NOVARTIS

Patient Safety & Pharmacovigilance

Iptacopan

LNP023

EU Safety Risk Management Plan

Active substance (INN or common name):	Iptacopan
Product concerned (brand name):	FABHALTA®
Document status:	Final
Version number:	2.3
Data lock point for this RMP	06-May-2024
Date of final sign off	25-Feb-2025

Rationale for submitting an updated RMP: This EU Risk Management Plan (RMP) has been updated to version 2.3 at CHMP request, as part of the submission dossier for the new indication of C3 glomerulopathy (Procedure No. EMEA/H/C/005764/II/0001).

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v2.2
Part I	No change.
Part II	No change.
Part III	Interim study report for CLNP023B12001B added as a study milestone. Statement added to reflect the inclusion of the C3G Early Access Program data in the upcoming PSURs.
Part IV	No change.
Part V	Interim study report for CLNP023B12001B added as a study milestone.
Part VI	No change.
Part VII	

Other RMP versions under evaluation

No other RMP versions are currently under evaluation.

Details of the currently approved RMP:
Version number: 1.2
Approved with procedure: EMEA/H/C/005764

Date of approval (opinion date): 21-Mar-2024

QPPV name: Dr. Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization applicant´s QPPV. The electronic signature is available on file.

Table of contents

List of tables

List of abbreviations

AA	Aplastic Anaemia
ACEI	Angiotensin-converting enzyme inhibitors
AE	Adverse Event
AML	Acute Myeloid Leukaemia
ARB	Angiotensin II receptor blockers
AUC	Area Under Curve
aRMMs	Additional Risk Minimization Measures
aPhV	Additional pharmacovigilance
C3G	Complement 3 glomerulopathy
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic kidney disease
CV	Cardiovascular
DDD	Dense deposit disease
DLP	Data Lock Point
EEA	European Economic Area
EFD	Embryo-fetal development
EMEA	Europe, Middle East, and Africa
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EVH	Extravascular Haemolysis
FB	Factor B
GPI	Glycosylphosphatidylinositol
HCPs	Healthcare Professionals
HMRN	Haematological Malignancy Research Network
HR	Heart rate
HSCT	Hematopoietic Stem Cell Transplantation
ICD	International Classification of Disease
IC-MPGN	Immune-complex membranoproliferative glomerulonephritis
IPIG	International PNH Interest Group
IVH	Intravascular Haemolysis
KDIGO	Kidney Disease: Improving Global Outcomes
LPLV	Last patient last visit
MA	Marketing Authorization
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPGN	Membranoproliferative glomerulonephritis
NOAEL	No-observed-adverse-effect-level
OS	Overall Survival
PASS	Post-authorization Safety Study

PL	Package Leaflet
PNH	Paroxysmal Nocturnal Haemoglobinuria
PSUR	Periodic Safety Update Report
RAS	Renin-angiotensin system
REP	Roll-over Extension Program
RMP	Risk Management Plan
RRT	Renal replacement therapies
RTP	Randomized Treatment Period
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SmPC	Summary of Product Characteristics

Part I: Product(s) Overview

Table Part I-1: Product(s) Overview

Active substance (INN or common name)	Iptacopan
Pharmacotherapeutic group (ATC Code)	Antineoplastic and Immunomodulating Agents (L04AJ08)
Marketing Authorization Applicant	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	FABHALTA
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class**: Iptacopan, is a novel, orally administered, small molecular weight, first in-class, selective protease inhibitor that binds to Factor B (FB) Bb domain.
	Summary of mode of action: Iptacopan is a proximal complement inhibitor that targets FB to selectively inhibit the alternative pathway. Inhibition of FB prevents the activity of alternative pathway related C3 convertase and the subsequent formation of C5 convertase.
	Important information about its composition: Iptacopan Finished Product is formulated as 200 mg hard gelatin capsules
Hyperlink to the Product Information	[Proposed SmPC]
Indications in the EEA	**Current**: Iptacopan is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.
	Proposed: Iptacopan is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. Iptacopan is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated.
Dosage in the EEA	**Current**: 200 mg twice daily
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** 200 mg, hard capsule (capsule)

	Proposed: Not Applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Module SI- Epidemiology of the indication(s) and target population

Indication: Paroxysmal nocturnal haemoglobinuria (PNH)

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

PNH is a rare haematological disorder that presents with haemolytic anaemia, thrombosis and smooth muscle dystonias, as well as bone marrow failure in some cases. PNH results from the clonal expansion of a mutated haematopoietic stem cell; these mutations lead to a deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins, such as complement decay-accelerating factor (also known as CD55) and CD59 glycoprotein (CD59), which are both complement inhibitors. Loss of CD55 and CD59 renders PNH erythrocytes susceptible to intravascular haemolysis, which can lead to thrombosis and much of the morbidity and mortality of PNH (Hill et al 2017). The International PNH Interest Group classifies PNH into three categories: classical PNH (in which patients have clinical manifestations of haemolysis or thrombosis); PNH in the context of other primary bone marrow disorders (such as aplastic anaemia or myelodysplastic syndromes); and sub clinical PNH, in which patients have low proportion of PNH granulocytes (PNH clone size) but no clinical or laboratory evidence of haemolysis or thrombosis (Hill et al 2017).

Incidence

In the recently published studies from the EU and UK the annual incidence rate of PNH ranged from 0.13 to 0.35 per 100,000 population. In addition, two studies from Denmark and from the US reported incidence of PNH with person-time in denominator, ranging from 0.08 to 0.57 per 100,000 person-years (Reported incidence of PNH in Europe and the US).

Europe

Hansen et al (2020) extracted incident cases from Danish national registries using International Classification of Disease (ICD) codes. Incidence of PNH in the period 2008 to 2016 was 0.08 per 100,000 person-years (95% CI: 0.06, 0.11), with no difference between genders.

One conference abstract reported the incidence of PNH from 2011 to 2016 in the Nordic countries (Denmark, Finland, Norway, and Sweden) using database records from the Stockholm and Gotland regions in Sweden, Copenhagen region in Denmark, Oslo region in Norway and from entire Finland. The mean annual incidence per 100,000 population of newly detected PNH clones (>0.1%) was 0.23 in the Nordic countries (Denmark 0.21, Finland 0.30, Norway 0.25, and Sweden 0.17) (Korkama et al 2018b). The mean age at detection of the clone was 52 years (range: 6 to 90), with no gender difference.

In a study using the data from 24 laboratories from 2011 to 2014 in Spain, Morado et al (2017) reported the overall incidence of newly detected PNH clones (>0.01%) of 0.25 per 100,000 population (ranging between 0.23 and 0.28 cases per 100,000 in 2011 and 2014, respectively).

To estimate the incidence and prevalence of PNH in the UK, researchers collected survival data of all patients diagnosed with PNH in the strategic health authorities of North, East and West Yorkshire, and Northern Lincolnshire, between January 1991 and July 2006 (Hill et al 2006). Seventy-six patients were diagnosed with PNH during this period, resulting in an annual incidence of 0.13 per 100,000.

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

United States

In the US, a conference abstract reported the incidence of PNH in 2015-2018 based on ICD-10 code D59.5 using records from Truven US Market Scan Commercial/Medicare database (Jalbert et al 2019). The incidence of PNH was 0.57 per 100,000 person-years, similar across sex, with mean age at diagnosis of 50 years.

Table Part II: Module SI-1:Reported incidence of PNH in Europe and the US

Country, study period	PNH definition	No of patients	Annual incidence / 100,000 population	Reference
Denmark, 2008-2016	ICD-10 code D59.5	NR	0.08†	Hansen et al (2020)
Nordic countries, 2011-2016	Detectable PNH clones by flow cytometry (>0.1%)	NR	All Nordic: 0.23* Denmark: 0.21* Finland: 0.30* Norway: 0.25* Sweden: 0.17*	Korkama et al (2018b)
Spain, 2011-2014	Detectable PNH clones by flow cytometry (>0.01%)	563	0.25*	Morado et al (2017)
UK, 2004-2018	Detectable PNH clones by flow cytometry (>0.01%)	197	0.35	Richards et al (2021)
UK, 1991-2006	Detectable PNH clones by flow cytometry	76	0.13	Hill et al (2006)
US, 2015-2018	ICD-10 59.5	257	0.57†*	Jalbert et al (2019)

†Reported with patient-years (PY) in denominator

*Reported per 1 million, recalculated to cases per 100,000 population or per 100,000 PY and rounded to standardize presentation

ICD=International Classification of Disease; PNH=Paroxysmal nocturnal hemoglobinuria; PYs=Person-years; UK=United Kingdom; US=United States, NR=Not reported

Prevalence

Five recent studies reporting prevalence of PNH in the EU, UK and the US were identified and are summarized in the table below. PNH point prevalence estimates in these studies ranged from 1.0 to 1.8 per 100,000 individuals. Two studies reported period prevalence over 15 years of observation, which ranged from 1.6 to 3.8 per 100,000 individuals.

Table Part II: Module SI-2:Reported prevalence estimates of PNH in Europe and the US

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

*Reported per 1 million, recalculated to cases per 100,000 to standardize presentation
ICD=International Classification of Disease; PNH=Paroxysmal nocturnal hemoglobinuria; UK=United Kingdom; US=United States

Europe

Hansen et al (2020) reported prevalence of PNH in several time periods between years 1977 and 2016 using Danish national registries. Most recently reported prevalence of PNH was 1.04 per 100,000 individuals (95% CI: 0.79,1.34) for year 2015; 1.09 per 100,000 in women (95% CI: 0.74,1.54) and 1.00 per 100,000 in men (0.66-1.44). PNH was most prevalent between 20 and 50 years of age.

Hill et al (2006) estimated the prevalence of PNH in the Northern Lincolnshire, North, East and West Yorkshire regions of UK between 1991 and 2006 using incidence and survival rates. The population of the study region was 3,742,835 (based on the 2001 census of Great Britain) and considering 76 patients diagnosed with PNH during this period, the estimated 15-year period prevalence of PNH was 1.59 per 100,000 individuals.

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

United States

One conference abstract reported the prevalence of PNH based on ICD-10 code D59.5 in the Truven US Market Scan Commercial/Medicare database (Jalbert et al 2019). Reported prevalence estimates were 1.2 and 1.3 per 100,000 individuals in 2016 and 2017, respectively.

Given the paucity of US epidemiological data, researchers have attempted to model the US prevalence of PNH. In a study of the evolutionary dynamics of PNH, the prevalence of clinical PNH cases, both monoclonal and multiclonal (reflecting multiple independently arising clones within the hematopoietic stem cell transplantation (HSCT) pool, was estimated. Using the stochastic evolutionary model and Markov chain model and population age distribution data obtained in 2010 by the US Census Bureau, the researchers estimated that prevalence of clinical PNH for US monoclonal and multiclonal cases was 1.76 cases per 100,000 individuals (Mon Pere et al 2018).

Further considerations

Some authors note that the prevalence of PNH in the Asian region (e.g. Japan, China, Korea) appears to be higher than in the Western countries (e.g. Hill et al 2017) but the epidemiological data from this region is scarce. A recent study in Japan reported that prevalence of diagnosed PNH was 2.1 per 100,000 in 2018; 10-year period prevalence was as high as 6.4 per 100,000 from 2009 to 2018 (Ninomiya and Okura 2022).

Both the incidence and prevalence of PNH would be higher if patients are registered with a PNH diagnosis due to very small PNH clones with unclear clinical significance for example in conjunction with aplastic anaemia (AA) or myelodysplastic syndrome (MDS) (Hill et al 2006, Gupta et al 2007, Gulbis et al 2010). This overlap in the diagnosis code for PNH between "classic PNH" and "PNH associated with other bone marrow disease" has been shown in a study by (Hansen et al 2020), where the incidence of PNH associated with AA or MDS increases markedly in 2008-2016 period compared to 1994-2007 period. The increase in PNH in this selected group could indicate an increased use of sensitive flow cytometry with increased finding of smaller PNH clones (Lima 2020). According to (Hansen et al 2020), the prevalence of PNH associated with AA or MDS began to rise after 2005, and in 2015 PNH associated with AA or MDS accounted for roughly 10-20% of all prevalent PNH patients. Moreover, the incidence of PNH without AA or MDS, increased steadily during the study period, which could indicate increasing incidence and/or increased awareness. The latter could be related to availability of PNH treatment options (for example eculizumab which has been available since 2007). Availability of treatment options could partly explain the increasing prevalence due to improved survival and, to some degree, increased PNH diagnoses, as physicians may consider referring and correct coding to be more important if the disease is considered treatment modifiable.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

PNH can affect any age group including young adults (Gulbis et al 2010, Yu et al 2016, Hill et al 2017). Children can also be affected by PNH, but it is uncommon (Ge et al 2015, Urbano-Ispizua et al 2017).

PNH is estimated to affect males and females equally (de Latour et al 2008, Socié et al 2016), although the proportion of women with PNH was lower in Asian countries (44.9%) than in Western countries (54.9%) in a meta-analysis (Yu et al 2016). This finding might correlate with

the observation that, in some countries in Asia, men have more access to medical care than women (Yu et al 2016).

The International PNH Registry (IPIG Registry) was established in 2003 by the company Alexion Pharmaceuticals Inc. and one of its purposes was to collect comprehensive data on the natural history of PNH (Socié et al 2016, Schrezenmeier et al 2014). Patients of any age with a clinical diagnosis of PNH (by any applicable diagnostic method) or a detectable fraction of PNH-affected blood cells (a PNH clone) of ≥ 0.01% of all blood cells are eligible for inclusion. As of 17-Jul-2017, 4,439 patients with non-missing demographic and other key data were enrolled; mean age at disease onset was 39.3 (SD: 18.6) years, and median was 35.5 years. Most of the patients were White (78.4%) and Asian (16.3%), and the rest were Black (3.0%) or other races (2.3%) (Schrezenmeier et al 2020).

