EU RMP	
Drug substance	Danicopan
EMA version number	1.0
Alexion version number, succession number	1,5
Data lock point	31 March 2023
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for VOYDEYA (danicopan)

The content of this EU RMP has been reviewed and approved by the deputy QPPV.

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Administrative Information

Rationale for submitting an updated RMP*:*

Not applicable for initial marketing authorisation submission.

Rationale for update to RMP*:*

Not applicable – Version 1

Summary of significant changes in this RMP

Not applicable – Version 1

Other RMP versions under evaluation	**Version Number:** Not applicable for Version 1 **Submitted:** Not applicable for Version 1 **Procedure number:** Not applicable for Version 1
Details of currently approved RMP	**Version Number:** Not applicable for Version 1 **Approved with procedure:** Not applicable for Version 1 **Date of approval:** Not applicable for Version 1

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ALT	alanine aminotransferase
AP	alternative pathway
ATC	anatomical therapeutic chemical classification
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24-hour time point
C3	complement component 3
C5	complement component 5
C_{max}	maximum plasma concentration
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EPAR	European Public Assessment Report
EU	European Union
EVH	extravascular haemolysis
FACIT	Functional Assessment of Chronic Illness Therapy
FB	complement factor B
FD	complement factor D
GPI	glycosylphosphatidylinositol
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	haematopoietic stem cell transplantation
INN	international nonproprietary name
IPIG	International PNH Interest Group
IVH	intravascular haemolysis
LTE	long-term extension
max	maximum
min	minimum
NA	not applicable
NOAEL	no-observed-adverse-effect level
PIGA	X-linked phosphatidylinositol glycan A
PL	Package Leaflet
PNH	paroxysmal nocturnal haemoglobinuria
QPPV	qualified person for pharmacovigilance
RMP	Risk Management Plan

Abbreviation/ Special term	**Definition/Explanation**
SD	standard deviation
SmPC	Summary of Product Characteristics
TBD	to be determined
TEAE	treatment-emergent adverse event
tid	three times a day
ULN	upper limit of normal

I. PART I: PRODUCT OVERVIEW

Table I-1 Product overview

Active substance(s) (INN or common name)	Danicopan
Pharmacotherapeutic group(s) (ATC code)	Complement inhibitors (L04AJ09)
Marketing Authorisation Applicant	Alexion Europe SAS
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	VOYDEYA
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Danicopan is a small-molecule, orally administered complement factor D (FD) protease inhibitor.
	Summary of mode of action: Complement FD is a serine protease that is required for activation of the complement alternative pathway (AP). FD mediates the cleavage of complement factor B (FB), when FB is bound to activated forms of complement component 3 (C3), to generate the C3 convertase – C3bBb. This C3 convertase elicits further complement activation and promotes the multiple effector functions of the complement system. FD circulates at lower concentration than most other complement proteins, and it is not an acute-phase protein. Danicopan is a small-molecule inhibitor that binds reversibly to FD and acts as a potent and selective inhibitor of FD function and consequently of AP activation. Although danicopan blocks the AP-mediated amplification of the complement classical pathway and lectin pathway, these 2 pathways remain active to provide residual complement-dependent protection against infectious pathogens. Danicopan can inhibit the AP-mediated deposition of C3 fragments on paroxysmal nocturnal haemoglobinuria (PNH) red blood cells; such deposition is a key cause of the extravascular haemolysis that is observed in a small subset of patients with PNH on treatment with a complement component 5 (C5) inhibitor.
	Important information about its composition: None

Table I-1 Product overview

Hyperlink to the Product Information	VOYDEYA, Product Information
Indication(s) in the EEA	**Current:** An add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia.
Dosage in the EEA	**Current:** **Adult patients with PNH** The recommended starting dose is 150 mg three times a day administered orally, approximately 8 hours apart (± 2 hours). Dose can be increased to 200 mg three times a day after a minimum of 4 weeks of treatment depending on clinical response.
Pharmaceutical form(s) and strengths in the EEA	**Current:** Film-coated tablet Each tablet contains 50 or 100 mg of danicopan.
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC, anatomical therapeutic chemical classification; EU, European Union; INN, international nonproprietary name; RMP, Risk Management Plan.

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Paroxysmal nocturnal haemoglobinuria

Incidence and prevalence:

Epidemiologic studies of the occurrence of paroxysmal nocturnal haemoglobinuria (PNH) are scarce. Incidence of PNH in the European Union has been reported to range from 0.08 to 0.57 per 100,000 person-years (Hansen et al 2020, Jalbert et al 2019).

