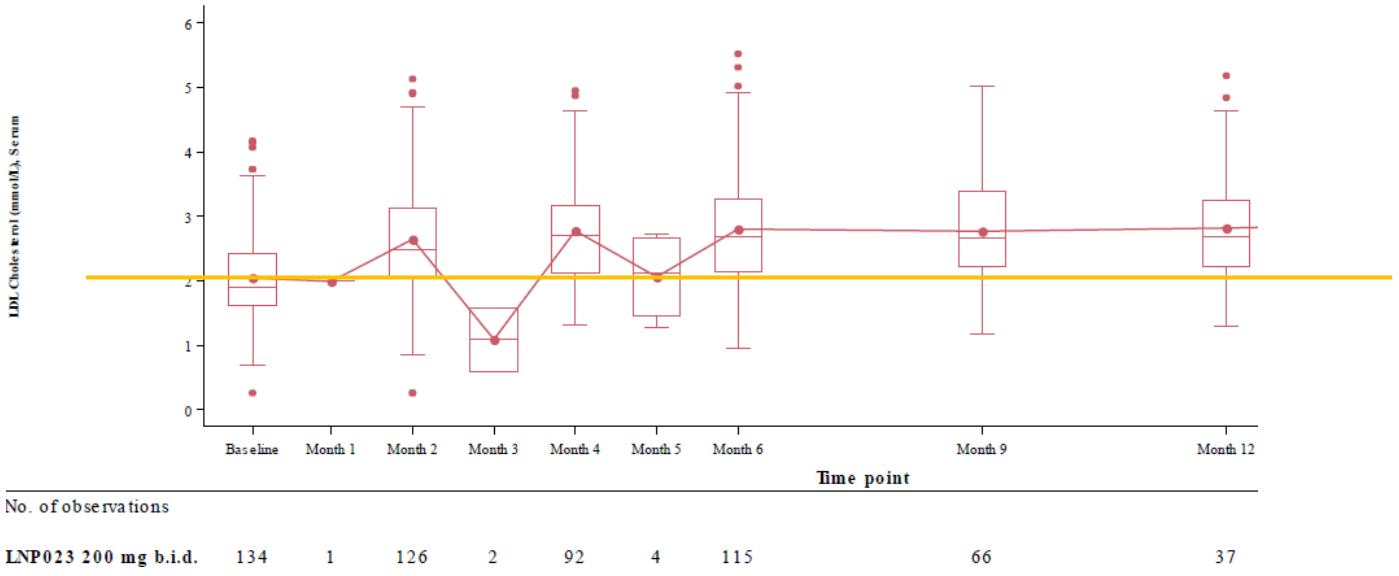
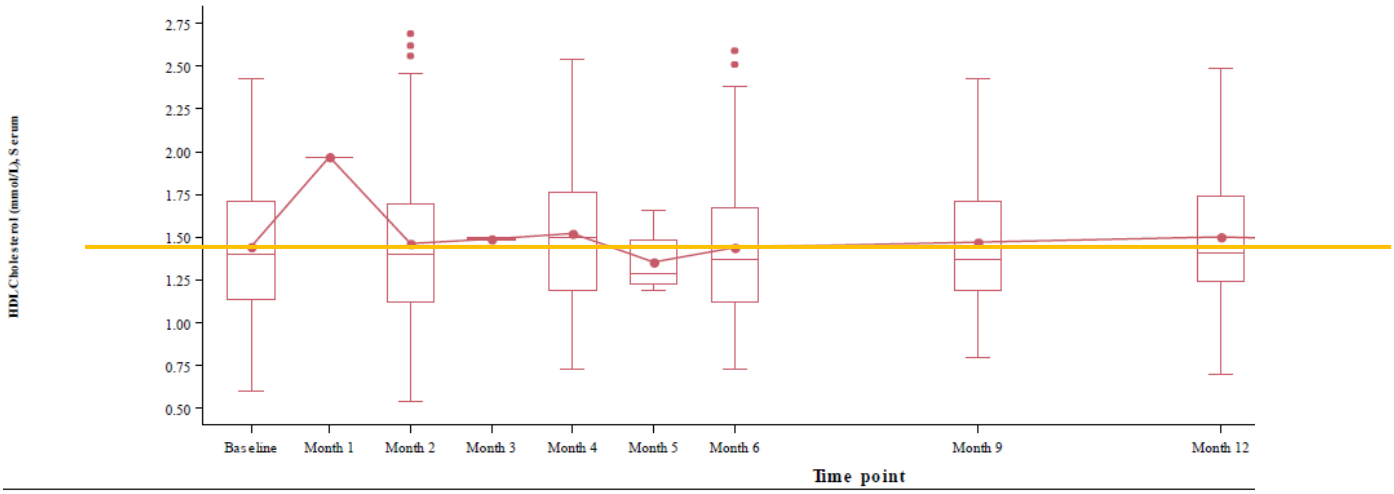