A limitation of the data from the IPIG Registry is that information on PNH is not available from all countries worldwide: In the Schrezenmeier et al (2020) publication, 67.9% of the analyzed patient population were from Europe and further 14.4% from North America; only 17.7% came from the rest of the world. Furthermore, many patients enrolled in the International PNH Registry had aplastic anaemia (rather than PNH) as their primary diagnosis, as the registry allows inclusion of patients with >0.01% PNH granulocytes.

Aplastic anaemia is the only known risk factor for PNH. In patients with aplastic anaemia, the absolute risk of developing clinical PNH is 15%-25% (Bektas et al 2020b).

The main existing treatment options

Available therapy, apart from supportive care, includes HSCT, complement C5 terminal inhibition (eculizumab/ravulizumab) (Bektas et al 2020a, Hill et al 2017) and a complement inhibitor targeting C3 in the proximal complement system (pegcetacoplan) (Hillmen 2021).

HSCT is the only curative therapy for PNH, but its indication is limited predominantly to PNH with severe bone marrow failure such as patients with severe aplastic anaemia-PNH syndrome (Peffault de Latour et al 2012). The risk of treatment-related morbidity and mortality after HSCT is relatively high, with graft-versus host disease (GvHD) accounting for most of the transplant-related deaths (Brodsky et al 2008, Brodsky 2010, Peffault de Latour et al 2012).

Currently there are three approved complement inhibitor therapies for PNH, the anti-C5 monoclonal antibodies, eculizumab and ravulizumab and most recently pegcetacoplan, a C3 inhibitor; all requiring either intravenous infusions or subcutaneous administration (either infusion or injection). Eculizumab changed the treatment of PNH, which until 2007 was inadequate and consisted of supportive care only. Anti-C5 antibodies are now the standard of care for PNH patients with haemolytic disease or thromboembolic complications. Due to their mechanism of action (terminal complement inhibition), anti-C5 treatments control intravascular haemolysis (IVH), but not extravascular haemolysis (EVH) which becomes the major haemolytic pathway under terminal complement inhibition and therefore haematological response to anti-C5 treatment is sub-optimal/incomplete in a large proportion of patients. Despite important improvements in morbidity and mortality, many patients treated with anti-C5 therapies remain anaemic, transfusion dependent and still suffer from substantially reduced quality of life, in particular debilitating fatigue (Risitano et al 2019, Debureaux et al 2021).

Pegcetacoplan, targeting C3 of the complement system, was approved in the EU and US in 2021. Although more efficacious than eculizumab with respect to change in hemoglobin levels and also transfusion avoidance in a study in PNH patients with anaemia despite eculizumab treatment (Hillmen et al 2021), not all patients became transfusion independent, and six patients discontinued pegcetacoplan treatment due to haemolysis AEs over the 48-week period of the PEGASUS study (Peffault de Latour et al 2022). Pegcetacoplan requires twice weekly subcutaneous infusion of a relatively large volume, with the associated burden on patients and the potential for adverse injection site reactions.

Adjunctive therapies (for example, immunosuppression) could be prescribed to patients with PNH and bone marrow failure to ameliorate the latter. However, these adjunctive treatments are not specific for PNH, nor do they have consistent effects on the expansion or reduction of PNH clones (Hill et al 2017).

Natural history of the indicated condition in the population, including mortality and morbidity:

The clinical spectrum of PNH varies. Signs and symptoms of PNH include haemolytic anaemia, pancytopenia, hemoglobinuria and thrombosis. Further clinical manifestations include smooth muscle dystonia, fatigue, chronic kidney disease and pulmonary hypertension (Hill et al 2017). The International PNH Interest Group classifies PNH into three categories: classical PNH (in which patients have clinical manifestations of haemolysis or thrombosis); PNH in the context of other primary bone marrow disorders (such as aplastic anaemia or myelodysplastic syndromes); and sub-clinical PNH, in which patients have low proportions of PNH clones but no clinical or laboratory evidence of haemolysis or thrombosis (Hill et al 2017).

Mortality in the pre-eculizumab era

Prior to the availability of specific therapy, PNH led to the death of around half of affected individuals within 10 to 20 years, mainly due to thrombotic complications, with a particularly grim prognosis for patients presenting with classic PNH (de Latour et al 2008, Loschi et al 2016). Based on historical studies in 1995 and 1996, the median survival in PNH was known to be 10 to 15 years from the time of diagnosis (Socié et al 1996, Hillmen et al 1995). With time, improved survival was reported by newer studies (such as median survival time of 22 years in a study by de Latour et al 2008). This improvement was likely to be related to modern supportive measures even though better management of thrombosis was still unsatisfactory for a non-malignant haematological disorder affecting young people.

Thromboembolism is the leading cause of mortality in patients with PNH, accounting for between 40% and 67% of deaths with known causes (Hill et al 2013), impacting morbidity and life expectancy of PNH patients most profoundly. Cumulative thrombosis incidence over an 8 to 10-year period was between 23% and 30% in the pre-eculizumab era (Ray et al 2000, de Latour et al 2008). Twenty percent of patients have multisite thrombosis, increasing the morbidity risk and complicating patient management (Ziakas et al 2007). Thrombosis in PNH can occur at any site; common sites include intraabdominal and cerebral veins, hepatic vein thrombosis (Budd-Chiari syndrome) and deep vein thrombosis of the lower limbs; arterial thrombosis may also occur in patients with PNH (Hill et al 2013).

Concerning the effect of race and ethnicity on PNH outcome, Yu et al (2016) showed that although the total death rates were identical between Asian countries and Europe/America (Western countries), the causes of death were different. The major cause of death in Western patients was thromboembolism, which accounted for 43.7% among all causes of death, significantly higher than in Asian countries ($p<0.001$). Other causes of death were serious infections, malignancies (MDS, acute myeloid leukaemia [AML] or other malignant tumors), hemorrhage, and renal failure successively. The major cause of death in Asian countries was serious infections, accounting for 40.2% among all causes of death, significantly higher than in Europe/America ($p=0.011$). Other causes of death, in descending order, were renal failure, hemorrhage, malignant tumors, and thrombosis. No significant difference was found in proportions of deaths caused by hemorrhage, malignant tumors, and renal failure between the Western and Asian PNH populations (Yu et al 2016).

Mortality after introduction of anti-C5 antibody therapy

The introduction in 2007 of eculizumab, an anti-C5 antibody, has significantly changed the life expectancy by reducing the thromboembolic risk of patients with PNH, with some studies indicating that the short term survival of eculizumab-treated patients is comparable to age- and sex-matched general population controls (Peffault de Latour et al 2022, Kelly et al 2011). There was a relative reduction of thrombotic events of 81.8% reported during long-term follow-up of eculizumab treatment (Hillmen et al 2007, Hillmen et al 2013).

In a French registry-based comparison study between 123 patients treated with eculizumab and 191 historical controls, overall survival (OS) at 6 years was 92% (95% CI: 87-98) in the eculizumab cohort. In contrast, in historical controls diagnosed after 1985, OS at 6 years was 80% (95% CI: 70-91), and for patients diagnosed between 1954 and 1985, it was estimated at 58% (95% CI: 48-70) (Loschi et al 2016).

Under eculizumab treatment, patients with haemolytic PNH have a more favorable prognosis than patients with a more profound bone marrow failure component, such as aplastic anaemia. The reason for this difference is that eculizumab does not treat the underlying production deficit in the bone marrow (Socié et al 2016).

Disease progression and remission

One aspect of PNH natural history is its progression to MDS or AML. In a comparative analysis of PNH patients between Asia and Europe/America, Yu et al (2016) showed proportions of patients in whom PNH had progressed to MDS/AML were 4.5% and 5.7% for Asia and Europe/America, respectively (not significantly different; P-value >0.05; follow-up ranging from 72 to 101 months in different studies). However, the proportion of patients with other concomitant tumors in Asian countries (1.4%) was significantly ($p=0.018$) lower than in Europe/America (4.5%) (Yu et al 2016).

In a retrospective study of 454 PNH patients diagnosed in 58 haematological centers in France from 1950 to 2005, progression to MDS and AML was reported in 21 and 8 cases, respectively. 10-year cumulative incidence rate of MDS was 5.2% (95% CI 2.9-7.6%) and that of AML was 2.4% (95% CI 0.7-4.0%) (de Latour et al 2008). In a study comparing characteristics of PNH

patients in the United States (Duke University) and Japan, the progression to MDS/AML was recorded in 7.9% of Duke patients and in 15.8% Japanese patients (Nishimura et al 2004).

Another aspect of the pathogenesis of PNH is the unique possibility of its spontaneous remission with disappearance of PNH cell populations and abatement of clinical symptoms. This phenomenon is estimated to occur in 3-15% of patients according to the different series of PNH patients between 10 and 20 years from disease onset (Hillmen et al 1995, Korkama et al 2018a, Gurnari et al 2021). Due to the orphan nature of the condition, no clinical predictors have been identified so far for this phenomenon and recent research highlights the need for a watchful evaluation of clinically apparent PNH remissions which, in some instances, can be replaced by conditions with a potential higher risk of malignant transformation (Gurnari et al 2021).

Important co-morbidities:

Further important comorbidities in the PNH population include kidney disease and infections (Hill et al 2017).

Patients with PNH have an increased risk of chronic kidney disease as a result of long-term intravascular haemolysis (Hill et al 2017). In an abstract using data from the 2016 US National Inpatient Sample data set, prevalence of renal failure in PNH patients was 17% (Aggarwal et al 2021). Among 3,257 patients enrolled in the IPIG Registry with non-missing estimated glomerular filtration rate (eGFR) data, 79 (2.4%) had eGFR <30 mL/min/1.73 m^2 at baseline; further 410 (12.6%) had eGFR from 30 to <60 mL/min/1.73 m^2 (Schrezenmeier et al 2020).

In a retrospective study of PNH patients diagnosed in 58 haematological centers in France from 1950 to 2005, infections were reported in 69 of 453 patients (15.2%) at presentation (de Latour et al 2008) In a study comparing characteristics of PNH patients in the United States (Duke University) and Japan, infection was recorded in 24/176 (13.6%) of Duke patients and in 7/209 (3.4%) Japanese patients at baseline. During the follow-up, severe infection occurred in 18.2% of Duke patients and in 9.1% Japanese patients; furthermore, severe infection was recorded as a cause of death in 14/38 (36.8%) deaths occurring in each group (Nishimura et al 2004). In a meta-analysis by (Yu et al 2016), however, severe infection as a cause of death occurred more frequently in Asian than in Western countries (40.2% vs 25.2%, p=0.011).

Indication: Complement 3 Glomerulopathy (C3G)

Iptacopan is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with RAS inhibitors, or in patients who are intolerant or for whom a RAS inhibitor is contraindicated. C3G consists of two classes – dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) (Bomback et al 2018).

Incidence

C3G is a rare disease with an annual incidence between 1 and 2 per 1,000,000 population worldwide (Medjeral-Thomas et al 2014, Caravaca-Fontan et al 2023).

Europe

A retrospective cohort study including 115 C3G patients of all ages from 35 nephrology departments belonging to the Spanish Group for the Study of Glomerular Diseases (GLOSEN) diagnosed between 1995 and 2020 reported the annual incidence of C3G of almost 1 per 1,000,000 population (Caravaca-Fontan et al 2023).

All patients (children and adults) with kidney biopsies fulfilling criteria for C3G from two quaternary renal centers within the United Kingdom (UK) and Ireland between 1992 and 2012 were retrospectively reviewed by Medjeral-Thomas et al (2014). Sixty-one C3G patients were in the Dublin cohort and 19 in the London cohort. The annual incidence of C3G in the Dublin cohort was 2 per 1,000,000 population and 1 per 1,000,000 population in the London cohort.

USA

There were no publications on the incidence of C3G in the United States (US) but two on the incidence of membranoproliferative glomerulonephritis (MPGN). The MPGN incidence generally overestimates the C3G incidence as MPGN is an umbrella term comprising C3G and immune-complex membranoproliferative glomerulonephritis (IC-MPGN) which have undergone recent reclassification; this limits the interpretability of articles published or data accrued prior to the C3G reclassification (Pickering et al 2013). One population-based study comprising all kidney biopsies in Olmsted County in Minnesota, US reported the annual incidence of MPGN as 4 (95% confidence interval [CI] 2-7) per 1,000,000 population (Swaminathan et al 2006). Another study based on the Kaiser Permanente Southern California (KPSC) reported the annual incidence of other glomerulopathies, including MPGN, as 20 per 1,000,000 population of which MPGN represented 7.3%. Thus, the MPGN annual incidence was estimated as 1.5 per 1,000,000 population (Basis calculation: annual incidence of other glomerulopathies*proportion of MPGN among other glomerulopathies=20 per 1,000,000 population*7.3%) (Sim et al 2016).

Prevalence:

No scientific publications directly measuring the prevalence of C3G or MPGN have been identified.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

C3G is commonly diagnosed in young patients. The published median age at diagnosis ranged from 21 to 40.9 years (Proudfoot et al 2023, Mirioglu et al 2023, Caravaca-Fontan et al 2023, Medjeral-Thomas et al 2014). A Spanish study reported 24% of C3G patients being younger than 18 years at diagnosis (Caravaca-Fontan et al 2023) while a British study reported 40% of C3G patients being diagnosed at less than 16 years of age (Medjeral-Thomas et al 2014). The mean age of the C3G subforms DDD and C3GN at diagnosis ranged between 28.3 and 30.3 years and 18.9 to 40.0 years respectively (Bomback et al 2018, Servais et al 2012). There is limited information on the incidence of recurrence in C3GN and DDD. In a small subset of 13 patients who underwent kidney transplantation, the disease recurred in all 6 patients with DDD and in 4 of 7 patients with C3GN (100% and 57%, respectively) (Medjeral-Thomas et al 2014).