Prevalence of PNH has been reported to range from 1.04 to 3.81 per 100,000 persons (Hansen et al 2020, Hill 2007, Jalbert et al 2019, Richards et al 2021).

A subset of patients with PNH who achieve durable intravascular haemolysis (IVH) control and associated disease control with ravulizumab or eculizumab, may experience emergence of clinically significant extravascular haemolysis (EVH) and may require transfusions (Hill et al 2010, McKinley et al 2017, Notaro and Sica 2018, Risitano et al 2019). Clinically significant EVH occurs in approximately 20% of complement component 5 (C5) inhibitor-treated patients, with approximately 10% of these patients requiring red blood cell transfusions (Kulasekararaj et al 2023).

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

PNH can occur at any age, although it is diagnosed most often in the fourth or fifth decade of life (Füreder et al 2020, Lee et al 2013, Schrezenmeier et al 2020, Villegas et al 2017). PNH is considered rare in children although it may manifest in some patients during teenage years (Hill et al 2017). In general, there is a slight female preponderance in PNH, as noted in several registries (Füreder et al 2020, Schrezenmeier et al 2020, Villegas et al 2017).

In an analysis of 4,439 patients enrolled in the International PNH Registry as of Jul 2017, 53% were female and median age at diagnosis was 35.5 years (Schrezenmeier et al 2020). Overall, 67.9% of patients were from Europe, 14.4% from the United States and 17.7% from the rest of the world, including Asia. In this registry, 78.4% of participants were White, 16.3% were Asian, 3% were Black and the remaining 2.3% were another race or unspecified (Schrezenmeier et al 2020).

A separate analysis of this registry, which evaluated Asian and non-Asian patients who were not eculizumab-treated at baseline and who had ≥ 1% PNH clone size, found no statistical difference in age, sex or disease duration between Asian and non-Asian patients (Sakurai et al 2019).

- **Risk factors**

Although PNH has a genetic basis, it is not a heritable condition as it is a somatic mutation of the X-linked phosphatidylinositol glycan A (*PIGA*) gene that occurs randomly (Sahin et al 2015). Patients who develop PNH often have some bone marrow dysfunction, such as aplastic anaemia or myelodysplastic syndrome, prior to or concurrently at time of PNH diagnosis (Parker 2012, Rachidi et al 2010). The leading theory suggests that many healthy individuals have some glycosylphosphatidylinositol (GPI)-deficient haematopoietic stem cells, which generally do not preferentially replicate. However, some event, enabling GPI-deficient cells to expand in the presence of bone marrow dysfunction, is needed to induce PNH (Parker 2012, Rachidi et al 2010, Sahin et al 2015).

The main existing treatment options:

Treatment of PNH consists primarily of anti-complement therapies. Eculizumab is a monoclonal antibody that specifically binds to the C5 with high affinity and inhibits terminal complement mediated IVH in PNH patients. Ravulizumab (also a C5 inhibitor) was subsequently designed to provide extended duration of terminal complement inhibition, while retaining the safety, efficacy, and low immunogenicity associated with eculizumab (Sheridan et al 2018). Among patients treated with eculizumab or ravulizumab, an unmet medical need exists to address clinically significant EVH in PNH by improving patients' haemoglobin values, fatigue, and reducing red blood cell transfusion requirements.

Pegcetacoplan, a complement component 3 (C3) inhibitor targeting the proximal complement cascade, is the most recent treatment approved for the treatment of PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months. However, this monotherapy does appear to not provide a sustained control of IVH in PNH patients, where an unmet medical need continues to exist (Notaro and Luzzatto 2022).

Prior to the introduction of eculizumab, ravulizumab and most recently of pegcetacoplan, the treatment of PNH was mainly supportive, aiming to control the clinical manifestations of the disease (ie, management of haemolysis, anaemia, thrombophilia, and bone marrow failure). This supportive treatment included blood transfusion, administration of erythropoiesis stimulating agents, corticosteroids, or anabolic steroids, iron therapy, thrombosis prophylaxis, and thrombolytic therapy (Al-Ani et al 2016).

The only available curative approach for PNH is allogeneic haematopoietic stem cell transplantation (HSCT). However, allogeneic HSCT is associated with high mortality and morbidity. Moreover, because of the high effectiveness of eculizumab and ravulizumab, HSCT is only considered for cases of severe marrow failure (Al-Ani et al 2016).