Figure 70: LDL-cholesterol changes over time

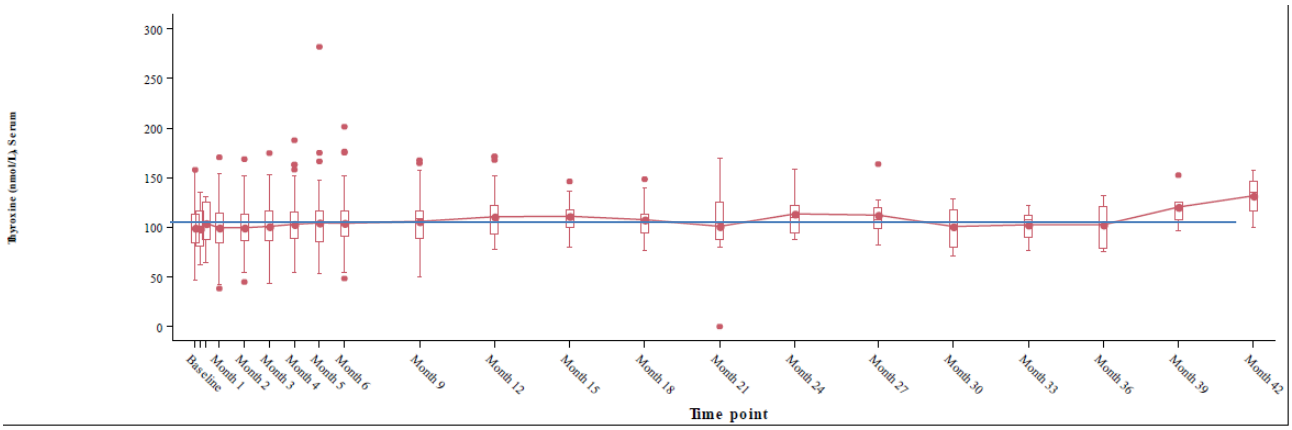


No. of observations									
LNP023 200 mg b.i.d.	135	1	128	2	93	4	116	67	38

Figure 71: HDL-cholesterol changes over time

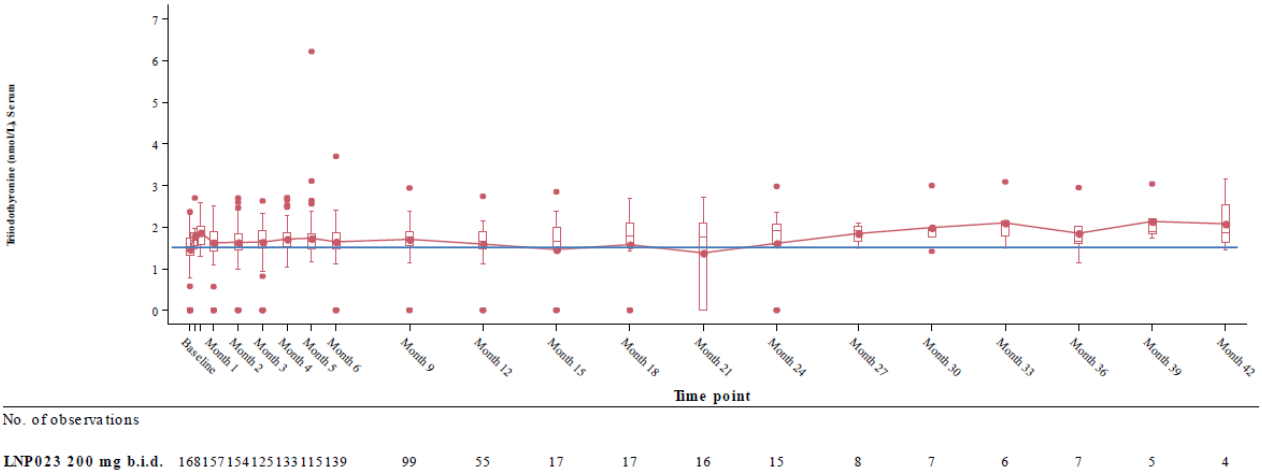
Hormone levels

Because of findings in animals, the applicant determined levels of thyroid and reproductive hormones in the serum of the study participants. A very small and questionable increase in serum T3 and T4 from baseline was observed; see figures below. TSH remained clearly unchanged.



No. of observations																		
LNP023 200 mg b.i.d.	158	152	149	120	133	115	134	95	51	12	13	11	11	8	7	6	7	5	4

(a)



(b)

Figure 72: Levels of T4 (a) and T3 (b) in the serum of the study participants over time

Measurement of serum sexual hormone levels revealed some variability over time, but no meaningful and consistent changes vs. baseline were observed. However, across the PNH and renal pools, one patient had two AEs of abnormal reproductive hormone levels and two patients had thyroid hormone changes (increased thyroid stimulating hormone and triiodothyronine, respectively).

Vital signs

There was an increase in diastolic blood pressure with iptacopan treatment compared to baseline and compared to anti-C5 treatment by around 5 to 10 mmHg. There was also a small decrease in heart rate (HR) compared to baseline, but there was no clear difference when compared to anti-C5 treatment. Iptacopan did not affect heart rate up to systemic concentrations >4-fold the mean C_{max} of the 200 mg b.i.d. dose in healthy volunteers. Nevertheless, in the pooled PNH studies, 21/155 (13.5%) subjects had decreased heart rate from baseline ≥25%.

Only a very small effect, if at all, on systolic blood pressure was observed. No ECG changes were observed; in particular the HR-corrected QT interval (QTcF) was unaffected by iptacopan. The time-course of diastolic blood pressure is shown in the figures below.