In other studies, comparably high rates of recurrence have been reported for C3GN (60-86%) and DDD (55-86%) (Servais et al 2012, Regunathan-Shenk et al 2019).

Important co-morbidities:

A retrospective review of adult patients diagnosed between 2006 and 2017 in the Helsinki University Hospital district, Finland, reported the proportion of the following comorbidities in 23 C3G patients at diagnosis: cardiovascular disease in 7 (30%), plasma cell dyscrasia excluding myeloma in 6 (26%), rheumatic disease in 4 (17%), malignancy in 4 (17%), diabetes in 4 (17%) and chronic infection in 3 (13%) (Kovala et al 2023). The proportion of C3G patients presenting with hypertension at diagnosis reported in observational studies ranged from 42% to 100% (Caravaca-Fontan et al 2023, Kovala et al 2023, Proudfoot et al 2023, Medjeral-Thomas et al 2014), while the proportion of C3G patients with high cholesterol was 13% (Proudfoot et al 2023).

Part II: Module SII- Non-clinical part of the safety specification

Table Part II: Module SII-1:Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Testicular effects (repeated dose toxicity studies up to 26 weeks in rats and 39 weeks in dogs) Findings of tubular degeneration in the testis and cell debris in the epididymis, associated with changes in reproductive organ weights (testis, epididymis and prostate), were consistently observed in dog toxicity studies up to 39 weeks of duration after iptacopan treatment at doses ≥30 mg/kg/day (approximately 3-fold above total AUC at clinical dose of 200 mg b.i.d.). In the rat, however, tubular degeneration in the testis was observed only at 500 mg/kg/day (approximately 5-fold above total AUC at clinical dose of 200 mg b.i.d) in the 13-week study, but not at higher doses or after 26-weeks of treatment. The microscopic findings of tubular degeneration in the testis and cell debris in the epididymis were of minimal to mild severity, did not progress in severity with longer treatment duration, and had no toxicologically relevant effect on sperm analysis (number, morphology or motility) in both species. Full recovery after a 27-week recovery period was noted in the 39-week dog study. In both species, the reversible changes in reproductive organ weight as well as trends for a subtle systemic increase in androgens, indicated compensatory hormonal responses which likely limited progression of the testicular findings. No obvious fertility issues were observed in the dedicated male rat fertility study, in the complement FB knockout mouse model (Matsumoto et al 1997, [Study 1820037]) or patients with genetic mutations in the complement AP (Skattum et al 2011). (See reproductive toxicity topic below for additional information)	Since the preclinical testicular effects were mild, fully reversible and appear to have no functional relevance (i.e., no effect on male fertility in rats or sperm parameters in dogs), the clinical relevance is considered to be low, and the potential risk is classified as 'non-important'. No AEs of clinical relevance have been reported, nor have relevant changes in reproductive hormone levels been detected in clinical studies. Nevertheless, reproductive hormone levels and testicular AEs are being monitored in ongoing iptacopan clinical studies.
Thyroid changes (repeated dose toxicity studies up to 26 weeks in rats and 39 weeks in dogs) Iptacopan treatment caused thyroid changes of follicular cell hypertrophy, correlating with increased thyroid weight and minor/transient changes in thyroid hormone levels, consistently in the rat and the dog - toxicity studies at doses ≥50 mg/kg/day after 26 weeks of treatment in the rat and at doses ≥5 mg/kg/day after 39 weeks of treatment in the dog (at total plasma exposures similar to human dose of 200 mg b.i.d.). The effects did not progress in severity with longer duration of treatment, they were fully reversible after the recovery period and not associated with adverse clinical signs of hypo- or hyperthyroidism. Detailed thyroid hormone monitoring in the rat and dog toxicity studies detected transient T3 and T4 changes, in both species, possibly underlying a subtle peripheral thyroid resistance. In vitro investigative	Since the preclinical thyroid changes were mild, fully reversible and non-symptomatic, the findings were assessed as non-adverse. Thyroid hormone monitoring was included in the clinical studies with no changes observed to date, suggesting a potential lack of translatability of those preclinical findings to humans and a low risk in patients. The potential risk is classified as 'non-important'.

Key safety findings (from non-clinical studies)	Relevance to human usage
assays indicated a potential interference with thyroid receptor signaling at very high doses/exposures.	Nevertheless, thyroid hormone levels and thyroid AEs continue to be monitored in ongoing studies (Part II: Module SVII- Identified and potential risks)
Cardiovascular effects (safety pharmacology studies, repeated dose toxicity studies in adult dogs) Minimal to slight QTc effects were observed after single dose ≥300 mg/kg (≥21-fold above total human Cmax at 200 mg b.i.d.) in a non-human primate rising dose study with jacketed telemetry, but in no other species. Dose-dependent decreases in blood pressure (BP) concurrent with a heart rate (HR) increase were observed in adult dog safety pharmacology studies at doses ≥50 mg/kg (≥8-fold above total human Cmax at 200 mg b.i.d). In repeated dose studies, the magnitude of the HR changes decreased with time at ≤150 mg/kg/day, pointing to an adaptive effect. Persistent tachycardia associated with long-term microscopic cardiac findings of focal cardiomyocyte degeneration in adult dogs was only observed at doses ≥300 mg/kg/day (~ 39-fold above total AUC at the clinical dose of 200 mg b.i.d). Tachycardia was not observed in rat or monkey.	No changes in QTc interval, heart rate or blood pressure were observed in the Phase I studies up to a 1200 mg dose. Based on safety margins, CV effects are unlikely to be observed clinically in humans at the therapeutic dose of 200 mg b.i.d.
Genotoxicity No genotoxic or mutagenic potential identified in *in vitro* Ames and *in vitro* and *in vivo* micronucleus genotoxicity studies.	Pre-clinical studies did not show evidence that treatment with iptacopan can be genotoxic to human usage.
Carcinogenicity Iptacopan did not show evidence of carcinogenicity potential in the 26-week rasH2 transgenic mouse study or in the 104-week rat carcinogenicity study at the highest dose tested, equivalent to total AUC0-24h exposures of 4.4- and 12.1-fold above human exposures at 200 mg b.i.d., respectively.	Pre-clinical studies did not show evidence that treatment with iptacopan can be carcinogenic to human usage.
Reproductive toxicity (fertility, embryo-fetal development, pre- and post-natal development studies) Potential effects on male or female reproductive organs have been assessed by standard histopathological examination of the ovaries and testes and accessory reproductive organs in the rat and dog repeated dose toxicity studies. There were no effects in female reproductive organs in these studies. Effects on male reproductive system in the repeated dose toxicity studies are described in the testicular toxicity above. In the dedicated male rat fertility study with iptacopan, no effect on mating, fertility and fecundity, no treatment-related microscopic findings in testis or epididymis and no effect in sperm analysis was noted up to the highest dose tested of 750 mg/kg/day (estimated total Area under curve (AUC)-based safety margins of ~5.7 as compared to the clinical dose of 200 mg b.i.d).	Iptacopan is not considered teratogenic, based on total AUC-safety margins >5.4 and 7.8, respectively, for the rat and rabbit embryo-fetal development (EFD) studies. The exposure to females based on the amount of semen transferred has been estimated as 20.6 ng/mL, which is 200 times lower compared to the human Cmax observed in at 200 mg b.i.d. Iptacopan is not considered to be embryotoxic, to affect embryo-fetal development or postnatal development at concentrations

Key safety findings (from non-clinical studies)	Relevance to human usage
In the female rat fertility and early embryonic development study, increased pre- and early post-implantation losses were recorded at the highest dose of 1000 mg/kg/day (~5.4-fold above human AUC-based exposure at 200 mg b.i.d). These findings are likely due to a maternally driven effect on the implantation process, as there was no embryo and fetal toxicity in the embryo fetal development studies in rat and rabbit at similar or higher exposure levels. NOAEL for fertility and early embryonic development was established at 300 mg/kg/day, with estimated total AUC-based safety margins of 2.4-fold as compared to the clinical dose of 200 mg b.i.d. Iptacopan was tested in a combined preliminary dose range finding / embryo-fetal development study in rats, as well as in a final embryo-fetal development study in rabbits. In the rat, based on the absence of clinical observations and no effect on maternal body weights, the NOAEL for dams is considered to be 1000 mg/kg/day, with total AUC-based exposure margins of 5.4, as compared to the clinical dose of 200 mg bid. In the iptacopan embryo-fetal development study in rabbits, reduced maternal body weight gain and food consumption was noted at 450 mg/kg/day. NOAEL for maternal toxicity was established at 250 mg/kg/day, with total AUC-based exposure margins of 3, as compared to the clinical dose. In the absence of any adverse fetal changes or toxicologically significant fetal abnormalities, the NOAEL for embryo fetal toxicity is 450 mg/kg/day, with total AUC-based exposure margins of 8 as compared to the clinical dose of 200 mg bid. Iptacopan was tested in a pre- and postnatal development study in pregnant rats during gestation, parturition and lactation with non-adverse findings for both parental females and off-spring development at the highest dose tested of 1000 mg/kg/day, with estimated total AUC exposure multiples of 5.4 (based on the rat plasma exposure from the rat embryo-fetal development study).	achieved in man following dosage of 200 mg bid.
Source: [Non-clinical overview], [SmPC]	

Based on the preclinical and clinical data available, testicular effects and thyroid changes were not considered relevant for inclusion in the list of safety concerns in the Risk management plan (RMP). Further details and rationale are provided in Part II: Module SVII- Identified and potential risks.

There are no important potential risks identified from non-clinical safety studies. Furthermore, there is no missing information identified in the non-clinical safety program.

Part II: Module SIII- Clinical trial exposure

Indication: Paroxysmal nocturnal haemoglobinuria (PNH)

This RMP contains safety information from the pivotal Phase III study CLNP023C12302 (APPLY-PNH), supported by the Phase III study CLNP023C12301 (APPOINT-PNH), three Phase II studies CLNP023X2201, CLNP023X2204 and CLFG316X2201, and an ongoing rollover extension Phase IIIb study, CLPN023C12001B, all in the PNH indication.

Table Part II: Module SIII-1:Overview of clinical studies providing safety data

Study, Status	Study design, population	Study duration	No. patients enrolled/ Treatment(s)
Studies in PNH indication			
CLNP023C12302 APPLY-PNH Ongoing Primary Endpoint completion date/Safety cut-off date: 26-Sep-2022	Multicenter, randomized, active-comparator controlled, open-label trial of oral, b.i.d. iptacopan in adult patients with PNH and residual anaemia despite treatment with an i.v. anti-C5 antibody	48 weeks (24 weeks randomized treatment period (completed) and 24 weeks open label iptacopan extension period)	Total: 97 N=62, iptacopan 200 mg b.i.d. in controlled period N=35, anti-C5 antibody in controlled period N=94, open label iptacopan 200 mg b.i.d. in extension period
CLNP023C12301 APPOINT-PNH Ongoing Primary endpoint completion date/ Safety cut-off date: 02-Nov-2022	Multi-center, single arm, open-label trial of oral, twice daily iptacopan in adult PNH patients naive to complement inhibitor therapy	48 weeks (24 weeks core Treatment period (completed) and 24 weeks extension treatment period)	N=40 Iptacopan 200 mg b.i.d.

Study, Status	Study design, population	Study duration	No. patients enrolled/ Treatment(s)
CLNP023X2201 Completed LPLV: 28-Feb-2022	Open-label, multiple dose study of iptacopan in addition to standard of care in patients with PNH with signs of active haemolysis	Cohort 1 Part 1: 13 weeks Part 2: extension up to 3 years Cohort 2 Part 1: 13 weeks Part 2: extension up to 3 years	N=10 Iptacopan 200 mg b.i.d.+ eculizumab N=6 Iptacopan 50 mg b.i.d.+ eculizumab with option to increase to 200mg b.i.d. from Day 15
CLNP023X2204 Completed LPLV: 09-Feb-2022	Multi-center, randomized, open-label efficacy, safety PK and PD study of iptacopan in adults patients with PNH and active haemolysis	12 weeks core and up to 2 years extension	N=13 Sequence 1 (n=7): Period 1 (4 weeks): Iptacopan 25 mg b.i.d., Period 2 (8 weeks): Iptacopan 100 mg b.i.d. Period 3 (2 years extension): maintain the same treatment regimen as used in Period 2. Sequence 2 (n=6): Period 1 (4 weeks): Iptacopan 50 mg b.i.d., (n=6) Period 2 (8 weeks): Iptacopan 200 mg b.i.d. (n=5) Period 3 (2 years extension): Iptacopan 200 mg b.i.d. (n=5)
CLFG316X2201 Completed LPLV: 24-May-2022	Open-label study in patients with PNH to assess the efficacy, safety and PK of LFG316	TP-1: 29 days TP-2: 48 weeks TP-3: 260 weeks TP-4: up to 21 weeks	TP-1 N=10 (LFG316) TP-2 N=10 (LFG316) TP-3 N=10 (LFG316) TP-4 N=9 (Week 1 to Week 4): LFG316 + Iptacopan 200 mg b.i.d.; Week 5 to Week 20: iptacopan monotherapy (200 mg b.i.d.)
CLNP023C12001B PNH REP Ongoing Safety cut-off date: 26-Sep-2022	Multi-center, open-label, roll-over extension program (REP) to characterize the long-term safety and tolerability of iptacopan in patients with PNH who have completed PNH Phase II and Phase III studies with iptacopan	At least 36 months	N=94 Iptacopan 200 mg b.i.d.