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

PNH is a chronic haematological disorder characterised by episodes of haemolysis and other important clinical manifestations including thrombosis, bone marrow failure and evolution to myelodysplastic syndrome (Hill et al 2017). Other serious clinical symptoms lead to poor quality of life in PNH, including anaemia, kidney disease, fatigue, and smooth muscle dystonia (Hill et al 2017). Specific to patients experiencing clinically significant EVH, an additional complication includes iron overload as the result of eculizumab and ravulizumab blocking IVH and subsequently preventing further urinary iron loss (Risitano et al 2019, Röth et al 2011).

Disease burden was high in an analysis of patients enrolled in an International PNH Registry, with 55.8% reporting haemolysis and 42.8% with an impaired estimated glomerular filtration rate (eGFR) at baseline (defined as the date of enrolment for never treated patients and date of eculizumab initiation for patients ever treated with eculizumab). Further, 63% of patients had a history of bone marrow failure and 18.8% had a history of a major adverse vascular event (Schrezenmeier et al 2020). In this registry, commonly reported PNH symptoms included: fatigue (80.9%), dyspnoea (45.3%), haemoglobinuria (45.0%), abdominal pain (35.2%), dysphagia (16.5%), and erectile dysfunction (24.2% of males) (Schrezenmeier et al 2020). The survival experience of patients with PNH has improved over time though among untreated patients, mortality remains higher as compared to the general population (Hill et al 2017, Kelly et al 2011). Among those patients treated with eculizumab, the survival experience of patients has been demonstrated to be similar to a matched general population (Füreder et al 2020, Kelly et al 2011, Terriou et al 2021).

Thromboembolism is generally considered the most common cause of mortality in PNH patients, accounting for approximately 40% to 67% of deaths with a known cause (Devos et al 2018, Heitlinger 2013, Hill et al 2013). In Western countries, thromboembolism was the leading cause of death, followed by serious infections, malignant tumours, haemorrhage, and renal failure, successively.

A subset of patients with PNH who have achieved disease control with ravulizumab or eculizumab may experience emergence of clinically significant EVH and some of these patients require transfusions (Hill et al 2010, McKinley et al 2017, Notaro and Sica 2018, Risitano et al 2019). Clinically significant EVH is characterised by persistent symptoms of anaemia such as low haemoglobin and elevated reticulocyte counts with or without transfusion requirements, fatigue, and decreased quality of life. The mortality experience of this subset of patients with PNH and EVH is not reported.

Important co-morbidities:

- Bone marrow abnormalities (i.e., aplastic anaemia, myelodysplastic syndrome)

II.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of key findings from non-clinical data

Toxicity

Acute or repeat dose toxicity

In a 9-month toxicity study in dogs, danicopan, at the dose of 150 mg/kg/day was not tolerated due to cholestatic liver injury and associated with preterminal sacrifice. At this dose, danicopan-related clinical pathology changes indicative of inflammation (increased neutrophil and monocyte counts, fibrinogen, and globulin and decreased albumin concentrations), stress (decreased lymphocytes), dehydration (increased red blood cell mass parameters, urea and creatinine), and liver injury (increases in aspartate aminotransferase, alanine aminotransferase [ALT], alkaline phosphatase, gamma-glutamyl transferase activities and in total, direct and indirect bilirubin concentrations) included bile duct hypertrophy/hyperplasia, pigment accumulation in Kupffer cells and hepatocytes, stress-related lymphoid depletion in thymus and/or cortical hypertrophy in the adrenals were observed. These danicopan-related clinical pathology and histopathology findings in the main study animals were no longer observed at the end of the 13-week recovery period. Hypertrophy/hyperplasia of the bile duct was observed in males at ≥ 75 mg/kg/day (~5-fold above human exposure at 200 mg three times a day [tid] based on AUC_{0-24}). The maximum plasma concentration (C_{max}) multiple, compared to human C_{max} at 200 mg tid, was approximately 11-fold.

Reproductive/developmental toxicity

Danicopan is unlikely to have effects on reproductive function or embryo-foetal development in humans at therapeutically relevant doses. Rabbit species were selected for developmental and reproductive toxicology studies, based on the absence of pharmacological activity of rats. In the fertility studies, reduced male and female reproductive performance was observed at 500 mg/kg/day, a dose associated with poor tolerability. The no-observed-adverse-effect level (NOAEL) was established at 250 mg/kg/day, although systemic toxicity was noted at 125 mg/kg/day in males and 250 mg/kg/day in females.