Diastolic blood pressure

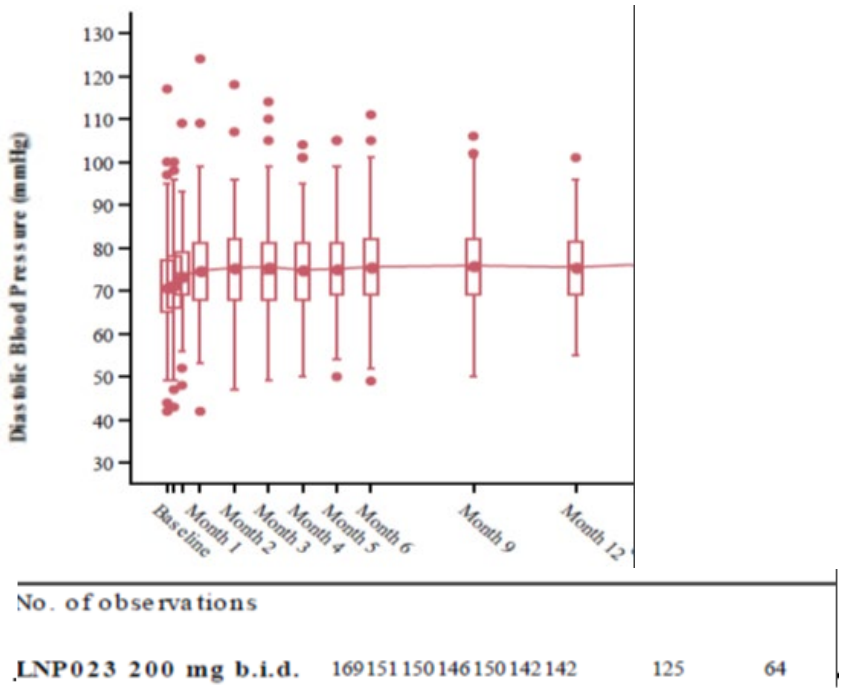


Figure 73: Diastolic blood pressure measurement for the whole data set

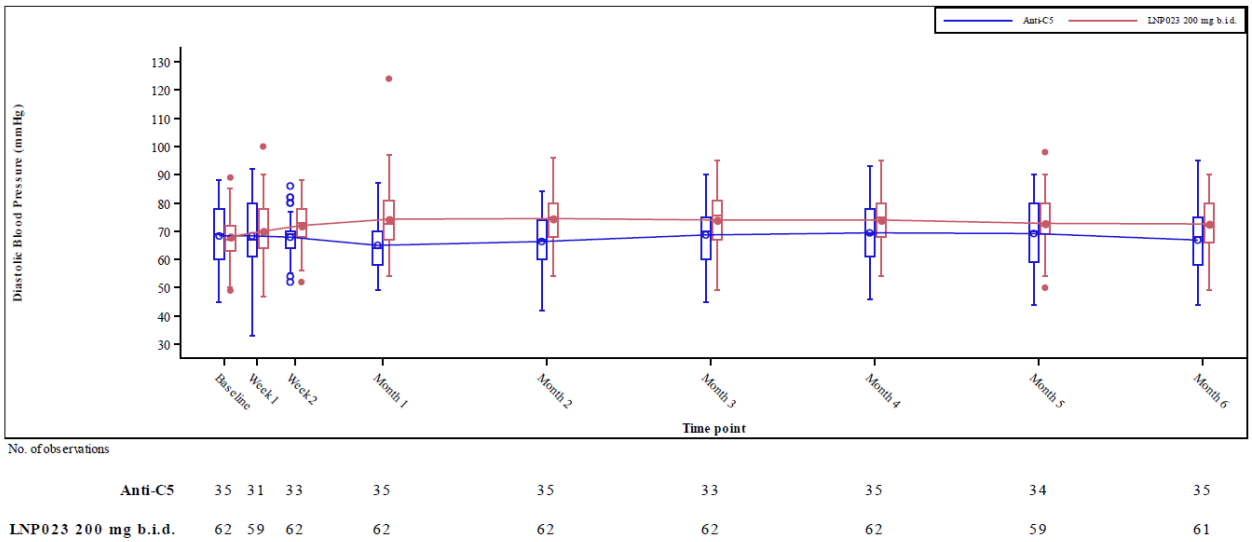


Figure 74: Diastolic blood pressure measurement for the controlled period

In accordance to the increased DBP, a small decrease in HR was observed in the PNH studies but not in the renal studies (see figure below). This indicates that the observed haemodynamic changes were related to correction of anaemia.

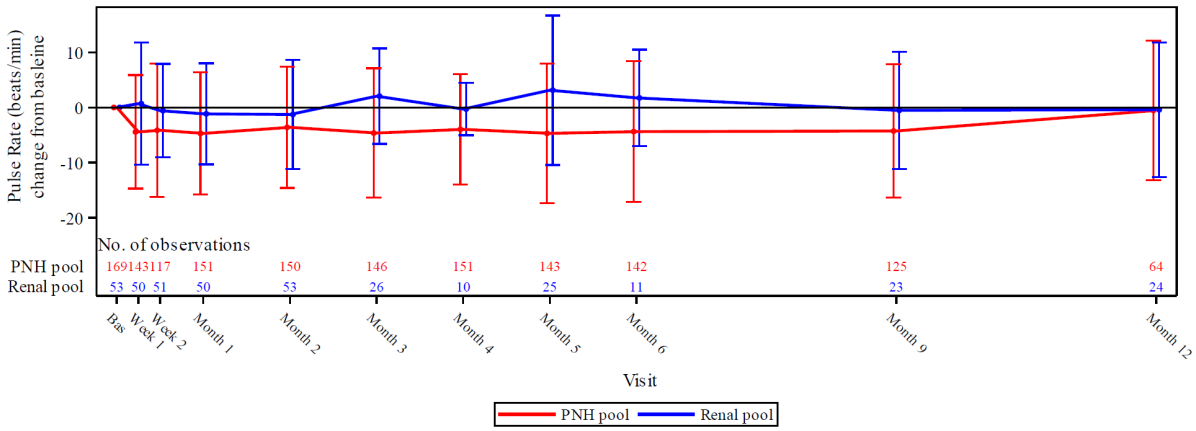


Figure 75: Mean change from baseline in pulse rate over 12 months in patients treated with 200 mg b.i.d. iptacopan in PNH studies (Controlled Study and 200 mg b.i.d. Safety Set) and Renal studies (200 mg b.i.d. Safety Set)

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Due to the low total number of study patients, special populations were not separately evaluated.

2.6.8.7. Immunological events

Since iptacopan is a small molecule, no specific evaluations for immunogenicity were performed.

2.6.8.8. Safety related to drug-drug interactions and other interactions

A major safety aspect of PNH treatment with anti-C5 or anti-C3 agents is the risk of severe breakthrough haemolysis (BTH). It is assumed that BTH risk is markedly reduced with combined anti-C3 and anti-C5 treatment. The rate of severe BTH was unexpectedly low with iptacopan; no severe events occurred in the controlled period of the pivotal study APPLY-PNH, and the incidence was lower than for anti-C5. Also, for another proximal complement inhibitor, pegcetacoplan, events of severe BTH were reported during the pivotal study (Kulasekararaj *et al*. NEJM 2021). With iptacopan only one severe BTH event occurred, around 7 months after start of treatment (as derived from the graphical overview of AEs). However, since the participants of the pivotal study APPLY-PNH switched from anti-C5 treatment to iptacopan without washout (factually there was an overlap), and due to the long half-life of the anti-C5 antibodies (especially ravulizumab, which was not applied in the pegcetacoplan phase 3 study), the concomitant presence of anti-C5 and anti-Factor B activity could have suppressed BTH. Alternatively, any features of iptacopan that distinguish it from pegcetacoplan could be responsible.

2.6.8.9. Discontinuation due to adverse events

No patient in the APPLY-PNH RTP and APPOINT-PNH core treatment period had a TEAE leading to treatment discontinuation. In the pooled PNH studies, one patient had a TEAE leading to discontinuation of study treatment, the AE of lymphoproliferative disorder. This event from Study

X2201 was an SAE suspected to be related to study medication. The applicant provided the following information on this patient: 45-year-old female; the patient had been receiving eculizumab at study entry. Lymphocytes at baseline were 0.22 ×10^9/L (lymphopenia). The patient developed widespread lymphadenopathies and multiple extralymphatic 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 336). 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.

Usually, it is very difficult to demonstrate causality between treatment and occurrence of a common kind of neoplasm in the individual case. It is not known why the investigator suspected that in this patient the lymphoproliferation was related to study drug.

2.6.8.10. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

Safety assessment was mainly based on pooled data from the PNH studies including their uncontrolled extension phases as well as on the active-controlled period of Study APPLY-PNH. The latter included a rather small number of patients (which can be explained by the rarity of the disease) and was rather short so that safety information is limited.

The uncontrolled study periods do not provide information whether a certain type of AE could be related to iptacopan. The observed AEs in general were rather unspecific so that spontaneous occurrence could not be excluded. Thus, one has to assume the worst-case scenario that all observed AEs in the uncontrolled periods were due to iptacopan. It is reassuring that the severity grade of far the most AEs was non-severe. Severe events included anaemia and reduced platelet count (which could be due to the underlying disease) as well as pneumonia, urinary tract infection and breakthrough haemolysis (which could be related to iptacopan based on mechanistic considerations). Breakthrough haemolysis is discussed in more detail below.

In the controlled study period, the most frequent iptacopan-related AEs, being also more frequent than with comparator anti-C5, were headache, diarrhoea and other gastrointestinal events.