Source: [LNP023-SCS]

Clinical studies in PNH patients

The safety data of iptacopan supporting the PNH indication includes a pool of 170 PNH patients exposed to iptacopan 200 mg b.i.d. from the following studies:

- Study CLNP023C12302 (herein referred to as Study C12302 or APPLY-PNH), a randomized, active-controlled pivotal Phase III study, comparing iptacopan 200 mg b.i.d. monotherapy to anti-C5 treatment (eculizumab and ravulizumab) in 97 PNH patients with residual anaemia despite prior anti-C5 therapy. A total of 95 subjects received 200 mg b.i.d. iptacopan monotherapy, either randomized to iptacopan or switched from anti-C5 treatment after the randomized treatment period.
- Study CLNP023C12301 (herein referred to as Study C12301 or APPOINT-PNH), a single arm, open-label, Phase III study, evaluating 200 mg iptacopan b.i.d. monotherapy in 40 complement-inhibitor naive PNH patients.
- Two additional open-label Phase II PNH studies (CLNP023X2201, herein referred to as Study X2201, in anti-C5 experienced patients and CLNP023X2204, herein referred to as Study X2204, in complement-inhibitor naive patients) with a total of 26 patients who received iptacopan 200 mg b.i.d. treatment during the Phase II study and/or the PNH REP study treatment period: i) 20 patients (15 from X2201 and 5 from X2204) started iptacopan 200 mg b.i.d. during the treatment period of the Phase II studies; ii) 6 patients (1 from X2201 and 5 from X2204) who initially received lower iptacopan doses in the Phase II studies but started iptacopan 200 mg b.i.d. after entering the PNH REP study.
- Study CLNP023C12001B (herein referred to as Study C12001B or PNH REP), an ongoing roll-over extension program in patients who completed PNH Phase II and Phase III studies with iptacopan includes 94 patients (56 from Study C12302, 7 from Study C12301, 13 from Study X2201, 9 from Study X2204, and 9 from Study CLGF316X2201) up to the data cut-off on 26-Sep-2022.
- Treatment period 4 of Study CLFG316X2201, an open-label study in adult PNH patients, who were naive to complement inhibitors (or experienced at least an 8 week wash out period). In 2015, Novartis initiated clinical investigations of a terminal pathway inhibitor, LFG316 (anti-C5 monoclonal antibody) in PNH patients. The program ended for strategic reasons and 9 patients from the study were offered the option to switch to iptacopan 200 mg b.i.d. treatment and to join the PNH REP study. The safety data from these patients is included in the pooled PNH analyses for completeness.

Duration of Exposure - PNH

A breakdown of exposure to iptacopan by duration of exposure in PNH controlled studies and pooled PNH studies are shown in Table SIII.1 through Table SIII.2.

Table Part II: Module SIII-2:Duration of exposure to study drug - APPLY-PNH (controlled treatment period and pooled PNH studies (200 mg bid Safety Set)

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

Duration of exposure in months is defined as days on exposure/(365.25/12) and duration of exposure in years is days on exposure/365.25, where days on exposure is derived as (last dose date in the corresponding treatment period - first dose date + 1 - days on temporary treatment interruptions). patient-time is the sum of each patient's treatment exposure in year.
Source: [Attachment to Annex 7-Table 4-1]

The overall extent of drug exposure from the PNH studies (controlled study and pooled iptacopan 200 mg b.i.d. safety set) by age and gender is presented below.

Table Part II: Module SIII-3: Duration of exposure to study treatment by Age and Gender – PNH studies (Controlled study and 200 mg bid Safety Set)

		C12302 LNP023 200 mg bid (N=62)		C12302 Anti-C5 (N=35)		PNH pool 200 mg bid. LNP023 (N=170)	
Subgroup 1	**Subgroup 2**	**Subjects n (%)**	**Subject-time (year)**	**Subjects n (%)**	**Subject-time (year)**	**Subjects n (%)**	**Subject-time (year)**
Total	Total	62 (100)	28.6	35 (100)	16.3	170 (100)	185.1
	Age group: >= 18 <= 45 years	26 (41.9)	11.9	18 (51.4)	8.5	89 (52.4)	103.7
	Age group: > 45 < 65 years	18 (29.0)	8.3	9 (25.7)	4.2	50 (29.4)	53.2
	Age group: >= 65 years	18 (29.0)	8.3	8 (22.9)	3.7	31 (18.2)	28.2
Male	Total	19 (30.6)	8.8	11 (31.4)	5.1	72 (42.4)	84.8
	Age group: >= 18 <= 45 years	8 (12.9)	3.7	5 (14.3)	2.4	34 (20.0)	41.7
	Age group: > 45 < 65 years	8 (12.9)	3.7	5 (14.3)	2.3	31 (18.2)	35.3
	Age group: >= 65 years	3 (4.8)	1.4	1 (2.9)	0.5	7 (4.1)	7.8
Female	Total	43 (69.4)	19.8	24 (68.6)	11.2	98 (57.6)	100.4
	Age group: >= 18 <= 45 years	18 (29.0)	8.2	13 (37.1)	6.1	55 (32.4)	62.0
	Age group: > 45 < 65 years	10 (16.1)	4.6	4 (11.4)	1.9	19 (11.2)	18.0
	Age group: >= 65 years	15 (24.2)	6.9	7 (20.0)	3.3	24 (14.1)	20.4

The percentage is calculated using N as the denominator.
Subject-time in years is the sum of each subject's days on treatment exposure/365.25, where days on treatment exposure is derived as (last dose date in the corresponding treatment period - first dose date + 1 - days on temporary treatment interruptions).
Pooled PNH studies include C12302, X2201, X2204, C12301, C12001B and CLFG316X2201.
Source: [Attachment to Annex 7-Table 5.1-1]

A breakdown of exposure to iptacopan by race is shown below.

Table Part II: Module SIII-4: Duration of exposure to study treatment by race – PNH studies (Controlled study and 200 mg bid Safety Set)

	C12302 LNP023 200 mg b.i.d (N=62)		C12302 Anti-C5 (N=35)		PNH pool LNP023 200 mg b.i.d. (N=170)	
Race	**Subjects n (%)**	**Subject-time (year)**	**Subjects n (%)**	**Subject-time (year)**	**Subjects n (%)**	**Subject-time (year)**
Total	**62 (100)**	**28.6**	**35 (100)**	**16.3**	**170 (100)**	**185.1**

Race	C12302 LNP023 200 mg b.i.d (N=62)		C12302 Anti-C5 (N=35)		PNH pool LNP023 200 mg b.i.d. (N=170)	
	Subjects n (%)	Subject-time (year)	Subjects n (%)	Subject-time (year)	Subjects n (%)	Subject-time (year)
White	48 (77.4)	22.2	26 (74.3)	12.2	102 (60.0)	114.0
Black or African American	2 (3.2)	0.9	2 (5.7)	0.9	5 (2.9)	3.4
Asian	12 (19.4)	5.5	7 (20.0)	3.2	62 (36.5)	65.2
Other	0	0	0	0	1 (0.6)	2.6

Subject-time in years is the sum of each patient's days on treatment exposure/365.25, where days on treatment exposure is derived as (last dose date in the corresponding treatment period - first dose date + 1 - days on temporary treatment interruptions).
Pooled PNH studies include C12302, X2201, X2204, C12301, C12001B and CLFG316X2201
Source: [Attachment to Annex 7-Table 5.1-2]

Indication: Complement 3 Glomerulopathy (C3G)

This RMP contains safety information supporting the C3G indication from a pivotal Phase III multicenter study CLNP023B12301 (APPEAR-C3G) supported by a Phase II study CLNP023X2202, and an ongoing rollover extension Phase IIIb study CLNP023B12001B.

Table Part II: Module SIII-5: Overview of clinical studies providing safety data

Study, Status	Study design, population	Study duration	No. patients enrolled/ Treatment(s)
Studies in C3G indication			
CLNP023B12301 APPEAR-C3G Ongoing for adolescent cohort Data cut-off date: 06-May-2024 (LPLV for adult cohort)	Phase 3 multicenter, randomized, double-blind, parallel group, placebo-controlled study in participants with biopsy confirmed C3G and native kidneys	12 months: 6 months randomized treatment period* 6 months open- label iptacopan extension period*	Adults N=74: N=38, iptacopan 200 mg b.i.d. in randomized treatment period N=36, placebo in randomized treatment period N=74 in open-label iptacopan 200 mg b.i.d treatment period Adolescent participants still being enrolled
CLNP023X2202 Completed LPLV: 23-Apr-2021	Phase 2 open-label, non-randomized study on efficacy, PK, PD, safety, and tolerability of iptacopan in 2 patient populations with C3G (Cohort A: C3G; Cohort B: recurrent C3G)	Cohort A: 3 months Cohort B: 3 months	N=27 (Cohort A: n=16; Cohort B: n=11) Iptacopan 200 mg b.i.d. after a 4-week dose escalation phase on 10 mg b.i.d. (Week 1), 25 mg b.i.d. (week 2), 100 mg b.i.d. (Week 3) and 200 mg b.i.d. (Week 4 and beyond)
CLNP023B12001B C3G roll-over extension study Ongoing Data cut-off date: 06-May-2024	Phase 3b open-label, non-randomized extension study of iptacopan in C3G and IC-MPGN patients	Approximately up to 66 months planned	Currently N=92 Adolescent participants still being enrolled Iptacopan 200 mg b.i.d.

*Completed for adult cohort.
Source: [Study B12301 12-month], [Study X2202], [Attachment to Annex 7 Table 1.2-4]

Clinical studies in C3G patients

The safety data of iptacopan supporting the C3G indication includes a pool of 101 C3G and recurrent C3G patients exposed to iptacopan 200 mg b.i.d. from the following studies:

- Study CLNP023B12301 (herein referred to as Study B12301 or APPEAR-C3G), the pivotal multicenter, randomized, double-blind, parallel group, placebo-controlled Phase 3, which evaluated the safety and efficacy of iptacopan in patients with biopsy-confirmed C3G and native kidneys. Adult and adolescent patients are randomized independently.
- Study CLNP023X2202 (herein referred to as Study X2202) was an open-label, two cohort, single arm, non-randomized Phase 2 study that evaluated the efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics, and dose/biomarker relation of iptacopan in two patient populations including C3G and recurrent C3G patients.
- Study CLNP023B12001B, herein referred to as Study B12001B. Roll-over extension study B12001B is a Phase 3b, open-label, non-randomized study investigating the efficacy, pharmacokinetics, pharmacodynamics, safety, and tolerability of iptacopan in participants

with C3G (from study X2202 Cohort A N=16 and APPEAR-C3G bid treatment period N=66). Participants with recurrent C3G (from Study X2202; Cohort B, N=10), or patients with IC-MPGN (APPARENT/B12302; planned N=35). Iptacopan 200 mg b.i.d. is the only study treatment administered during this trial.

Duration of Exposure – C3G

A breakdown of exposure to iptacopan by duration of exposure to C3G controlled studies and pooled C3G studies are shown below.

Table Part II: Module SIII-6: Duration of exposure to study drug - C3G studies Controlled 200mg b.i.d Safety Set and Broad 200mg b.i.d Safety Set

	Controlled 200mg b.i.d. Safety Set		Broad 200mg b.i.d. Safety Set
	LNP023 200mg b.i.d. N=38	Placebo N=36	LNP023 200mg b.i.d. N=101
Total number of patients receiving study treatment -n (%)	38 (100)	36 (100)	101 (100)
Duration of exposure (months)			
Mean (SD)	5.69 (0.759)	5.89 (0.304)	22.39 (14.988)
Median	5.90	5.95	17.22
Q1-Q3	5.72-6.05	5.82-6.00	12.19-27.04
Min-Max	2.76-6.37	4.86-6.60	2.66-57.26
Duration of exposure categories -n (%)			
>= 1 day	38 (100)	36 (100)	101 (100)
>= 7 day	38 (100)	36 (100)	101 (100)
>= 1 month	38 (100)	36 (100)	101 (100)
>= 3 months	36 (94.7)	36 (100)	100 (99.0)
>= 6 months	13 (34.2)	9 (25.0)	95 (94.1)
>= 9 months	0	0	89 (88.1)
>= 12 months	0	0	78 (77.2)
>= 18 months	0	0	44 (43.6)
>= 24 months	0	0	31 (30.7)
>= 30 months	0	0	21 (20.8)
>= 36 months	0	0	20 (19.8)
>= 4 years	0	0	12 (11.9)
>= 5 years	0	0	0
Patient-time (years)	18.0	17.7	188.5

	Controlled 200mg b.i.d. Safety Set		Broad 200mg b.i.d. Safety Set
	LNP023 200mg b.i.d. N=38	Placebo N=36	LNP023 200mg b.i.d. N=101

Duration of exposure in months is defined as days on exposure/(365.25/12) and duration of exposure in years is days on exposure/365.25, where days on exposure is derived as (last dose date in the corresponding treatment period -first dose date+1-days on temporary treatment interruptions).

Patient-time is the sum of each patient's treatment exposure in years.

Includes data from Studies CLNP023B12301, CLNP023X2202, and CLNP023B12001B

Source: [Attachment to Annex 7-Table 1.2-2]

The overall extent of drug exposure from the C3G studies (controlled 200mg b.i.d. safety set and broad 200mg b.i.d. safety set) by age and gender is presented below.

Table Part II: Module SIII-7: Duration of exposure to study treatment by age and sex - C3G studies Controlled 200mg b.i.d. Safety Set and Broad 200mg b.i.d. Safety Set

		Controlled 200mg b.i.d. Safety Set				Broad 200mg b.i.d. Safety Set	
		LNP023 200mg b.i.d. N=38		Placebo N=36		LNP023 200mg b.i.d. N=101	
Sex	Age	Patients n (%)	Patient-time (year)	Patients n (%)	Patient-time (year)	Patients n (%)	Patient-time (year)
Total	Total	38 (100)	18.0	36 (100)	17.7	101 (100)	188.5
	>= 18 <= 45 years	34 (89.5)	16.1	31 (86.1)	15.3	89 (88.1)	163.8
	> 45 < 65 years	4 (10.5)	2.0	5 (13.9)	2.4	10 (9.9)	16.0
	>= 65 years	0	0	0	0	2 (2.0)	8.6
Male	Total	27 (71.1)	12.9	20 (55.6)	9.9	65 (64.4)	134.1
	>= 18 <= 45 years	23 (60.5)	10.9	17 (47.2)	8.4	55 (54.5)	110.6
	> 45 < 65 years	4 (10.5)	2.0	3 (8.3)	1.5	8 (7.9)	15.0
	>= 65 years	0	0	0	0	2 (2.0)	8.6
Female	Total	11 (28.9)	5.1	16 (44.4)	7.8	36 (35.6)	54.3
	>= 18 <= 45 years	11 (28.9)	5.1	14 (38.9)	6.9	34 (33.7)	53.2
	> 45 < 65 years	0	0	2 (5.6)	0.9	2 (2.0)	1.1

The percentage is calculated using N as the denominator.
Patient-time in years is the sum of each patient's days on treatment exposure/365.25, where days on treatment exposure is derived as (last dose date in the corresponding treatment period -first dose date+1-days on temporary treatment interruptions).
Source: [Attachment to Annex 7-Table 5.1-1]

A breakdown of exposure to iptacopan by race is shown below.