In the embryo-foetal development study in rats, at the highest dose of 1,000 mg/kg/day, a mild reduction (up to 8.3%) in foetal body weights was observed.

In the pre- and postnatal development study conducted in rabbits, NOAEL was established at 250 mg/kg/day, the maximum dose tested in the study. However, a reduction of mean caudal epididymal sperm concentration in the F1 males was reported in the study report. This finding was noted in all dose groups (50, 125 and 250 mg/kg/day), being statistically significant in the

low and mid dose groups (19, 20 and 18%, respectively), although it was not observed in parallel with any alteration of reproductive performance or histopathological findings.

Genotoxicity

Danicopan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays, including a bacterial Ames assay, an *in vitro* micronucleus assay in human peripheral blood lymphocytes, and an *in vivo* micronucleus assessment in female rats.

The metabolite of danicopan, ACH-0144240 (2-amino-6-bromopyridine), did not show any evidence of genotoxic activity in a bacterial Ames assay (*in vitro* mutagenicity).

Findings from the nonclinical studies indicated that a potential for genotoxicity in humans is negligible.

Carcinogenicity

Danicopan was not carcinogenic in the 2-year carcinogenicity study in rats and in the 6-month carcinogenicity study in hemizygous rasH2 mice. In the rat study, a higher incidence of endometrial epithelium neoplasmas at the highest dose of 500 mg/kg/day compared to control animals was observed, although the rat strain can have a high background incidence of endometrial carcinomas. Danicopan is unlikely to be carcinogenic in humans at therapeutically relevant doses.

Safety pharmacology

Cardiovascular system, including potential effect on the QT interval

No noteworthy danicopan-related effects on cardiovascular function (electrocardiography or haemodynamic parameters) in conscious telemetered beagle dogs up to 500 mg/kg/day.

Nervous system

No noteworthy danicopan-related effects on nervous system function in dogs up to 1000 mg/kg/day.

Respiratory system

No noteworthy danicopan-related effects on respiratory function in dogs up to 1000 mg/kg/day.

Administration of danicopan to humans at therapeutically relevant doses is unlikely to have any effects on cardiovascular, respiratory, or nervous system function.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Paroxysmal nocturnal haemoglobinuria

The clinical trial exposure below pools data from 4 studies in participants with PNH as of 31 March 2023, including 2 studies with danicopan as add-on therapy (Phase 2 Study ACH471-101 and pivotal Phase 3 Study ALXN2040-PNH-301; N = 96) and 2 studies with danicopan as monotherapy (Phase 2 Study ACH471-100 and Phase 2 Study ACH471-103; N = 10).

Table II-1 Duration of exposure to danicopan

Variable	All PNH population (N = 106)	Person time (patient-years)
Treatment duration (days)		
Mean (SD)	562.9 (390.38)	NA
Median	469.0	NA
Min, Max	1, 1631	NA
Treatment duration category		
1 day to 12 weeks	6	0.7
> 12 to 24 weeks	2	0.5
> 24 to 48 weeks	24	17.3
> 48 to 72 weeks	26	30.1
> 72 to 96 weeks	22	35.3
> 96 to 120 weeks	10	19.7
> 120 to 144 weeks	2	5.1
> 144 to 168 weeks	0	0
> 168 to 192 weeks	5	18.0
> 192 weeks	9	36.6
Total	**106**	**163.4**

max, maximum; min, minimum; NA, not applicable; PNH, paroxysmal nocturnal haemoglobinuria; SD, standard deviation.

Table II-2 Exposure to danicopan by age group and gender

Variable	All PNH population (N = 106)		Person time (patient-years)	
Age group (years), n (%)	**Male**	**Female**	**Male**	**Female**
< 18	0	1	0	2.2
18 to 64	29	52	44.4	86.3
65 to 74	7	8	10.4	8.4
75 to 84	3	6	4.1	7.6

Table II-2 Exposure to danicopan by age group and gender

Variable	All PNH population (N = 106)		Person time (patient-years)	
Age group (years), n (%)	**Male**	**Female**	**Male**	**Female**
≥ 85	0	0	0	0
Total	**39**	**67**	**58.9**	**104.5**

PNH, paroxysmal nocturnal haemoglobinuria.