Regarding headache, there was a marked discrepancy between renal and NPH studies. In the controlled NPH study (APPLY-NPH), the incidence of headache appeared markedly increased with iptacopan vs. comparator (anti-C5) whereas in the controlled kidney study X2203, incidence of headache was low in the iptacopan group but was rather high in the placebo group. The applicant explained that free haemoglobin in the blood is a scavenger for nitric oxide (NO). Hence, with decreasing haemolysis and free haemoglobin, NO levels increase and can cause cerebral vasodilation. The latter can be associated with headache. This mechanism is only relevant in case of haemolysis but not for kidney disease.

Serious adverse events were fairly balanced between iptacopan and comparator groups in the controlled study period. Overall, i.e. also including the uncontrolled periods, most SAEs were related to infection or neoplasia. Seven patients in the pooled PNH studies reported malignancy events. Confounding factors were identified for some subjects but for others, a causal role to study treatment could not be excluded. In the rat carcinogenicity study, a slightly increased incidence in combined benign and malignant thymomas was noted in females. Notwithstanding, neoplasms are labelled in section 4.8 of the SmPC for the C5-inhibitor Soliris and the potential role of complement inhibition in

malignancy is not fully elucidated. Based on mechanistic plausibility and to harmonise with the recommendations for other complement inhibitors, malignancy was added as an important potential risk.

A causal relationship between iptacopan and infections cannot be excluded based on mechanistic considerations because the complement system, which is inhibited by iptacopan, has a physiological role in defence against pathogens. During the controlled study period, SAEs of infections were numerically less frequent with iptacopan than with the active comparator anti-C5, which likewise inhibits the complement system and thereby could favour infections. This is reassuring; nevertheless, a contribution of iptacopan to infections cannot be excluded but has to be expected from all therapeutics of this kind (i.e. complement inhibitors). Overall, there were seven patients on iptacopan therapy with infections considered likely to be caused by encapsulated bacteria. All patients had been vaccinated as per protocol. Patients were required to have vaccination at least 2 weeks prior to first dosing with iptacopan if locally available. If iptacopan treatment had to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment was required. Absence of vaccination against *S. pneumonia* and *N. Meningitidis* is labelled in SmPC section 4.3, while vaccination against *H. Influenzae* is labelled in section 4.4. The applicant points out that the Haemophilus Influenzae vaccine is currently not broadly available in the EU. Therefore, the proposed wording "It is recommended to vaccinate patients against Haemophilus influenzae type B if available" in section 4.4 of the SmPC is considered acceptable.

Three patients in the PNH pool and one patient in the renal pool died during the study or the study follow-up. All three PNH patients were from Cohort 1 in study X2201, representing 3/16 subjects in this study. The deaths were due to squamous cell carcinoma, sepsis following salvage chemotherapy for lymphoproliferative disorder, and general deterioration of physical health following E. coli sepsis after surgery for aortic ulcer. Overall, there was a longer duration of exposure for patients in X2201 compared to APPLY-PNH RTP. All patients who died had received eculizumab prior and during the study. This raises a concern on the safety aspects of dual complement inhibition. Therefore, it should be stated in the indication that iptacopan is proposed to be used as monotherapy (see also efficacy section).

Based on mechanistic considerations, AEs of breakthrough haemolysis, thrombosis and decrease in all types of blood cells require special attention. Breakthrough haemolysis was observed in the comparator (anti-C5) group and was markedly less frequent in the iptacopan group as desired. However, it has to be considered that in the iptacopan group residual anti-C5 activity still was present (as patients in this group were switched from anti-C5 treatment at study start). Therefore, the low number of breakthrough events may be due to double complement blockade (inhibition at the level of C3 and C5). The applicant argued that residual anti-C5 activity is not the reason for the low BTH rate with iptacopan. The applicant pointed out that the BTH rate was lower than with anti-C5 even in the second 24 weeks of iptacopan treatment, where residual anti-C5 activity is no longer expected, and that the BTH rate was also low in the APPOINT-PNH study, where no pre-treatment with anti-C5 took place. It is agreed, that low BTH rates in study periods during which iptacopan worked as monotherapy argue against protection from BTH through carry-over from anti-C5. The applicant assumed that favourable pharmacological properties of iptacopan such as strong inhibition of the alternative pathway were responsible for the apparently low BTH rate. For further discussion of potential carry-over of anti-C5 activity and the consequences thereof, see efficacy section.

In the pooled extension period, there was one event of severe breakthrough haemolysis. In this case, complement activation most likely was caused by the presence of cold agglutinins. The need for monitoring of signs of haemolysis both during treatment and with treatment disruption is reflected in the SmPC.

Regarding thrombosis and decrease in blood cells, the number of events and affected patients was too low for meaningful conclusions. Reassuringly, laboratory measurements did not reveal meaningful changes over time in the number of white cells, their subtypes and platelets over time.

Information on AEs from the pooled uncontrolled study periods revealed that the safety profile of iptacopan is acceptable, even if assuming that all observed events were due to iptacopan (as a control group is lacking). Most events were mild or moderate in intensity; the severe event of breakthrough haemolysis is discussed above. The serious events often were related to malignancy. It is highly unlikely that the malignancies were caused by iptacopan because the treatment duration was too short for the development of malignancies. Other SAEs were related to infection. Notably, the frequency of infections was numerically lower with iptacopan compared to C5 inhibitors in APPLY-PNH, despite the assumption of an at least temporary dual complement inhibition in the iptacopan group. However, no conclusion on whether and to which extent iptacopan increases the risk of (serious) infections can be drawn from this limited dataset. Further follow-up is necessary post-marketing.

Laboratory evaluation (haematology, coagulation and clinical chemistry) mainly revealed effects that can be considered related to the desired action of iptacopan, i.e. reducing haemolysis. However, there was a small but consistent increase in total and LDL cholesterol in the iptacopan group vs. baseline. This was considered related to the correction of the underlying disease. The applicant presented published literature demonstrating that haemolytic anaemia is related to a decrease in serum cholesterol, probably due to increased cholesterol consumption during erythropoiesis. In fact, in a post-hoc analysis of study data, the applicant could demonstrate a positive correlation between Hb increase and cholesterol increase. Hence, with the increase in serum cholesterol level upon treatment of haemolytic anaemia, serum cholesterol returns to its normal level.

Non-clinical studies suggested potential testicular effects and thyroid changes at doses slightly above the equivalent proposed dose in humans. Across the PNH and renal pools, one patient had two AEs of abnormal reproductive hormone levels and two patients had thyroid hormone changes (increased thyroid stimulating hormone and tri-iodothyronine respectively). Based on the non-clinical data and lack of corresponding clinical findings to date from all PNH studies and completed studies in other indications, it is considered sufficient to address these effects within the section 5.3 of the SmPC. Also, thyroid and testicular adverse events will continue to be monitored in the ongoing studies in patients with PNH. This is considered sufficient.