Table Part II: Module SIII-8: Duration of exposure to study treatment by race - C3G studies Controlled 200mg b.i.d. Safety Set and Broad 200mg b.i.d. Safety Set

	Controlled 200mg b.i.d. Safety Set				Broad 200mg b.i.d. Safety Set	
	LNP023 200mg b.i.d. N=38		Placebo N=36		LNP023 200mg b.i.d. N=101	
Race	Patients n (%)	Patient-time (year)	Patients n (%)	Patient-time (year)	Patients n (%)	Patient-time (year)
Total	38 (100)	18.0	36 (100)	17.7	101 (100)	188.5
White	27 (71.1)	13.5	24 (66.7)	11.8	76 (75.2)	162.4
Black or African American	1 (2.6)	0.2	1 (2.8)	0.5	3 (3.0)	2.2
Asian	9 (23.7)	3.8	9 (25.0)	4.4	18 (17.8)	19.1
Other	1 (2.6)	0.5	2 (5.6)	1.0	4 (4.0)	4.8

Patient-time in years is the sum of each patient's days on treatment exposure/365.25, where days on treatment exposure is derived as (last dose date in the corresponding treatment period -first dose date+1-days on temporary treatment interruptions).

Source: [Attachment to Annex 7-Table 5.1-2]

Part II: Module SIV- Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table Part II: Module SIV-1: Important exclusion criteria in pivotal clinical studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar chemical classes	Prevention of hypersensitivity reactions.	No	Hypersensitivity is a contraindication therefore such patients are not expected to receive iptacopan.
Active systemic bacterial, viral (including COVID-19) or fungal infection 14 days prior to study drug administration. Presence of fever ≥38°C (100.4°F) within	Due to the mechanism of action of iptacopan, blocking FB and thereby the alternative pathway, immunological responses to infections, in particular caused by encapsulated bacteria, may be decreased. This may	No	Unresolved serious infection caused by encapsulated bacteria, is a contraindication therefore such patients are not expected to receive iptacopan. For other infections, data in the clinical program to

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
7 days prior to study drug administration	change the course of active infections.		date have shown no worsening or increased frequency in the presence of iptacopan.
A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus	Patients with inherited complement deficiencies experience recurrent infections caused by encapsulated bacteria. These patients would confound efficacy and safety data. In addition, patients with a history of recurrent invasive infections caused by encapsulated bacteria are at greater risk of infection on iptacopan.	No	It is not anticipated that these patients will be treated with a complement inhibitor due to increased risk of infections.
Concomitant use of immunosuppressants or systemic corticosteroids given for haematological conditions, unless on stable regimen	To avoid increased risk of infections.	No	Some patients in PNH studies were receiving immunosuppressants (5-10%) and so there will be some data on safety in these patients. Also, kidney transplant patients were included in Phase II C3G studies, providing further data on the risk of infections in patients taking concomitant systemic immunosuppressants.
Pregnant women, nursing mothers, or women of child-bearing potential not using appropriate contraception	In animal reproduction studies, no evidence of fetal harm from iptacopan was observed. However, there are limited data in humans.	Yes	Not applicable.

SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Given the rare nature of PNH and C3G, the clinical development program included 170 PNH patients and 101 C3G patients. It is therefore unlikely to detect certain types of adverse reactions

such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure [LNP023 SCS-Table 1.2-2].

SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table Part II: Module SIV-2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program for PNH and C3G studies, although there were 2 patients on iptacopan who became pregnant in the APPLY-PNH study, both patients discontinued treatment.
Women who are breastfeeding	Not included in the clinical development program for PNH and C3G studies.
Pediatric patients	Not yet included in the clinical development program for PNH studies. For the pivotal C3G study (CLNP023B12301, APPEAR), adolescent patients (aged 12-17 years) are being enrolled in a separate cohort.
Patients with relevant comorbidities: • Patients with hepatic impairment	A clinical pharmacology study (CLNP023A2105) has examined the pharmacokinetics of iptacopan in patients with mild (n=8), moderate (n=8) and severe (n=6) hepatic impairment. No dose adjustment is required patients with mild or moderate impairment. The use of iptacopan is not recommended in patients with severe hepatic impairment (Child-Pugh class C).
• Patients with renal impairment	The kidney is not a major route of elimination for iptacopan or its metabolites, hence patients with renal impairment are not expected to have any adjustments to the dose of iptacopan. Iptacopan is being studied in a number of renal indications, including IgA nephropathy and C3 glomerulopathy, which will provide data on patients with renal impairment. In the ongoing IgA nephropathy Phase 3 study (CLNP023A2301), there is a specific cohort of patients with severe renal impairment. No dose adjustment is required in patients with mild (eGFR between 60 and <90 mL/min) or moderate (eGFR 30 and <60 mL/min) renal impairment. No data are currently available in patients with severe renal impairment or on dialysis and no dose recommendation can be given.
• Patients with cardiovascular impairment	Patients with severe advanced cardiac disease (e.g., NYHA class IV heart failure) are not included in the iptacopan clinical program if the investigator considers that it will interfere with their study participation. However, some patients with PNH have been included with cardiovascular medical history.
Immunocompromised patients	Some patients with PNH have been included in the studies whilst taking stable immunosuppressants e.g. for pre-existing aplastic

	anaemia and for haematological malignancies such as myelodysplastic syndrome, for which PNH is a risk factor. No dose adjustments are required in immunocompromised patients.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	In study LFG316X2201, six patients, who had a polymorphism that confers resistance to eculizumab (Acid exchange (Arg885His) in the C5 protein) were included. All six patients were treated with iptacopan in Part 4 of the study.
Source: [SmPC], [LNP023-SCS]	

Part II: Module SV- Post-authorization experience

SV.1 Post-authorization exposure

First worldwide approval for iptacopan was obtained in the US on 05-Dec-2023 (international birthdate). Post-marketing safety data will be discussed in the forthcoming Periodic Safety Update Reports (PSUR), starting with the first PSUR with a DLP of 05-Jun-2024.

Part II: Module SVI- Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the nature of the drug, and the mode of action, no recreational or abuse potential has been identified for iptacopan.

Part II: Module SVII- Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Table Part II: Module SVII-1: Risks not considered important for inclusion in the list of safety concerns

Risk	Reason for not including as a safety concern in the RMP: Other reasons for considering the risks not important
Testicular effects	The preclinical effects seen were mild, fully reversible and non-functional (no effect on male fertility in rats or sperm morphology, motility or numbers in dogs). There have been no clinically relevant AEs or trends in changes from baseline in reproductive hormone levels in clinical trials to date and therefore no evidence of testicular effects (Key safety findings from non-clinical studies and relevance to human usage).
Thyroid changes	Based on the mild nature of the effect seen in preclinical studies, and the fact that no symptoms were reported in the preclinical studies, such that the effects were considered 'non-adverse'. There have been no trends in changes from baseline for any of the thyroid hormone levels monitored in clinical trials to date and no clinically relevant adverse events.

Both of the risks above will be followed up via routine pharmacovigilance activities. Specific statements are proposed in the preclinical safety section of the label, and no additional pharmacovigilance or risk minimization activities are deemed necessary.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table Part II: Module SVII-2: Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Infections caused by encapsulated bacteria	Iptacopan binds to complement FB and inhibits the alternative complement pathway, which is an important part of the innate immune system. As such, complement inhibition by iptacopan (as for other complement inhibitors) may expose treated patients to a higher risk of infections caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*. As of the data lock point (DLP, 02-Nov-2022) of the first RMP (v1.0), 170 patients with PNH were included in a pool of patients exposed to iptacopan 200 mg bid and 2 patients experienced serious bacterial lobar pneumonia, which was likely to have been caused by encapsulated

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	bacteria. Both patients were treated with antibiotics and recovered whilst continuing on iptacopan treatment. Infections caused by these bacteria can be life-threatening and require emergency care. The clinical significance and the potential for life-threatening outcome, the established mechanism of the risk, as well as the serious infection cases observed in iptacopan clinical studies and attributed to iptacopan based on medical evidence of causality justify the classification of this safety topic as an important identified risk.

Table Part II: Module SVII-3: Important potential risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Serious haemolysis following discontinuation of iptacopan (PNH indication)	Treatment with complement inhibitors, including iptacopan, increases the proportion of PNH-type RBCs (Risitano et al 2021). Although a large RBC clone size per se does not increase the risk of haemolysis, if haemolysis occurs it could be more severe in patients with a large PNH RBC clone size (Peffault de Latour et all 2022). As with other complement inhibitors, discontinuation of iptacopan treatment leaves PNH RBCs unprotected against complement-mediated haemolysis, which may be severe or serious. Serious haemolysis following discontinuation of iptacopan may be life-threatening or result in significant disability if not prevented or managed appropriately. As of the DLP (02-Nov-2022) of this RMP, there has been no AE report of haemolysis following temporary or permanent discontinuation of iptacopan. Based on the absence of relevant cases in clinical studies conducted to date, but considering the possible clinical significance, this risk is classified as an important potential risk for iptacopan in PNH patients.
Malignancies	Literature on the role of complement system on tumor development is inconclusive, suggesting both tumor promotion and inhibition (Revel et al 2020). There is some evidence that alternative pathway Factor B levels are increased in the presence of squamous cell carcinoma (SCC) and enhance migration and proliferation of SCC cells (Riihila et al 2017). Thus, the effect of FB inhibition by iptacopan on tumor pathogenesis is unclear. Malignancies are life-threatening conditions which require medical treatment and significantly impair the patient's quality of life. As of the DLP (02-Nov-2022) of this RMP, there have been 6 patients with malignancies in the pool of 170 patients with PNH exposed to iptacopan 200 mg bid. One case was suspected to be related to iptacopan treatment (lymphoproliferative disorder). Iptacopan preclinical carcinogenicity studies did not show carcinogenic potential. Nevertheless, previous experience with other complement inhibitors suggests a possible class effect, so that a potential risk cannot be ruled out. Considering the overall conflicting evidence, malignancies is classified as an important potential risk.

Table Part II: Module SVII-4: Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Use in pregnant patients	Pregnancy in a patient with PNH is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, as well as adverse fetal outcomes, including fetal death and premature delivery (Panse 2023). PNH can affect any age group including young adults who may want to start a family (Gulbis et al 2010, Yu et al 2016, Hill et al 2017). PNH is estimated to affect males and females equally (de Latour et al 2008, Socié et al 2016). In preclinical studies iptacopan was not genotoxic, mutagenic or teratogenic and there was no evidence of embryotoxicity in preclinical embryofetal toxicity studies (Part II: Module SII- Non-clinical part of the safety specification). Therefore, it is considered unlikely for iptacopan to have an adverse effect on a pregnancy. Due to limited exposure of pregnant patients during clinical trials, the risk due to treatment with iptacopan cannot be assessed, therefore, this topic is classified as missing information.
Long-term safety (>2 years)	PNH requires life-long treatment with iptacopan. The number of subjects in clinical studies who received iptacopan for >2 years is limited and therefore, safety data beyond this duration is limited. Iptacopan demonstrated a well-tolerated and favorable safety profile in the clinical development program so far, however it cannot be excluded that unexpected and unforeseen adverse reactions occur or known adverse drug reactions (ADRs) occur in a more severe form, with prolonged treatment. Limited long-term safety information is available for iptacopan, therefore this topic is classified as "missing information".

SVII.2: New safety concerns and reclassification with a submission of an updated RMP

This is an updated RMP to include the indication C3G, no new safety concerns were identified.