Table II-3 Exposure to danicopan by dose

Dose regimen	PNH add-on population (N = 96)	Person time (patient-years)
100 tid	13	6.7
150 mg tid	95	52.1
200 mg tid	67	82.7
Total	**96**	**141.5**

Note: Exposure to danicopan by dose regimen includes only PNH add-on population (N = 96) and not the overall PNH population (N = 106). Participants may be counted in multiple danicopan dose groups based on the dosing regimen they received during study treatment but are only counted once in the total population exposed to danicopan. Most participants received a starting dose of 150 mg tid and could be escalated to the next dose level according to protocol-specified requirements.

PNH, paroxysmal nocturnal haemoglobinuria; tid, three times a day.

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion criteria in pivotal clinical studies within the development programme

Pregnant or breastfeeding women

Reason for exclusion: Women who were pregnant or breastfeeding were excluded from the clinical studies to avoid potential harm to the unborn foetus or breastfed infants.

Is it considered to be included as missing information: Yes

Active bacterial or viral infection or history of any febrile illness within 14 days prior to first study drug administration

Reason for exclusion: Patients with active infection were excluded to avoid factors that may confound a complete understanding of the safety profile of danicopan.

Is it considered to be included as missing information: No

Rationale: Although patients with active infections were excluded prior to study entry, patients who developed an infection during the course of the study were not discontinued from the study. As such, the data on use of danicopan during infections were collected and there was no difference in the safety profile for patients who developed an infection during the study compared to those that did not. Therefore, this population is not relevant for consideration as missing information.

ALT > 2 × upper limit of normal (ULN) (> 3 × ULN in the case of participants with documented liver iron overload defined by serum ferritin values ≥ 500 ng/mL) and direct bilirubin > 2 × ULN (unless due to EVH or documented Gilbert's syndrome)

Reason for exclusion: Given that patients with PNH may have liver enzyme elevations due to haemolysis as part of clinical presentation and evolution of PNH, patients with moderate or severe laboratory abnormalities in liver tests were excluded to avoid factors that may confound a complete understanding of the safety profile of danicopan.

Is it considered to be included as missing information: No

Rationale: Patients with ALT and direct bilirubin abnormalities were excluded prior to study entry, but patients who presented with the abnormalities above those thresholds during the course of the study continued in the study. Although some patients experienced elevated liver enzymes higher than the above thresholds, there was no observed difference in the safety profile.

eGFR < 30 mL/min/1.73 m^2 and/or are on dialysis

Reason for exclusion: PNH patients with severe renal impairment were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy profile of danicopan. Severe renal impairment (i.e., eGFR < 30 mL/min) is known to increase intrinsic factor D (FD) levels.

Is it considered to be included as missing information: No

Rationale: A clinical pharmacology study conducted in subjects with renal impairment (ACH471-009) indicated that systemic area under the concentration-time curves of danicopan increased by approximately 50% in patients with severe renal impairment (creatinine clearance < 30 mL/min) compared to subjects with normal renal function, but there was no meaningful change in C_{max}, time to maximum drug concentration, or terminal half-life.

Renal excretion is a minor route for clearing danicopan from the body. As such, the safety profile of danicopan in PNH patients with renal impairment is not expected to differ from the general, danicopan-treated population and this population is not relevant for consideration as missing information.

Evidence of human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections at screening

Reason for exclusion: Since patients with HIV, HBV, or HCV active infections may present with additional co-morbidities, which may confound the analysis of safety data of danicopan, they were excluded from the pivotal programme.

Is it considered to be included as missing information: No

Rationale: There is no scientific evidence to suggest that the safety profile of danicopan in patients with HIV, HBV or HCV active infections is different to that of the general, danicopan-treated population.

History of a major organ transplant (eg, heart, lung, kidney, liver) or HSCT

Reason for exclusion: Patients with a history of major organ transplant or HSCT were excluded in order to avoid factors that may confound a complete understanding of the efficacy and safety of danicopan.

Is it considered to be included as missing information: No

Rationale: There is no scientific rationale to suspect that the safety profile of participants with a history of major organ transplant may differ to that characterised so far for the general, danicopan-treated population. PNH patients who underwent curative HSCT do not represent the target population for danicopan.

Known aplastic anaemia or other bone marrow failure that requires HSCT or other therapies

Reason for exclusion: Patients requiring HSCT due to aplastic anaemia or other bone marrow failure were excluded in order to avoid factors that may confound the efficacy of danicopan.

Is it considered to be included as missing information: No

Rationale: PNH patients who underwent curative HSCT do not represent the target population for danicopan. PNH patients with aplastic anaemia receiving stable treatment for aplastic anaemia during the 12-week duration of study were allowed and included in the pivotal study.