Assessment of vital signs revealed a small increase in diastolic blood pressure (DBP) with iptacopan vs. baseline and vs. comparator. Accordingly, there were three patients reporting hypertension in the controlled study period vs. zero in the comparator group. In line with the DBP increase, a small decrease in heart rate (HR) was observed in the PNH population (but not in the patients with renal disease). In the pooled PNH studies, 21/155 (13.5%) subjects had decreased heart rate from baseline >= 25%. Thus, iptacopan may affect haemodynamics to some extent in PNH patients. The applicant stated that the possible explanation of the observed increase in DBP and decrease in heart rate in PNH patients is not a direct drug effect but can be ascribed to the decrease of the compensatory cardiac output following improvement of anaemia, which is reflected in the decrease of heart rate. This approach is in principle understood and agreed. This has been reflected in the SmPC. Most likely, the smaller effect size of pegcetacoplan in respect to Hb increase results in smaller (and thereby undetectable) haemodynamic changes.

However, it has to be considered that the effect size in respect to Hb increase appeared lower with pegcetacoplan than with iptacopan so that the resulting haemodynamic change is expected to be smaller. Since the HR change was already small with iptacopan, this effect may not have become obvious in pegcetacoplan.

Information about Educational material has been reflected in the SmPC section 4.4.

2.6.10. Conclusions on the clinical safety

Data from the active-controlled period of the pivotal study APPLY-PNH indicate that the safety profile of iptacopan is comparable to anti-C5 treatment. Compared to anti-C5, a higher rate of headache and gastrointestinal AEs was reported. SAEs included several types of infection. BTH is adequately addressed in the product information.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 66: Summary of safety concerns

Important identified risks	• Infections caused by encapsulated bacteria
Important potential risks	• Serious haemolysis following discontinuation of iptacopan • Malignancies
Missing information	• Use in pregnant patients • Long-term safety (>2 years)

2.7.2. Pharmacovigilance plan

Table 67: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
CLNP023C12001B Long-term safety and tolerability of iptacopan in patients with Paroxysmal Nocturnal Haemoglobinuria (PNH). Status: Ongoing	The purpose of this study is to evaluate the long-term safety, tolerability and efficacy of iptacopan in patients with PNH and to provide continued access to patients who have completed the treatment extension period (without tapering down) of the Phase II and Phase III trials and derived benefit from iptacopan treatment.	Infections caused by encapsulated bacteria, Serious haemolysis following discontinuation of iptacopan, Malignancies, Long-term safety (>2 years)	Final report submission	31-May-2029
CLNP023C12003 PASS in iptacopan-treated patients using registry data Status: Planned	The purpose of this study is to characterise the identified and potential risks of iptacopan in the real-world clinical practice. Further study objectives are to provide additional data for the missing information (use in pregnancy and long-term safety) and to evaluate	Infections caused by encapsulated bacteria, Serious haemolysis following discontinuation of iptacopan, Malignancies, Long-term safety (>2 years), Use in	Annual update	Progress reports on enrolment and intermediate analysis results to be provided annually with the PSUR.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	effectiveness of additional risk minimisation measures (aRMMs) related to the required and recommended vaccinations in the iptacopan-treated PNH population. This study will use data collected through the International PNH Inter est Group (IPIG) registry. The aim of the IPIG PNH registry is to develop an international database to prospectively collect observational data on patients with PNH (regardless of treatment received) covering clinical outcomes, patient reported outcomes, and health-resource utilisation on all enrolled patients, as well as long term safety data. According to the IPIG PNH Registry protocol, Novartis will only have access to the data from PNH patients treated with iptacopan. The iptacopan PASS (a secondary analysis of the data collected in the registry) will thus be a single-arm study with no internal comparator.	pregnant patients		

2.7.3. Risk minimisation measures

Table 68: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infections caused by encapsulated bacteria	**Routine risk communication** Risk addressed in SmPC Sections: - Contraindications (Section 4.3) - Warning and Precautions (Section 4.4) - Undesirable Effects (Section 4.8) Risk addressed in Package Leaflet (PL) - Section 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CLNP023C12001B **Final study report date**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.3 and 4.4 where advice is given on vaccination/prophylactic antibiotic requirements. - SmPC section 4.4 where recommendation for monitoring of early signs and symptoms of infections is given. Legal status: Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional guide • Patient/caregiver guide • Patient safety card • System for controlled access • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines)	31-May-2029 CLNP023C12003, PASS in iptacopan-treated patients using registry data **Final study report date** 31-Mar-2030
Serious haemolysis following discontinuation of iptacopan	**Routine risk communication** Risk addressed in SmPC Sections: - Posology and administration (Section 4.2) - Warning and Precautions (Section 4.4) Risk addressed in PL - Section 3 SmPC section 4.2 where description of the risk, along with treatment guidance is provided. - SmPC section 4.4 where monitoring of PNH manifestations after discontinuation is discussed. Calendarised packaging to aid in patient adherence to the dosing schedule. Legal status: Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional guide • Patient/caregiver guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CLNP023C12001B **Final study report date** 31-May-2029 CLNP023C12003, PASS in iptacopan-treated patients using registry data **Final study report date** 31-Mar-2030
Malignancies	**Routine risk communication** Legal status: Prescription only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CLNP023C12001B **Final study report date** 31-May-2029

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		CLNP023C12003, PASS in iptacopan-treated patients using registry data **Final study report date** 31-Mar-2030
Use in pregnant patients	**Routine risk communication** Missing information addressed in SmPC sections - Fertility, pregnancy and lactation (Section 4.6) **-** Preclinical safety data (Section 5.3) Missing information addressed in PL - Section 2 Preclinical data and risks of pregnancy in PNH patients described. Lack of data on iptacopan in pregnancy and need for a risk-benefit assessment stated. Legal status: Prescription only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** CLNP023C12003, PASS in iptacopan-treated patients using registry data **Final study report date** 31-Mar-2030
Long-term safety (>2 years)	**Routine risk communication:** Legal status: Prescription only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CLNP023C12001B **Final study report date** 31-May-2029 CLNP023C12003, PASS in iptacopan-treated patients using registry data: **Final study report date** 31-Mar-2030

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP and PRAC considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 05.12.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fabhalta (iptacopan) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

To most effectively manage PNH, both intravascular and extravascular haemolysis (IVH and EVH) need to be controlled. This is reflected in improvements across the following key markers of disease activity: haemoglobin (Hb) level, LDH level, absolute reticulocyte count (ARC), bilirubin level, and transfusion requirements. Key symptoms are captured by the FACIT-Fatigue score. The C5 inhibitors eculizumab and ravulizumab have shown increased survival and improved outcomes in PNH by controlling IVH, reflected in LDH improvements; however, C5 inhibitors do not control EVH. In many patients treated with C5 inhibitors, although LDH is largely controlled, ARC and bilirubin levels remain elevated, indicative of ongoing haemolysis. Despite the availability of eculizumab over the past 13 years, approximately one third of patients remain transfusion dependent (Risitano *et al*. AM J Hematol 2018). Danicopan, a reversible inhibitor of complement factor D, was recently approved as an add-on to

ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia.