SVII.3: Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Infections caused by encapsulated bacteria

Table Part II: Module SVII-5: Important identified risk: Infections caused by encapsulated bacteria: Other details

Infections caused by encapsulated bacteria	Details
Potential mechanisms	Iptacopan is an inhibitor of Factor B, a key component of the complement alternative pathway. Complement plays a role in host defense against infections, particularly infections caused by encapsulated bacteria, such as *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae*.
Evidence sources and strength of evidence	Individuals with deficiencies in Factor B have an increased risk of infections caused by encapsulated bacteria (*N. meningitidis* and *S. pneumoniae*) (Slade et al 2013, Gauthier et al 2021) and activation of the alternative complement pathway has been shown to be one of the innate immune defense mechanisms against pneumococcal infection during the early stage of acute otitis media in a mouse model (Li et al 2011). The membrane attack complex (MAC) plays a role in host defense against infections caused by *N. meningitidis* and patients who are deficient in C5, a terminal component of the complement pathways, experience recurrent infections caused by *N. meningitidis. In vitro* research has shown that the serological response to meningococcal infection (serum bactericidal activity) is markedly reduced after blockade of the terminal pathway with anti-C5 therapies such as eculizumab, which dramatically increases the risk of meningococcal infections in patients treated with C5 inhibitors (Soliris USPI 2020, Ultomiris USPI 2022), but is largely maintained during AP blockade (Konar and Granoff 2017, Ispasanie et al 2021). C5 inhibitors have no effect, however, on complement-mediated host defense against *S. pneumoniae* (opsonophagocytosis) since it occurs earlier in the complement pathway. C3 inhibitors, such as the recently approved pegcetacoplan, have been shown to have an effect on opsonophagocytosis against pneumococci *in vitro*, consistent with the types of infections observed in C3-deficient patients. The effect was greater than that seen with more selective inhibitors of Factor D or Factor B (Muri et al 2021). Infections caused, or likely to have been caused, by encapsulated bacteria have been observed in clinical studies in patients treated with iptacopan.
Characterization of the risk:	Infections caused by encapsulated bacteria can range from non-serious respiratory tract infections to serious, and potentially fatal, pneumonia, sepsis and meningitis infections. To characterize this risk for iptacopan, a MedDRA grouping was defined to identify infections that were, or were likely to have been, caused by encapsulated bacteria. This grouping conservatively includes infections

Infections caused by encapsulated bacteria	Details
	such as erysipelas, furuncle, otitis media and pneumonia bacterial that are usually caused by encapsulated bacteria, but where the causative organism has not been confirmed. In addition to the MedDRA grouping search, all serious and severe AEs that occurred in the SOC Infections and infestations and in the HLGT Microbiology and serology investigations were manually assessed for information that could potentially indicate an encapsulated bacteria as the causative organism. **PNH studies** Infections caused by, or likely to be caused by, encapsulated bacteria occurred in 7 (4.1%) of patients treated with iptacopan 200 mg b.i.d. in the PNH clinical development program and included non-serious reports of: bronchitis caused by *H. Influenzae* (mild severity), erysipelas, furuncle, otitis media (all reported as not suspected to be related to iptacopan) and staphylococcal skin infection (reported as suspected to be related to iptacopan). The most common pathogens in these infections are Group A streptococci, *Staphylococcus aureus, S. pneumoniae* and *H. influenzae,* which are encapsulated bacteria. None of these infections was reported in more than one patient. Two cases reported in the 170 patients (185.5 patient-years) in the pool of patients with PNH treated with 200 mg b.i.d., both bacterial lobar pneumonia, were serious and considered likely to have been caused by encapsulated bacteria since the most frequent causative organisms in this infection are *S. pneumoniae* or *H. influenzae.* Both patients were fully vaccinated as per protocol and fully recovered upon treatment with antibiotics, whilst continuing treatment with iptacopan. **C3G Studies** Across the Controlled safety set and Broad safety set, there were, in total, 10patients on iptacopan and 1 patient on placebo with infections caused by encapsulated bacteria [Attachment to Annex 7 Table 2.1-14], [Attachment to Annex 7 Listing 1.4-1]. Non-serious infections included otitis media in five patients, acute otitis media and cellulitis in one patient each that resolved with antibiotics; all except one episode of otitis media were not suspected to be related to iptacopan. Although the organism was not confirmed, the common pathogens in these infections include Group *A.* streptococci, *Staphylococcus aureus, S. pneumoniae* and *H. influenzae* that are encapsulated bacteria. Serious infections included pneumonia pneumococcal and pneumococcal sepsis in 1 case and an episode of blood culture positive for *S. pneumoniae* in the same patient, and pneumonia pneumococcal (serotype 24F not covered by vaccines) in another patient on triple immunosuppressants. All three infections were confirmed to be caused by encapsulated bacterium *S. pneumoniae* and were suspected to be related to iptacopan; infections resolved with antibiotics and iptacopan interruption; both patients were vaccinated as per protocol. Another serious infection reported was intervertebral discitis caused by *Streptococcus gallolyticus* in a patient on broad immunosuppression to prevent transplant rejection, which was not

Infections caused by encapsulated bacteria	Details
	suspected to be related to iptacopan by the investigator and resolved with antibiotics. Notably, no cases of meningococcal infection were reported across all PNH and C3G studies.
Risk factors and risk groups	Risk factors for infection include history of immunodeficiency diseases, history of recurrent infections, patients with diabetes, transplant patients, elderly patients and children. Other risk factors include: • Unvaccinated or incompletely vaccinated patients. • Patients with PNH-associated bone marrow failure (including aplastic anaemia PNH, myelodysplastic syndrome), due to neutropenia. • Immunosuppressive treatment (e.g., high-dose steroids, mycophenolate mofetil, cyclosporine, tacrolimus, B-cell depleting agents). • Individuals exposed to certain bacteria through work or travel. • Chronic kidney disease. Potential risk factors for infection among patients with CKD include hypoalbuminemia, immunosuppressive therapy, presence of central vascular access (for plasma exchange, hemodialysis), nephrotic syndrome, uremia, anaemia, and malnutrition.
Preventability	Vaccination is predicted to be an effective mitigation strategy to reduce the risk for individuals treated with iptacopan. Patients treated with iptacopan must be vaccinated against meningococcal and pneumococcal infections and are recommended to also be vaccinated against *H. influenzae* infections, according to local availabilities. In addition, patients should be monitored for signs and symptoms of infection. Information on signs and symptoms to look for and actions to take (immediate administration of antibiotics) will be provided to patients/caregivers and physicians through a patient safety card. Refer to Part V.2. Additional Risk minimization measures for additional risk minimization measures.
Impact on the benefit-risk balance of the product	The impact of infections caused by encapsulated bacteria on an individual patient can be life-threatening and require emergency care. This safety concern has a high impact on the benefit-risk balance of iptacopan. However, taking into account the risk minimization measures in place for this risk, the low frequency, the nature and course of the infections observed in the clinical trials, and that this is a therapeutic-class risk also applicable to other complement inhibitors, the benefit-risk balance is positive for iptacopan in the treatment of PNH and C3G.
Public health impact	The infections may be serious or fatal. In addition, majority of infections are contagious by definition and so an increased incidence of infection may have an impact on public health. However, given the low prevalence of PNH and C3G in the overall population and the relatively low frequency of infections observed in iptacopan treated population the expected public health impact is very low.

Important potential risk: Serious haemolysis following discontinuation of iptacopan (PNH indication)

Table Part II: Module SVII-6: Important potential risk: Serious haemolysis following discontinuation of iptacopan (PNH indication): Other details

Serious haemolysis following discontinuation of iptacopan (PNH indication)	Details
Potential mechanisms	Treatment with complement inhibitors, including iptacopan, increases the proportion of PNH-type RBCs (Risitano 2021; Peffault de Latour et al 2022). Although a large RBC clone size per se does not increase the risk of haemolysis, if haemolysis occurred it could be more severe in patients with a large PNH RBC clone size (Peffault de Latour et al 2022). As with other complement inhibitors, discontinuation of iptacopan treatment leaves PNH RBCs unprotected against complement-mediated haemolysis, increasing the risk of haemolysis, which may be severe or serious.
Evidence source and strength of evidence	This potential risk is a theoretical possibility in patients with PNH treated with complement inhibitors, based on the mode of action and nature of PNH. Haemolytic events are of noteworthy concern in patients with PNH who are receiving treatment with complement inhibitors which decrease both intravascular haemolysis (IVH) and extravascular haemolysis (EVH), owing to the potential for increased RBC clone size (Peffault de Latour et al 2022, Risitano 2021) and subsequent serious haemolysis. Haemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed (Aspaveli SmPC). No adverse events of serious haemolysis following discontinuation of iptacopan were observed in the PNH clinical studies.
Characterization of the risk:	Very few patients with PNH discontinued iptacopan, with only one patient in the controlled period of APPLY-PNH, one patient in the open-label extension of APPLY-PNH and one patient in the rollover extension program (REP) discontinuing. Of these three patients, two discontinued due to pregnancy and one due to physician's decision. In all three patients, a decrease of hemoglobin level (Hb) (≥ 2 g/dL) was seen without marked increases in lactate dehydrogenase (LDH) after iptacopan discontinuation, however, there were no AEs of haemolysis or thrombosis reported in these patients post-discontinuation. All patients were switched back to anti-C5 treatment, and one patient received RBC transfusions.
Risk factors and risk groups	Patients with PNH treated with complement inhibitors which decrease both IVH and EVH are at increased risk of serious haemolysis if treatment is discontinued, temporarily or permanently, due to increased PNH RBC clone size. In particular, patients who have not been established on an effective alternative therapy at the time of discontinuation are at higher risk for intravascular haemolysis (IVH) after drug discontinuation.
Preventability	Prevention of haemolysis involves ensuring a high level of adherence to the dosing schedule.

Serious haemolysis following discontinuation of iptacopan (PNH indication)	**Details**
	If permanent discontinuation of therapy is required, close monitoring of signs of haemolysis can be managed by assessing LDH, haemoglobin, serum creatinine etc. and treating with either an alternative complement inhibitor or packed RBCs should be considered.
Impact on the benefit-risk balance of the product	The impact of serious haemolysis on the individual patient is potentially life-threatening. However, taking into account the risk minimization measures in place for this risk, and the absence of observed cases of serious haemolysis upon discontinuation in the clinical trials, the benefit-risk balance is positive for iptacopan for the treatment of PNH.
Public health impact	The effects will be limited to the affected individual. Therefore, there is no impact on public health.

Important potential risk: Malignancies

Table Part II: Module SVII-7: Important potential risk: Malignancies: Other details

Malignancies	Details
Potential mechanisms	Complement Factor B (FB) has been found to have potential for tumor promoting role in some type of cancers, associated with tumorigenesis, inflammation or up-regulation of FB mRNA expression (Lee et al 2021, Shimazaki et al 2021, Rihilla et al 2017), suggesting that inhibition of Factor B would be beneficial. However, in general, the effect of complement on the mechanisms at the basis of cancer development or promotion is unclear and it is suggested that complement can be pro- or anti-tumoral (Mamidi et al 2017, Bareke, Akbuga 2018, Macor et al 2018) depending on the cancer type and different models present opposite effects for the same type of cancer (Revel et al 2020). Due to their effect of immunosuppression, malignancies could potentially be a class effect of complement inhibitors.
Evidence source and strength of evidence	Previous experience with other complement inhibitors (Ultomiris EPAR assessment report, Aspaveli EPAR assessment report), suggests a possible class effect for these drugs. However, there is inconclusive literature evidence, with publications both suggesting tumor promotion and tumor inhibition by complement components (Revel et al 2020). Malignancies were observed in some patients with PNH treated with iptacopan 200 mg bid, however, most of these had relevant confounding conditions at study entry. Comprehensive preclinical carcinogenicity studies on iptacopan were negative.
Characterization of the risk:	To characterize this risk for iptacopan, a MedDRA grouping (SMQ Malignant or unspecified tumors) was used to identify all haematological or non-haematological malignancies reported in patients treated with iptacopan 200 mg bid. **PNH Studies** Overall, 6/170 (3.5%) patients experienced 7 malignancy events during treatment with iptacopan 200 mg bid, of which 1 was suspected to be related to iptacopan (lymphoproliferative disorder) by the investigator and 5 had confounders at study entry. Events were severe in 4 patients and of moderate and mild severity in the remaining two patients. The outcome of the malignancies was fatal in two out of six patients. In addition, one patient died after the DLP (02-Nov-2022) of the RMP. The remaining patients fully recovered (2) or recovered with sequelae (1). There was variability in types of cancer reported (with 2 patients having basal cell carcinoma, 1 squamous cell carcinoma, 1 lymphoproliferative disorder, 1 bladder cancer and 1 colon cancer). **C3G Studies** There were no malignancies reported in C3G studies with 101 patients exposed to iptacopan 200mg b.i.d for 188.5 patient-years [Attachment to Annex 7-Table 7.2].
Risk factors and risk groups	There is some evidence suggesting that patients with PNH may be more prone to develop tumors, with a prevalence of malignancies (other than MDS/AML) ranging from 2.2% - 14.2% (Yu et al 2016, Muñoz-Linares et al 2014).

Malignancies	Details
	As per general (non-treated) patient population, older patients or patients with pre-cancerous conditions are risk groups. Patients on immunosuppressants and in particular transplant recipients, as is the case for recurrent C3G patients, are at increased risk of malignancies (Au E et al 2018). Additionally, incidence rate of cancer is relatively higher in CKD patients than in the general population (Lees et al 2023).
Preventability	Unknown
Impact on the benefit-risk balance of the product	The impact of the occurrence of malignancies on the individual patient is potentially life-threatening. This risk requires medical treatment and significantly impairs the patient's quality of life. However, given the lack of sufficient evidence for iptacopan in association with an increased risk of malignancy as opposed to the highly efficacious treatment effect on PNH and C3G demonstrated in clinical trials, the benefit-risk balance is positive for iptacopan for the treatment of PNH and C3G.
Public health impact	The effects will be limited to the affected individual. Therefore, there is no impact on public health.

SVII.3.2. Presentation of the missing information

Table Part II: Module SVII-8: Missing information: Use in pregnant patients

Use in pregnant patients	Details
Evidence source	There are currently limited data on the use of iptacopan in pregnant patients.
Anticipated risk/consequence of the missing information	Preclinical studies have shown that iptacopan is not genotoxic, mutagenic or teratogenic and there was no evidence of embryotoxicity in preclinical embryofetal toxicity studies (Part II: Module SII- Non-clinical part of the safety specification). Therefore, it is considered unlikely for iptacopan to have an adverse effect on pregnancy. Prior to availability of complement inhibitor therapies for PNH, many pregnancies failed and were characterized with high maternal morbidity and mortality (de Guibert et al 2011, Higgins et al 2004). Recent observational data suggests that the proportion of successful pregnancies may be higher and maternal mortality and morbidity may be lower when the patient is taking a complement inhibitor, such as eculizumab (Kelly et al 2015). Diagnosis of C3G in pregnant women may be associated with adverse maternal and fetal outcomes (Fergus et al 2021). Collection of information on the use of iptacopan in pregnancy and the pregnancy outcomes is planned to help inform the patients and healthcare providers.