II.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions, such as adverse reactions with a frequency lower than the detection ability of the programme for a rare disease, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

II.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table II-4 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patient with relevant comorbidities:	
Patients with hepatic impairment	Danicopan was investigated in 8 subjects with mild and moderate hepatic impairment. There was no significant difference in danicopan exposure in subjects with moderate hepatic impairment (Child-Pugh Class B). PNH patients with severe hepatic impairment (Child-Pugh Class C) were not excluded from clinical studies, however, no patients fitting this criterion were enrolled and exposure data for this population are not available. Therefore, the use in patients with severe hepatic impairment represents missing information (refer to II.7).
Patients with renal impairment	Danicopan has been investigated in 13 patients with mild renal impairment and 13 patients with moderate renal impairment.

Table II-4 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Patients with cardiovascular impairment or any other co-morbidity/disease severity were not specifically investigated within the clinical development programme for danicopan.
Patients with relevant different ethnic origin	Not applicable.
Subpopulations carrying relevant genetic polymorphism	Not applicable.

PNH, paroxysmal nocturnal haemoglobinuria.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

Not applicable since danicopan has not yet been approved for marketing in any country.

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Considering the mode of action and overall characteristics, the potential of danicopan for misuse for illegal purposes is negligible.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of safety concerns in the initial RMP submission

II.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

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

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- **Liver enzyme elevations:** Liver enzyme elevations have been observed during the PNH development programme and are considered a non-important identified risk associated with danicopan use.

  In study ALXN2040-PNH-301, during Treatment Period 1 (ie, a 12-week treatment period), the incidence of treatment-emergent adverse events (TEAEs) related to hepatic abnormalities was slightly higher in the danicopan group compared to placebo (14.0% [8/57] versus 10.3% [3/29]). Based on chemistry results, laboratory abnormalities related to elevations in ALT levels were higher in the danicopan group with 14.0% (8/57) compared to 3.4% (1/29) of participants on placebo. In danicopan-treated participants, ALT elevations > 3 × ULN and ≤ 5 × ULN occurred in 8.8% of participants, and > 5 × ULN and ≤ 10 × ULN in 5.3% of participants. There were no elevations > 10 × ULN.

  All elevations were transient and asymptomatic. In 3 danicopan-treated participants, TEAEs related to hepatic abnormalities led to treatment discontinuation. Treatment was interrupted and subsequently discontinued in a single participant as the ALT values increased a second time following drug taper. The other 2 participants were discontinued for meeting the protocol stopping criteria related to liver laboratory values. One of these participants experienced liver enzyme elevations in the context of cholelithiasis and subsequent pancreatitis.

  Some elevations occurred concurrent with increased lactate dehydrogenase values or concurrent to event of haemolysis. Patients with PNH may have elevated hepatic enzymes during haemolysis as part of the natural history and clinical presentation of the disease. Patients with high transfusion requirements may also present with hepatic enzyme abnormalities associated with transfused related liver iron overload.

  Across all clinical studies conducted in patients with PNH at the data lock point of this document, there have been no confirmed Hy’s Law cases. Elevations in liver enzymes do not appear to be manifestation of clinically important liver injury, but

rather mild effects with spontaneous resolution or adaptation. No drug-induced liver injuries or other significant undesirable clinical outcomes of liver enzyme elevations have been observed.

Given the nature of this risk in the context of the intended target population, this identified risk is not considered important and will continue to be monitored via routine pharmacovigilance. Although there are clinical measures included in the label, these chemistry assessments, including liver enzyme tests, represent part of routine PNH disease management and are frequently monitored in patients being treated with danicopan.

- **Medication errors leading to overdose or underdose:** Danicopan is a small molecule medication, available in two strengths (50 and 100 mg) and orally administered tid. As such, a potential for medication errors exists. However, should a medication error occur there are no important risks as a result. The anticipated clinically meaningful adverse outcomes of medication errors associated with orally administered tablets, including danicopan, would be signs and symptoms of either overdose or underdose.

  In case of overdose, elevations in aminotransferases and other liver parameters may occur. In a multiple ascending dose study conducted in health volunteers, 2 subjects who received 500 mg and 800 mg twice a day had ALT elevations after treatment cessation without a taper. These abnormal ALT findings were transient, with no evidence of hepatic function abnormality and resolved spontaneously.