Pegcetacoplan, targeting C3 in the proximal complement system, was approved in 2021 for patients *who are anaemic after treatment with a C5 inhibitor for at least 3 months*. It is administered twice weekly by subcutaneous infusion (1080 mg/20 mL) via a pump. In the phase 3 PEGASUS study in adult patients with a haemoglobin level <10.5 g/dL despite prior eculizumab therapy, pegcetacoplan was superior to eculizumab in improving haemoglobin levels. Pegcetacoplan also improved other clinical and haematological parameters of haemolysis, as well as quality of life outcomes (Hillmen *et al.* N Engl J Med. 2021). Pegcetacoplan was recently approved in the EU as monotherapy for the treatment of adult patients with PNH who have haemolytic anaemia.

There may be no clear unmet medical need for iptacopan, which likewise targets the proximal complement system, but an easy to take oral monotherapy would be advantageous compared to the parenteral administration necessary for the currently available complement inhibitors (see section 2.1.5)

3.1.3. Main clinical studies

The efficacy and safety of iptacopan in adult patients with PNH were evaluated in two multicentre, open-label, 24-week phase III studies: an active comparator-controlled study (APPLY-PNH) and a single-arm study (APPOINT-PNH).

APPLY-PNH enrolled adult PNH patients (RBC clone size ≥10%) with residual anaemia (haemoglobin <10 g/dl) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomisation. Patients (N=97) were randomised in 8:5 ratio either to receive iptacopan 200 mg orally twice daily (N=62) or to continue anti-C5 treatment (eculizumab N=23; or ravulizumab N=12) throughout the duration of the 24-week randomised controlled period (RCP). Randomisation was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months. Efficacy was based on two primary endpoints to demonstrate superiority of iptacopan to anti-C5 in achieving haematological response after 24 weeks of treatment, without a need for transfusion, by assessing the proportion of patients demonstrating: 1) sustained increase of ≥2 g/dl in haemoglobin levels from baseline (haemoglobin improvement) and/or 2) sustained haemoglobin levels ≥12 g/dl. Secondary endpoints included s transfusion avoidance, changes from baseline in haemoglobin levels, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores, absolute reticulocyte counts (ARCs) and annualised rate of clinical breakthrough haemolysis.

APPOINT-PNH was a single-arm study in 40 adult PNH patients (RBC clone size ≥10%) with haemoglobin <10 g/dl and LDH >1.5 x ULN who were not previously treated with a complement inhibitor. All 40 patients received iptacopan 200 mg orally twice daily during the 24-week open-label core treatment period. Efficacy was based on the primary endpoint assessing the effect of iptacopan treatment on the proportion of patients achieving haemoglobin improvement (sustained increase of ≥2 g/dl in haemoglobin levels from baseline, without a need for RBC transfusion, after 24 weeks).

3.2. Favourable effects

Pivotal study APPLY-PNH[2]: Iptacopan monotherapy 200 mg bid was statistically significantly superior to anti-C5, with an estimated treatment difference (95% CI) in the co-primary endpoint of:

1. 80.2% (71.2, 87.6) for Hb increase ≥2g/dL from baseline in the absence of transfusion (unadjusted two-sided p-value <0.0001),
2. 67.0% (56.4, 76.9) for Hb ≥12g/dL in the absence of transfusion (unadjusted two-sided p-value <0.0001).

Secondary endpoints showed statistically significant differences vs anti-C5 therapy as regards transfusion avoidance (estimated treatment difference of 68.9%, unadjusted two-sided p<0.0001; 59 of 62 patients in the iptacopan group and 14 of 35 patients in the anti-C5 group did not require RBC transfusions between day 14 and day 168. This went along with an increase in Hb levels from baseline, with a treatment difference in adjusted mean change from baseline in Hb of +3.66 g/dL (unadjusted two-sided p<0.0001). Absolute reticulocyte count (ARC; marker of EVH) was reduced with iptacopan to a clinically meaningfully greater extent as compared to anti-C5 therapy, with a treatment difference in adjusted mean change from baseline of - 116.2 $\times 10^9$/L (-132.0, -100.3) unadjusted two-sided p<0.0001). The ULN for absolute reticulocyte count is 123 x 10^9/L (central laboratory). Patient-reported fatigue improved with iptacopan, with a treatment difference in adjusted mean change from baseline in FACIT-F score of 8.29 points (unadjusted two-sided p<0.0001).

Supportive phase 3 study APPOINT*:* in complement inhibitor naïve patients, iptacopan resulted in a 92.2% (95% CI: 82.5%, 100.0%) marginal proportion of patients achieving clinically meaningful Hb increases of 2 g/dL or more in the absence of transfusions. The lower bound of the two-sided 95% confidence interval was 82.5%, which was above the study protocol pre-specified threshold of 15%.

Results of secondary endpoints supported the anti-haemolytic benefit: mean Hb at baseline was 8.16 (1.09) g/dL. The adjusted mean change from baseline in Hb as mean of visits between Day 126 and Day 168 was +4.28 g/dL (95% CI: 3.87, 4.70). In order to factor out the effect of transfusions in this analysis, if a patient had a transfusion during the core treatment period, the Hb values during the 30 days following the transfusion were excluded and Hb data were imputed.

Baseline mean LDH was 1698.8 (683.33) U/L and the median (range) LDH was 1581.5 U/L (522 – 3244 U/L). Treatment with iptacopan resulted in an adjusted mean percent change from baseline in LDH levels as mean of visits between day 126 and day 168 of -83.55% (95% CI -84.90%, -82.08%). At day 168 of the core treatment period, mean LDH was 261.3 U/L, which was close to the ULN of 250 U/L.

Baseline mean (SD) absolute reticulocyte count was 154.33 (63.666) x 10^9/L. The adjusted mean (95% CI) change from baseline in absolute reticulocyte count as mean of visits between day 126 and day 168 was -82.48 x 10^9/L (-89.33, -75.62).

The adjusted mean (95% CI) FACIT-Fatigue score change from baseline between Day 126 and Day 168 was +10.75 points (8.66, 12.84).

Extension phases

In APPLY-PNH, at Week 48, patients randomised to iptacopan, mean (SD) haemoglobin was 8.93 (0.70) g/dL at baseline, 12.61 (1.43) g/dL at Day 168 (24 weeks) and 12.19 (1.57) g/dL at Day 336

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

(48 weeks). In patients randomised to anti-C5 who switched to iptacopan 200 mg b.i.d. in the extension period, mean (SD) haemoglobin was 8.85 (0.90) g/dL at baseline, 9.15 (1.41) g/dL at Day 168 (24 weeks) (last assessment before switch) and 12.12 (1.41) g/dL at Day 336 (48 weeks).