Table Part II: Module SVII-9: Missing information: Long-term safety (>2 years)

Long term safety >2 years	Details
Evidence source	PNH and C3G require life-long treatment with iptacopan, with limited knowledge on long-term safety concerns. The number of patients in iptacopan clinical studies who received iptacopan for >2 years is limited.

Long term safety >2 years	**Details**
Anticipated risk/consequence of the missing information	Iptacopan treatment of PNH and C3G is anticipated to be long term and therefore it is important to determine whether there are new safety findings, or known safety findings which worsen in severity, after long-term treatment. Long-term safety data will continue to be collected in the roll-over extension programs and IPIG Registry (PNH indication only).

Part II: Module SVIII- Summary of the safety concerns

Table Part II: Module SVIII-1:Summary of safety concerns

Important identified risks	• Infections caused by encapsulated bacteria
Important potential risks	• Serious haemolysis following discontinuation of iptacopan (PNH indication) • Malignancies
Missing information	• Use in pregnant patients • Long-term safety (>2 years)

Part III: Pharmacovigilance plan (including post-authorization safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

None

Other forms of routine pharmacovigilance activities:

None

III.2. Additional pharmacovigilance activities

Study CLNP023C12001B – Roll-over Extension Program for patients with PNH in Phase II and Phase III studies

Study short name and title: CLNP023C12001B, long-term safety and tolerability of iptacopan in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH).

Rationale and study objectives: 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.

To collect data to help further characterize and/or closely monitor each of the respective safety concerns:

- Infections caused by encapsulated bacteria
- Serious haemolysis following discontinuation of iptacopan
- Malignancies
- Long-term safety (>2 years)

Study design: this study is an open-label, single arm, multicenter, roll-over extension study which enrolls patients with PNH who have completed the treatment extension period of the Novartis-sponsored Phase II or III studies with iptacopan.

Study population: the study will enroll patients who have been diagnosed with PNH and have completed the treatment extension period of Phase II or Phase III iptacopan studies.

Up to 250 study participants will be enrolled in the study.

Milestones:
Final study report: 31-May-2029

Study CLNP023C12003 – Post-Authorization Safety Study of iptacopan treated patients with PNH, using data from the IPIG Registry

Study short name and title: PASS in iptacopan-treated patients using IPIG Registry data.

Rationale and study objectives: The purpose of this study is to characterize 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 effectiveness of additional risk minimization 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 Interest Group (IPIG) Registry (IPIG Registry). The aim of the IPIG 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 utilization on all enrolled patients, as well as long term safety data. According to the IPIG 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 IPIG Registry) will thus be a single-arm study with no internal comparator.

Study design: This post-authorization safety study (PASS) CLNP023C12003 is an observational single-arm descriptive cohort study based on the secondary use of data collected on iptacopan-treated patients through the IPIG Registry.

The primary objective of the proposed PASS is to describe the frequency, incidence rate and occurrence rate of infections due to encapsulated bacteria in patients with PNH treated with iptacopan.

The secondary objectives of the PASS are to describe the frequency, incidence and occurrence rate of serious infections, haemolysis-related events, major adverse vascular events (MAVEs), haematological malignancies, solid tumors and other serious adverse events (SAEs) in patients with PNH treated with iptacopan. In addition, the study aims to describe the proportion of iptacopan-treated PNH patients not compliant with mandatory and recommended vaccinations against encapsulated bacteria, the characteristics of pregnancies exposed to iptacopan and frequency of selected pregnancy outcomes.

Study population: Patients with PNH confirmed by flow cytometry and who meet the inclusion/exclusion criteria will be invited to participate in the IPIG Registry. All patients with PNH will be eligible for IPIG Registry, regardless of whether they are receiving PNH-specific therapy and regardless of what type of therapy they are receiving. According to the IPIG Registry protocol, Novartis will only have access to the data from PNH patients treated with iptacopan. The proposed PASS will thus only analyze data from adult PNH patients treated with iptacopan that are enrolled in the IPIG Registry, with no internal comparator.

Milestones:

Interim study reports: to be provided annually with the PSUR

Final study report: 31-Mar-2030

Study CLNP023B12001B - An open-label, non-randomized extension study to evaluate the long-term efficacy, safety and tolerability of iptacopan (LNP023) in C3 glomerulopathy or idiopathic immune complex- membranoproliferative glomerulonephritis

Study short name and title: Long-term efficacy, safety and tolerability of iptacopan in C3G or IC-MPGN

Rationale and study objectives: The primary purpose of this extension study is to collect and evaluate long-term efficacy, safety and tolerability data in eligible participants receiving open-label iptacopan (LNP023) after completing treatment in the C3G Phase 2 proof of concept (PoC) study CLNP023X2202, C3G Phase 3 study CLNP023B12301 or IC-MPGN Phase 3 study CLNP023B12302. Efficacy and safety assessments at the 9-month visit of this extension study in combination with data from CLNP023X2202 (baseline plus 3 months of treatment) allowed evaluation of the effects of iptacopan on primary endpoint(s) at 12 months (3months in X2202 + 9 months in B12001B) of iptacopan treatment in C3G participants. The enrollment of C3G and IC-MPGN participants (adults and adolescents) from Phase 3 studies CLNP023B12301 and CLNP023B12302 permits long-term evaluation of the persistence of effects observed after iptacopan treatment up to 36 months. Planned maximum duration of exposure is 36 months. These longer-term efficacy and safety assessments may be used as supportive information for registration purposes.

Participants enrolling from study CLNP023X2202

- Primary Efficacy Objective (Cohort A - C3G): To assess the effect of iptacopan on a 3-component composite renal endpoint in C3G participants at the 9-month visit
- Primary Efficacy Objective (Cohort B - transplanted kidney with recurrent C3G): To assess the effect of iptacopan on C3 deposit score at the 6 to 9 month visit
- Primary Safety Objective: To evaluate the long-term safety and tolerability of iptacopan in participants with C3G

Participants enrolling from study CLNP023B12301 or CLNP023B12302

- Primary Objective: To evaluate the long-term safety and tolerability of iptacopan in participants with C3G or IC-MPGN

Study design: CLNP023B12001B is an open-label extension of CLNP023X2202, a Phase 2, open-label study evaluating iptacopan in two patient populations with C3G, native kidneys (Cohort A) and kidney transplant with recurrence (Cohort B). Furthermore, all participants completing iptacopan treatment from two ongoing Phase 3 studies are given the option to transition into this extension study: CLNP023B12301 (C3G) and CLNP023B12302 (IC-MPGN).

Participants completing treatment in the CLNP023X2202, CLNP023B12301 or CLNP023B12302 studies, who want to continue treatment and meet the inclusion/exclusion requirements of the extension study have the opportunity to receive iptacopan until drug product becomes commercially available and accessible, or the benefit-risk profile is no longer positive, or the program is discontinued for business or strategic reasons.

Study population: Participants with C3 glomerulopathy, completing treatment in the CLNP023X2202 and CLNP023B12301 studies or participants with IC-MPGN, completing treatment in the CLNP023B12302 study will have the opportunity to enroll in this C3G/IC-MPGN extension study. Approximately 183 participants are expected to enter the extension study.

Milestones:

Interim study report: 30-Jun-2027

Final study report: 31-Dec-2034

III.3 Summary Table of additional pharmacovigilance activities

Table Part III-1: Ongoing 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 Hemoglobinuria (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 PNH patients using IPIG Registry data Status: Planned	The purpose of this study is to characterize 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-	Infections caused by encapsulated bacteria, Serious haemolysis following discontinuation of iptacopan, Malignancies, Use in pregnant	Annual update	Progress reports on enrollment and intermediate analysis results to be provided annually with the PSUR.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	term safety) and to evaluate effectiveness of additional risk minimization 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 (IPIG Registry). The aim of the IPIG 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 utilization on all enrolled patients, as well as long term safety data. According to the IPIG 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 IPIG Registry) will thus be a single-arm study with no internal comparator.	patients, Long-term safety (>2 years)	Final report submission	31-Mar-2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
CLNP023B12001B Extension study to evaluate the long-term efficacy, safety and tolerability of iptacopan (LNP023) in C3G and IC-MPGN patients. Status: Ongoing	The purpose of this study is to evaluate the long-term safety, tolerability and efficacy of iptacopan in patients with C3G, recurrent C3G or IC-MPGN and to provide continued iptacopan access to patients who have completed the Phase II and Phase III trials	Infections caused by encapsulated bacteria, malignancies, use in pregnant patients, long-term safety (>2 years)	Interim Study Report Final Study Report	30-Jun-2027 31-Dec-2034

In addition, a summary of the available safety and eGFR data from all patients with recurrent C3G enrolled in CLNP023B12002I and CLNP023B12004M; the C3G Early Access Program (EAP) will be included in the upcoming PSURs until 31-Aug-2027.

Part IV: Plans for post-authorization efficacy studies

Not applicable

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

V.1. Routine risk minimization measures

Table Part V-1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization 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 risk minimization activities recommending specific clinical measures to address the risk:** **Need for vaccinations:** - SmPC section 4.3 and 4.4: Patients must be vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae*. If vaccine is available locally, it is recommended to vaccinate patients against *Haemophilus influenzae type B*. Vaccination should occur 2 weeks prior to treatment initiation, otherwise patients must be covered by prophylactic antibiotics. Patients may be revaccinated in accordance with local guidelines. - SmPC section 4.4: Patients should be monitored for early signs and symptoms of infections. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only medicine
Serious haemolysis following discontinuation of iptacopan (PNH indication)	**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 **Routine risk minimization activities recommending specific clinical measures to address the risk:** - SmPC section 4.2: Physicians are reminded that PNH requires chronic treatment and discontinuation is not recommended unless clinically indicated. Physicians are also advised to counsel patients on the importance of adherence to the dosing schedule. - SmPC section 4.4: In case of discontinuation patients should be closely monitored for signs and symptoms of haemolysis for at least 2 weeks after the last dose If haemolysis occurs after discontinuation, restart of treatment with iptacopan or switch to an alternate complement inhibitor should be considered. **Other routine risk minimization measures beyond the Product Information:** Calendarized packaging to aid in patient adherence to the dosing schedule. Legal status: Prescription only medicine

Safety concern	Routine risk minimization activities
Malignancies	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only medicine
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 **Routine risk minimization activities recommending specific clinical measures to address the risk:** There are no or limited amount of data from the use of iptacopan in pregnant women. 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). PNH and C3G in pregnancy are associated with adverse maternal and fetal outcomes. Given potential adverse effects of untreated PNH and C3G, Healthcare professionals (HCPs) may only consider iptacopan treatment following a careful assessment of the risk and benefits, in patients who are pregnant or planning to become pregnant. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only medicine
Long-term safety (>2 years)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only medicine

V.2. Additional Risk minimization measures

Additional risk minimization 1

Educational Materials

- Healthcare professional guide
- Patient/caregiver guide
- Patient safety card

Objectives: To provide healthcare professionals (HCPs) and patients/caregivers with educational information on the following safety areas of interest:

- Infections caused by encapsulated bacteria, for all patients.

- Serious haemolysis following discontinuation of iptacopan (HCP guide and Patient/caregiver guide), for PNH patients only.

Rationale for the additional risk minimization activity: Iptacopan increases the risk of infections caused by encapsulated bacteria in all patients. Discontinuation of iptacopan may increase the risk of serious haemolysis in PNH patients.

Target audience and planned distribution path: HCP Guide will be distributed to healthcare professionals who intend to prescribe iptacopan. Patients (and/or their caregivers) receiving iptacopan will be counseled by the treating prescriber and handed the Patient/caregiver guide and Patient safety card.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The plan to evaluate effectiveness of risk mitigation of infections caused by encapsulated bacteria in all patients, and serious haemolysis following discontinuation of iptacopan in PNH patients will focus on the following aspects:

- Will be mainly assessed in the context of risk evaluation in the periodic safety update report (PSUR). Assessment of sustainability of intended RMM impact: the PSUR will monitor any change in frequency of the reported AEs related to infections caused by encapsulated bacteria, and serious haemolysis following discontinuation of iptacopan in PNH patients.

In addition, the planned PASS in PNH based on data from the IPIG registry (see Study CLNP023C12003 – Post-Authorization Safety Study of iptacopan treated patients with PNH, using data from the IPIG Registry) will describe:

- Frequency, incidence and occurrence of safety events related to infections and serious haemolysis following iptacopan discontinuation within the first 5 years after iptacopan marketing.
- Proportion of patients not compliant with mandatory and recommended vaccinations against encapsulated bacteria among the iptacopan-treated patients in the IPIG PNH Registry. The aim of this planned analysis is to monitor compliance with the vaccination requirements and recommendations. The details of the planned analyses evaluating the effectiveness of the additional RMMs related to infections will be provided in the study protocol and the statistical analysis plan.

Additional risk minimization 2

Controlled Access System

Objectives: The MAH shall ensure that in each Member State where iptacopan is marketed, a system aimed to control access beyond the level of routine risk minimization 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 treatment (in accordance with national guidelines).

To mitigate the following risk:

- Infections caused by encapsulated bacteria, for all patients

Rationale for the additional risk minimization activity: Iptacopan increases the risk of infections caused by encapsulated bacteria.

Target audience and planned distribution path: Physicians or pharmacists who prescribe/dispense iptacopan need to ensure that their patients are vaccinated or receiving prophylactic antibiotic treatment prior to iptacopan being prescribed/dispensed.

Plans to evaluate the effectiveness of the interventions and criteria for success: The effectiveness of risk mitigation of infections caused by encapsulated bacteria will be assessed in the context of risk evaluation in the PSUR.

In addition, the planned PASS in PNH (see Study CLNP023C12003 – Post-Authorization Safety Study of iptacopan treated patients with PNH, using data from the IPIG Registry) will describe:

- Frequency, incidence and occurrence of safety events related to infections within the first 5 years after iptacopan marketing.
- Proportion of patients not compliant with mandatory and recommended vaccinations against encapsulated bacteria among the iptacopan-treated patients in the IPIG Registry. The aim of this planned analysis is to monitor compliance with the vaccination requirements and recommendations. The details of the planned analyses evaluating the effectiveness of the additional RMMs related to infections will be provided in the study protocol and the statistical analysis plan.