  In case of underdose, based on clinical pharmacology studies, lower exposures will not maintain alternative pathway inhibition necessary to achieve EVH control. However, IVH continues to be controlled under treatment with eculizumab or ravulizumab, and potential life-threatening complications of PNH are therefore mitigated. Signs and symptoms of EVH (such as development of anaemia and fatigue) should be monitored in these cases.

  Medication errors noted in the clinical development programme were infrequent and did not show any specific trends or patterns. In PNH patients in the clinical programme who have experienced accidental medication error, none were associated with any adverse events.

  The routine risk minimisation measures in place (i.e., posology of danicopan presented in the Product Information, differentiated debossing between strengths), are intended to minimise the potential for medication errors.

Given the data collected on danicopan from the clinical programme, there are no safety concerns related to the potential adverse outcomes of medication errors, and medication errors will continue to be monitored via routine pharmacovigilance. No specific clinical measures are required in the product label or additional risk minimisation measures to minimise the risk of medication errors.

II.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks:

There is no important identified risk for danicopan.

Important Potential Risk 1: Meningococcal infection

Risk-benefit impact:

Danicopan is an FD inhibitor and individuals with complement system deficiencies have been associated with an increased risk of *Neisseria meningitidis* infection (Biesma et al 2001, Hiemstra et al 1989, Sprong et al 2006). However, the relevance of this risk to FD inhibitor danicopan remains to be elucidated.

Important Potential Risk 2: Serious infections

Risk-benefit impact:

Danicopan is an FD inhibitor that selectively targets the alternative pathway. Therefore, since danicopan does not impact the classical or lectin pathway-mediated early complement components, the ability to clear most non-neisserial infections remains intact. The mechanism which may lead to serious infections other than those caused by *N meningitidis* in patients treated with danicopan remains unclear. PNH patients receiving danicopan are often at increased risk of infection due to the underlying medical condition or its complications. Considering the mode of danicopan action and the currently missing evidence, serious infections represent a potential risk of danicopan.

Important Potential Risk 3: Malignancies and haematologic abnormalities

Risk-benefit impact:

The natural evolution of PNH disease makes PNH patients more prone to development of haematologic abnormalities or malignancies as approximately 30 to 70% of PNH patients eventually develop aplastic anaemia or myelodysplastic syndrome (de Latour, 2008; Hillmen, 1995; Socié, 1996). The potential role of danicopan in such abnormalities or malignancies is unknown.

Missing Information 1: Use in pregnant or breastfeeding women

Risk-benefit impact:

The nonclinical studies did not show any embryo-foetal toxicity or teratogenic effects associated with danicopan but there are no clinical data on use of danicopan during pregnancy or on excretion of danicopan in human breast milk and potential effects on breast-fed child.

Missing Information 2: Use in patients with severe hepatic impairment

Risk-benefit impact:

A single-dose study to evaluate the effect of moderate hepatic impairment (Child-Pugh Class B) on the pharmacokinetics, safety, and pharmacodynamics of danicopan did not show significant difference in danicopan exposure compared to demographically matched healthy subjects. Since no significant clinical effect was observed, danicopan was not evaluated in mild or severe hepatic impaired patients.

Since danicopan is extensively metabolised in the liver and data cannot be extrapolated to patients with severe hepatic impairment, danicopan plasma concentrations cannot be predicted.

Missing Information 3: Long-term safety

Risk-benefit impact:

Danicopan is intended for a long-term use and the typical clinical development programme is not designed to detect all adverse effects with long latency or those that are infrequent. As such, more data on long-term safety of danicopan use are needed.

II.7.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

II.7.3 Details of important identified risks, important potential risks and missing information

II.7.3.1 Presentation of important identified risks and important potential risks

II.7.3.1.1 Important Potential Risk 1: Meningococcal Infection

Potential mechanisms:

Danicopan is an FD inhibitor and since the primary function of the complement system is to fight infections, pharmacologic inhibition of the complement system can potentially lead to an increased rate or severity of infections. As suggested by individual case reports of patients with complement system deficiencies, including FD deficiency, inhibition of the complement

system may result in an increased risk of infection with *N meningitidis* (Biesma et al 2001, Figueroa and Densen 1991, Hiemstra et al 1989, Sprong et al 2006).

Evidence source(s) and strength of evidence:

This important potential risk is based on danicopan mode of action, experience from individuals with complement deficiencies (Biesma et al 2001, Figueroa and Densen 1991, Hiemstra et al 1989, Sprong et al 2006), and terminal complement inhibitors, eculizumab and ravulizumab (Röth et al 2018).