In APPOINT-PNH the increase in mean haemoglobin achieved in the core treatment period (up to Day 168; 24 weeks) was maintained throughout the extension period (i.e., to Day 336; 48 weeks). At baseline, patients had a mean (SD) haemoglobin level of 8.16 (1.087) g/dL, 12.56 (1.486) g/dL at Day 168 and 13.24 g/dL (1.798) at Day 336.

3.3. Uncertainties and limitations about favourable effects

The merely transient decrease in LDH-levels in the APPLY versus the APPOINT trial raised a question on the sustainability of the positive iptacopan treatment effect after switch from anti-C5-treatment. however, exploratory analyses could not demonstrate a correlation between PNH RBC clone size and LDH dynamics in the iptacopan group of APPLY-PNH.

Further efficacy data will be prospectively collected through the IPIG PNH registry as observational data covering clinical outcomes, patient reported outcomes, and health-resource utilisation in PNH patients treated with iptacopan (see RMP).

3.4. Unfavourable effects

A total of 223 patients (170 patients with PNH and 53 patients from studies in renal indications) received at least one dose of iptacopan 200 mg b.i.d. In the pooled PNH studies, the median duration of exposure was 10.6 months.

Patients with serious AEs (SAEs) were numerically more frequent in the anti-C5 group. (9.7% vs. 14.3%, iptacopan vs. anti-C5). No discontinuations due to AE occurred during the controlled period of APPLY-PNH. The most frequent AEs occurred more often with iptacopan than with anti-C5 were headache, diarrhoea and nausea. Seven patients in the pooled PNH studies (4.1%) reported serious adverse events related to malignancy.

Furthermore, 3.2% of patients in the iptacopan group experienced breakthrough haemolysis (BTH). - less frequent than with comparator anti-C5, 17.1% of patients

In APPLY-PNH, infections were numerically more frequent with anti-C5 than with iptacopan (38.7% vs. 48.6%, iptacopan vs. anti-C5).

Limited safety information can be derived from the uncontrolled data pool, however, it is reassuring that most reported AEs in this pool were mild in severity; 17.1% of patients suffered at least one SAE.

Laboratory evaluation revealed an increase from baseline in the serum level of total cholesterol (by around 20%) and LDL cholesterol (by around 35%) during iptacopan treatment as well as an increase from baseline in diastolic blood pressure (DBP, by around 5 mmHg) in the pooled data set; a positive correlation between Hb and cholesterol or DBP has been shown in a post-hoc analysis of study data.

Across the PNH and renal pools, cases of AEs of abnormal reproductive hormone levels and thyroid hormone changes (increased thyroid stimulating hormone and triiodothyronine respectively) were identified. Non-clinical studies suggested potential testicular effects and thyroid changes at doses slightly above the equivalent proposed dose in humans.

3.5. Uncertainties and limitations about unfavourable effects

Safety evaluation of iptacopan is limited by the fact that the controlled period of the pivotal study APPLY-PNH was short and that a low number of patients were included due to the rarity of the disease. Thus, it is unlikely that rarer but potentially serious AEs would have been captured. Most AEs occurred in uncontrolled studies or study periods so that the relationship to iptacopan is difficult to assess. Furthermore, only patients who displayed treatment success and tolerated iptacopan well entered the extension periods. Therefore, the uncontrolled extension periods can be biased in favour of good tolerability of iptacopan. The number of patients in iptacopan clinical studies who received iptacopan for >2 years is limited. Limited long-term safety information is available for iptacopan, long term data are expected to be provided post-authorisation (see Pharmacovigilance plan in the RMP).

Infections by encapsulated bacteria (*Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*) are important safety concerns with complement inhibitors and are classified and monitored as important an identified risk (see RMP).

Seven patients in the pooled PNH studies reported malignancy events. Among them, two were reported during the controlled period vs, none in the anti-C5 group. From these findings, it is difficult to establish a link between malignancy and iptacopan treatment. In the RMP malignancies are classified and monitored as important potential risks (see RMP).

A category 3 long term safety and tolerability study is ongoing and a category 3 PASS study using registry data is planned to address concerns regarding long term safety, infections caused by encapsulated bacteria, serious haemolysis following discontinuation of iptacopan, malignancies, long-term safety and use in pregnancy (See Pharmacovigilance plan in the RMP).

3.6. Effects Table

Table 69: Effects Table for iptacopan in the treatment of PNH (APPLY-PNH (data cut-off: 26-Sep-2022).

Effect	Short Description	Unit	Treatment - Iptacopan	Control - Anti-C5	Difference %; Ipta vs Anti-C5 treatment effect	Un-certainties
Primary endpoints:						
≥2g increase in Hb from BL in the absence of RBC transfusions[2]	N/A	N of patients meeting criterion	51/60	0/35	80.2 (71.2-87.6); P<0.0001	**SoE:** Study APPOINT-PNH supports the results of the pivotal study
Hb≥12g/dl in the absence of RBC transfusions[2]	N/A	N of patients meeting criterion	42/60	0/35	67.0 (56.4, 76.9); P<0.0001	
Secondary endpoints:						
Transfusion avoidance	N/A	N of patients meeting criterion	59/62	14/35	68.9 (51.4-83.9); P<0.0001	

Change from BL in Hb	Mean value; difference between means	g/dL	3.6	-0.06	3.7 (3.2,4.1): P<0.0001	
Change from baseline in FACIT-Fatigue-score[1]	N/A	Score	8.6	0.3	8.3 (5.3, 11.3); P<0.0001	
Ratio to baseline in LDH [1]	Geometric mean; ratio of geometric mean	U/L	0.96	0.98	0.99 (0.89,1.10) P=0.8361	

Unfavourable Effects

Effect	Unit	Treatment - Iptacopan	Control - Anti-C5		Pooled PNH studies	Un-Certainties SoE
All TEAES	% of patients	82.3	80.0		84.7	
All SAEs	% of patients	9.7	14.3		17.1	
Nervous system disorders	% of patients	25.8	2.9		24.7	
Breakthrough haemolysis (BTH)	% of patients	3.2	17.1		4.7	

Abbreviations: N= number
Notes:
[1]Assessed between day 126-day 168
[2]between day 14 and day 168

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

Overall, the anti-haemolytic effect size demonstrated in APPLY and APPOINT is considered significant.