Additional risk minimization 3

Annual reminder of mandatory revaccinations

Objectives: Novartis shall send to prescribers or pharmacists who prescribe/dispense iptacopan, an annual reminder in order that the prescriber/pharmacist checks if a revaccination (booster vaccination) against N. *meningitidis and* S. *pneumoniae* is required for their patients on treatment with iptacopan, in accordance with current national vaccination guidelines.

To mitigate the following risk:

- Infections caused by encapsulated bacteria, for all patients.

Rationale for the additional risk minimization activity: Iptacopan increases the risk of infections caused by encapsulated bacteria.

Target audience and planned distribution path: Physicians or pharmacists who prescribe/dispense iptacopan need to be reminded to check if revaccination for their patients is required while on treatment with iptacopan.

Plans to evaluate the effectiveness of the interventions and criteria for success: The effectiveness of risk mitigation of infections caused by encapsulated bacteria will be assessed in the context of risk evaluation in the PSUR.

In addition, the planned observational PASS in PNH (see Study CLNP023C12003 – Post-Authorization Safety Study of iptacopan treated patients with PNH, using data from the IPIG Registry) will describe:

- Frequency, incidence and occurrence of safety events related to infections within the first 5 years after iptacopan marketing
- Proportion of patients not compliant with mandatory and recommended vaccinations against encapsulated bacteria among the iptacopan-treated patients in the IPIG PNH Registry. The aim of this planned analysis is to monitor compliance with the vaccination requirements and recommendations. The details of the planned analyses evaluating the effectiveness of the additional RMMs related to infections will be provided in the study protocol and the statistical analysis plan.

Removal of additional risk minimization activities

Not applicable.

V.3. Summary of risk minimization measures

Table Part V-2: Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization 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 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 minimization measures:** • Healthcare professional guide • Patient/caregiver guide • Patient safety card • Controlled access system • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines)	**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 IPIG Registry data **Final study report date** 31-Mar-2030 Study CLNP023B12001B **Interim study report date** 30-Jun-2027 **Final study report date** 31-Dec-2034
Serious haemolysis	**Routine risk communication**	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimization measures	Pharmacovigilance activities
following discontinuation of iptacopan (PNH indication)	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. Calendarized packaging to aid in patient adherence to the dosing schedule. Legal status: Prescription only medicine **Additional risk minimization measures:** • Healthcare professional guide • Patient/caregiver guide	**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 IPIG Registry data **Final study report date** 31-Mar-2030
Malignancies	**Routine risk communication** Legal status: Prescription only medicine **Additional risk minimization 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 Study CLNP023B12001B **Interim study report date** 30-Jun-2027 **Final study report date** 31-Dec-2034
Use in pregnant patients	**Routine risk communication** Missing information addressed in SmPC sections	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	- 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 minimization measures:** None	**reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data **Final study report date** 31-Mar-2030 Study CLNP023B12001B **Interim study report date** 30-Jun-2027 **Final study report date** 31-Dec-2034
Long-term safety (>2 years)	**Routine risk communication:** Legal status: Prescription only medicine **Additional risk minimization 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 IPIG Registry data: **Final study report date** 31-Mar-2030 Study CLNP023B12001B **Interim study report date** 30-Jun-2027 **Final study report date** 31-Dec-2034

Part VI: Summary of the risk management plan for FABHALTA

This is a summary of the risk management plan (RMP) for FABHALTA. The RMP details important risks of FABHALTA, how these risks can be minimized, and how more information will be obtained about FABHALTA's risks and uncertainties (missing information).

FABHALTA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FABHALTA should be used.

This summary of the RMP for FABHALTA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of FABHALTA's RMP.

The medicine and what it is used for

FABHALTA is authorized as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with RAS inhibitors, or in patients who are intolerant or for whom a RAS inhibitor is contraindicated. It contains iptacopan as the active substance and it is given as a 200 mg twice daily oral hard gelatin capsule.

Further information about the evaluation of FABHALTA’s benefits can be found in FABHALTA’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of FABHALTA, together with measures to minimize such risks and the proposed studies for learning more about FABHALTA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of FABHALTA, routine risk minimization measures are supplemented with aRMMs mentioned under relevant important risks, outlined in the next sections.

In addition to the risk minimization measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of FABHALTA is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of FABHALTA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of FABHALTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table Part VI-1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Infections caused by encapsulated bacteria
Important potential risks	Serious haemolysis following discontinuation of iptacopan (PNH indication)
	Malignancies
Missing information	Use in pregnant patients
	Long-term safety (>2 years)

II.B: Summary of important risks

Table Part VI-2: Important identified risk: Infections caused by encapsulated bacteria

Evidence for linking the risk to the medicine	Individuals with deficiencies in Factor B have an increased risk of infections caused by encapsulated bacteria (*N. meningitidis* and *S. pneumoniae*) (Slade et al 2013, Gauthier et al 2021) and activation of the alternative complement pathway has been shown to be one of the innate immune defense mechanisms against pneumococcal infection during the early stage of acute otitis media in a mouse model (Li et al 2011). The membrane attack complex (MAC) plays a role in host defense against infections caused by *N. meningitidis* and patients who are deficient in C5, a terminal component of the complement pathways, experience recurrent infections caused by *N. meningitidis. In vitro* research has shown that the serological response to meningococcal infection (serum bactericidal activity) is markedly reduced after blockade of the terminal pathway with anti-C5 therapies such as eculizumab, which dramatically increases the risk of meningococcal infections in patients treated with C5 inhibitors (Soliris USPI 2020, Ultomiris USPI 2022), but is largely maintained during AP blockade (Konar and Granoff 2017, Ispasanie et al 2021). C5 inhibitors have no effect, however, on complement-mediated host defense against *Streptococcus pneumoniae* (opsonophagocytosis), since it occurs earlier in

	the complement pathway. C3 inhibitors, such as the recently approved pegcetacoplan, have been shown to have an effect on opsonophagocytosis against pneumococci *in vitro*, consistent with the types of infections observed in C3-deficient patients. The effect was greater than that seen with more selective inhibitors of Factor D or Factor B (Muri et al 2021). Infections caused, or likely to have been caused, by encapsulated bacteria have been observed in clinical studies in patients treated with iptacopan.
Risk factors and risk groups	Risk factors for infection include history of immunodeficiency diseases, history of recurrent infections, patients with diabetes, transplant patients, elderly patients and children. Other risk factors include: • Unvaccinated or incompletely vaccinated patients. • Patients with PNH-associated bone marrow failure (including aplastic anaemia PNH, myelodysplastic syndrome), due to neutropenia. • Immunosuppressive treatment (e.g., high-dose steroids, mycophenolate mofetil, cyclosporine, tacrolimus, B-cell depleting agents). • Individuals exposed to certain bacteria through work or travel. • Chronic kidney disease. Potential risk factors for infection among patients with CKD include hypoalbuminemia, immunosuppressive therapy, presence of central vascular access (for plasma exchange, hemodialysis), nephrotic syndrome, uremia, anaemia, and malnutrition.
Risk minimization measures	**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 • 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 minimization measures:** • Healthcare professional guide • Patient/caregiver guide • Patient safety card • Controlled access system • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines)
Additional pharmacovigilance activities	Study CLNP023C12001B, REP in iptacopan-treated PNH patients Study CLNP023C12003, PASS in iptacopan-treated PNH patients using IPIG Registry data Study CLNP023B12001B, REP in iptacopan-treated C3G patients

	See section II.C of this summary for an overview of the post-authorization development plan.

Table Part VI-3: Important potential risk: Serious haemolysis following discontinuation of iptacopan (PNH Indication)

Evidence for linking the risk to the medicine	This potential risk is a theoretical possibility in patients with PNH treated with complement inhibitors, based on the mode of action and nature of PNH. Haemolytic events are of noteworthy concern in patients with PNH who are receiving treatment with complement inhibitors which decrease both intravascular haemolysis (IVH) and extravascular haemolysis (EVH), owing to the potential for increased RBC clone size (Peffault de Latour et al 2022) (Risitano 2021) and subsequent serious haemolysis. Haemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed (Aspaveli SmPC). No adverse events of serious haemolysis following discontinuation of iptacopan were observed in the PNH clinical studies.
Risk factors and risk groups	Patients with PNH treated with complement inhibitors which decrease both IVH and EVH are at increased risk of serious haemolysis if treatment is discontinued, temporarily or permanently, due to increased PNH RBC clone size. In particular, patients who have not been established on an effective alternative therapy at the time of discontinuation are at higher risk for intravascular haemolysis (IVH) after drug discontinuation.
Risk minimization measures	**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. Calendarized packaging to aid in patient adherence to the dosing schedule. Legal status: Prescription only medicine **Additional risk minimization measures:** • Healthcare professional guide • Patient/caregiver guide
Additional pharmacovigilance activities	Study CLNP023C12001B Study CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data See section II.C of this summary for an overview of the post-authorization development plan.

Table Part VI-4: Important potential risk: Malignancies

Evidence for linking the risk to the medicine	Previous experience with other complement inhibitors (Ultomiris EPAR assessment report, Aspaveli EPAR Assessment report), suggests a possible class effect for these drugs. However, there is inconclusive

	literature evidence, with publications both suggesting tumor promotion and tumor inhibition by complement components (Revel et al 2020). Malignancies were observed in some patients with PNH treated with iptacopan 200 mg bid, however, most of these had relevant confounding conditions at study entry. Comprehensive preclinical carcinogenicity studies on iptacopan were negative.
Risk factors and risk groups	There is some evidence suggesting that patients with PNH may be more prone to develop tumors, with a prevalence of malignancies (other than MDS/AML) ranging from 2.2% - 14.2% (Yu et al 2016, Muñoz-Linares et al 2014). As per general (non-treated) patient population, older patients or patients with pre-cancerous conditions are risk groups. Patients on immunosuppressants and in particular transplant recipients, as is the case for recurrent C3G patients, are at increased risk of malignancies. Additionally, incidence rate of cancer is relatively higher in CKD patients than that in the general population.
Risk minimization measures	**Routine risk communication** Legal status: Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Study CLNP023C12001B CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data Study CLNP023B12001B See section II.C of this summary for an overview of the post-authorization development plan.

Table Part VI-5: Important missing information: Use in pregnant patients

Risk minimization measures	**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 and C3G patients described. Lack of data on iptacopan in pregnancy and need for a risk-benefit assessment stated. Legal status: Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Study CLNP023B12001B CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data Study CLNP023B12001B See section II.C of this summary for an overview of the post-authorization development plan.

Table Part VI-6: Important missing information: Long-term safety (>2 years)

Risk minimization measures	**Routine risk communication:** Legal status: Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Study CLNP023C12001B CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data Study CLNP023B12001B See section II.C of this summary for an overview of the post-authorization development plan.

II.C: Post-authorization development plan

II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of FABHALTA.

II.C.2. Other studies in post-authorization development plan

Table Part VI-7: Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CLNP023C12001B Long-term safety and tolerability of iptacopan in patients with Paroxysmal Nocturnal Hemoglobinuria.	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. To collect further data to help further characterize and/or closely monitor each of the respective safety concerns: • Infections caused by encapsulated bacteria • Serious haemolysis following discontinuation of iptacopan • Malignancies • Long-term safety (>2 years)
CLNP023C12003 PASS in iptacopan-treated patients using registry data	The purpose of this study is to characterize 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 effectiveness of additional risk minimization 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 Interest Group (IPIG) registry (IPIG Registry). The aim of the IPIG 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 utilization on all enrolled patients, as

Study short name	Rationale and study objectives
	well as long term safety data. According to the IPIG 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.

CLNP023B12001B
C3G rollover extension study in iptacopan-treated patients
	The primary purpose of this extension study is to collect long-term efficacy, safety and tolerability data in eligible participants receiving open-label iptacopan after completing treatment in the C3G Phase III study CLNP023B12301, IC-MPGN Phase III study CLNP023B12302 and Phase II C3G proof of concept study CLNP023X2202.
	This protocol allows:
	• Continued access to iptacopan to patients enrolled in the Phase 2 and Phase 3 programs (C3G and IC-MPGN)
	  • Phase 2 C3G Study (CLNP023X2202): adults (C3G and recurrent C3G)
	  • C3G study (CLNP023B12301): adults and adolescents
	  • IC-MPGN study (CLNP023B12302): adults and adolescents
	• Provision of additional efficacy and safety information following longer-term treatment with iptacopan in C3G and IC-MPGN populations.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key messages:

For patients with PNH and C3G:

- 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* and *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 flulike symptoms, clammy skin, eyes sensitive to light. If bacterial infection is suspected, treat with antibiotics immediately.
- Healthcare professionals should advise patients about the importance of adherence to the dosing schedule.

Additionally, in patients with PNH:

- 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.
- <For IPIG Registry participating countries>: Data for the FABHALTA PASS will be collected from IPIG Registry participating centers. Please inform patients about the PASS.

The patient information pack:

- Package leaflet
- Patient/caregiver guide
- Patient safety card

The Patient/caregiver guide shall contain the following key messages:

For patients with PNH and C3G:

- 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 center.
- 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 it is important that you report them immediately.

Additionally, if you have PNH:

- 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.
- <For IPIG Registry participating countries>: A post-authorization safety study (PASS) is a study that is carried out after a medicine has been approved. For FABHALTA, data for the PASS will be collected from IPIG Registry participating centers. If your healthcare center participates you may be invited to enroll, and your healthcare provider will support with comprehensive information about the study.

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.

Controlled Access System:

- The MAH ensures that in each Member State where FABHALTA is marketed, a system aimed to control access beyond the level of routine risk minimization 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* 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.