The most important favourable effect is a meaningful improvement in haemoglobin levels approximating normalisation in the absence of RBC transfusions. This key benefit is further substantiated by consistent results in favour of iptacopan over a range of secondary endpoints relevant to haemolytic PNH: transfusion avoidance, change in Hb from baseline, and changes in ARC and Fatigue score improvements.

Further, iptacopan is an easy to take oral formulation as opposed to the currently available complement inhibitors that need to be administered via SC or IV infusion, which is considered an advantage.

The most important risks associated with currently approved complement inhibitors are severe breakthrough haemolysis (BTH) and infections, especially those due to encapsulated bacteria.

Although, the frequency of infections was numerically lower with iptacopan compared to C5 inhibitors in APPLY-PNH, no conclusion on whether and to which extent iptacopan increases the risk of (serious)

infections can be drawn from this limited dataset or from the uncontrolled extension studies. Further follow-up on this important issue is necessary post-marketing (see RMP).

An educational programme providing healthcare professionals (HCPs) and patients/caregivers with information on infections caused by encapsulated bacteria and serious haemolysis following discontinuation of iptacopan –aims to mitigate these risks.

A rather frequently AE class observed with iptacopan, markedly more than with comparator anti-C5, was nervous system disorders (mostly headache and dizziness). Furthermore, nausea and diarrhoea were reported. These conditions are inconvenient for the patient but do not pose a major hazard.

3.7.2. Balance of benefits and risks

Clinically relevant anti-haemolytic activity of significant magnitude has been demonstrated in APPLY and supported by APPOINT in pre-treated and treatment-naïve PNH patients. The AEs frequently observed in the clinical programme such as nausea and headache do not pose a major risk to the patient so that they hardly affect the positive B/R ratio. Data from registry studies will provide more information related to long term treatment.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Fabhalta as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Fabhalta is not similar to Aspaveli and Voydeya within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Fabhalta is favourable in the following indication(s):

Fabhalta is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Fabhalta in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The educational programme is aimed at providing healthcare professionals (HCPs) and patients/caregivers with educational information on the following safety areas of interest:

- Infections caused by encapsulated bacteria
- Serious haemolysis following discontinuation of iptacopan

The MAH shall ensure that in each Member State where Fabhalta is marketed, all HCPs and patients/caregivers who are expected to prescribe or use Fabhalta have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:
- The Summary of Product Characteristics
- Guide for healthcare professionals

- **The Guide for healthcare professionals shall contain the following key messages:**
  - Fabhalta may increase the risk of serious infections with encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae.*
  - Ensure patients are vaccinated against *N. meningitidis* and *S. pneumoniae* before starting treatment, and/or receive antibiotic prophylaxis until 2 weeks after vaccination.
  - Recommend vaccination against *H. influenzae* to patients where vaccines are available.
  - Ensure that Fabhalta is only dispensed after a written confirmation that the patient has received vaccination against *N. meningitidis* and *S. pneumoniae,* in accordance with current national vaccination guidelines, and/or is receiving prophylactic antibiotic.

- Ensure prescribers or pharmacists receive annual reminders of mandatory revaccinations in accordance with current national vaccination guidelines (including *N. meningitidis*, *S. pneumoniae*, and, if appropriate, *H. influenzae*)
- Monitor patients for signs and symptoms of sepsis, meningitis or pneumonia, such as: fever with or without shivers or chills, headache and a fever, fever and a rash, fever with chest pain and cough, fever with breathlessness/fast breathing, fever with high heart rate, headache with nausea or vomiting, headache with a stiff neck or stiff back, confusion, body aches with flu-like symptoms, clammy skin, eyes sensitive to light. If bacterial infection is suspected, treat with antibiotics immediately.
- Discontinuation of Fabhalta may increase the risk of serious haemolysis, therefore advice on adherence to the dosing schedule is important, as is close monitoring for signs of haemolysis following treatment discontinuation. If discontinuation of Fabhalta is necessary, alternative therapy should be considered. If haemolysis occurs after discontinuation of Fabhalta, restarting Fabhalta treatment should be considered. Possible signs and symptoms you need to look out for are: elevated lactate dehydrogenase (LDH) levels along with sudden decrease in haemoglobin or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, dysphagia, erectile dysfunction or major adverse vascular events including thrombosis.
- Details about the PASS and how to enter patients, if applicable.

The patient information pack:
- Package leaflet
- Patient/caregiver guide
- Patient safety card

- **The Patient/caregiver guide shall contain the following key messages:**
  - Treatment with Fabhalta may increase the risk of serious infections.
  - Doctors will inform you about which vaccinations are required prior to treatment and/or the need to receive antibiotic prophylaxis.
  - Signs and symptoms of serious infection are: fever with or without shivers or chills, headache and a fever, fever and a rash, fever with chest pain and cough, fever with breathlessness/fast breathing, fever with high heart rate, headache with nausea or vomiting, headache with a stiff neck or stiff back, confusion, body aches with flu-like symptoms, clammy skin, eyes sensitive to light.
  - Contact your doctor in case you experience any of the signs and symptoms above and seek immediate medical care at the nearest medical centre.
  - Discontinuation of Fabhalta may increase the risk of serious breakdown of red blood cells (haemolysis). It is important that you adhere to the scheduled treatment regimen. Possible signs and symptoms you need to look out for are: fatigue, blood in the urine, abdominal pain, shortness of breath, difficulty swallowing, erectile dysfunction or major adverse vascular events including thrombosis.
  - Tell your doctor before discontinuing Fabhalta.
  - If you miss a dose, take it as soon as you can, even if it is close to the next dose.
  - You will receive a patient safety card and will need to carry it with you and tell any treating healthcare professional that you are being treated with Fabhalta.
  - If you have any adverse reactions, including infections or serious haemolysis, it is important that you report them immediately.
  - You will be informed of the details to enrol in the PASS.

- **Patient Safety Card:**
  - Statement that the patient is receiving Fabhalta.
  - Signs and symptoms of serious infection caused by encapsulated bacteria and warning to seek immediate treatment with antibiotics if bacterial infection is suspected.
  - Contact details where a healthcare professional can receive further information.

- **System for Controlled Access:**
  - The MAH shall ensure that in each Member State where Fabhalta is marketed, a system aimed to control access beyond the level of routine risk minimisation measures is in place. The following requirement needs to be fulfilled before the product is dispensed:

- Submission of written confirmation of the patient's vaccination against *N. meningitidis* and *S. pneumoniae* infections and/or receipt of prophylactic antibiotic according to national guidelines.

- **Annual reminder of mandatory revaccinations:**
  - The MAH shall send to prescribers or pharmacists who prescribe/dispense Fabhalta an annual reminder in order that the prescriber/pharmacist checks if a revaccination (booster vaccination) against *N. meningitidis* and *S. pneumoniae* infections is required for their patients on treatment with Fabhalta, in accordance with current national vaccination guidelines.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that iptacopan is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.