The link between terminal complement components deficiency states and (serious) infections caused by *N meningitidis* is firmly established and evidenced by the scientific literature (Figueroa and Densen 1991, Lewis and Ram 2014, Ram et al 2010, Ross and Densen 1984). However, this risk remains potential for FD inhibitors since classical and lectin pathways of complement are not inhibited by FD blockade.

Characterisation of the risk:

The frequency of meningococcal infection has not yet been established for danicopan as no event was observed in association with danicopan administration within the clinical development programme.

In general, meningococcal infections (presenting either as sepsis or meningitis) are rapidly life-threatening conditions with potentially fatal outcomes if not promptly diagnosed and treated. Timely diagnosis and treatment initiation immediately after presentation of the infection has shown to markedly impact the outcome (Vyse et al 2013).

Meningococcal infections may leave patients with disabling permanent sequelae including physical, neurological, cognitive, behavioural and psychological consequences such as behavioural difficulties, seizures, motor deficits, visual impairment, and hearing loss (Pace and Pollard 2012, Vyse et al 2013).

Risk factors and risk groups:

No risk factors specific to danicopan were identified. General risk factors for meningococcal infection include the following:

- Underlying disease (eg, splenectomised patients with sickle cell disease), genetic complement deficiency or therapeutic inhibition of complement (eg, C5 inhibitors eculizumab and ravulizumab)
- Lack of commercially available vaccine against certain meningococcus serogroup
- (Partial) resistance of meningococcal strain to prophylactic antibiotics
- Professionals who are exposed to environments of greater risk for meningococcal disease

- Research, industrial, and clinical laboratory personnel who are routinely exposed to *N meningitidis*
- Military personnel during recruit training (military personnel may be at increased risk of meningococcal infection when accommodated in close quarters)
- Day-care centre workers
- Living on a college or university campus
- Travelling to endemic areas for meningococcal meningitis (eg, India, Sub Saharan Africa, pilgrimage to Saudi Arabia for Hajj).

Preventability:

Danicopan therapy must not be initiated in patients with unresolved *N meningitidis* infection or in patients with unknown history of vaccination or who are not up to date on their meningococcal vaccines as per local guidelines.

Patients must be vaccinated or revaccinated according to current national guidelines for vaccination use.

It has been shown *in vitro* that C5 inhibitor eculizumab interferes with the bactericidal and opsonophagocytic-mediated protection elicited by meningococcal vaccines (Granoff et al 2019, Konar and Granoff 2017, van den Broek et al 2019). Since FD inhibitors, including danicopan, appear to have little impact on serum bactericidal activity in vaccinated or previously exposed patients (Granoff et al 2019), vaccination should provide protection from meningococcal infections in subjects receiving danicopan.

Patients who initiate danicopan treatment less than 2 weeks after receiving a meningococcal vaccine, must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, and W135 are recommended in preventing the commonly pathogenic meningococcal serogroups. Vaccination against serogroup B, where available, is also recommended. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

All patients treated with danicopan should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and steps should be taken to seek medical care immediately.

Impact on the risk-benefit balance of the product:

Meningococcal infection is a serious, life-threatening acute condition with potentially fatal outcomes if not recognised in a timely manner and appropriately treated.

Increased risk of meningococcal infections is directly associated with the inhibition of (terminal) complement components. The long-term post-marketing experience with the C5 inhibitor eculizumab showed stable overall reporting rates of meningococcal infection in eculizumab treated patients at 0.3 to 0.5 per 100 patient-years with fatalities occurring at a rate similar to that reported in the general population (MacNeil et al 2018, van Deuren et al 2000).

Furthermore, the FD inhibitors showed advantages over terminal complement inhibitors in the prevention of meningococcal infection by prophylactic vaccination (Granoff et al 2019). Therefore, the risk minimisation measures in place for the prevention and overall management of meningococcal infections appear to be appropriate and effective.

Public health impact:

No impact on the public health is expected for this risk.

II.7.3.1.2 Important Potential Risk 2: Serious Infections

Potential mechanisms:

The complement system plays an important role in the host defence against infection. Activation of the classical or the alternative pathway results in the cleavage of C3, the central component of the system. Factor D has an essential role in the initiation and propagation of the alternative pathway of complement activation and in the amplification loop of C3 activation (Biesma et al 2001).

Danicopan is an FD inhibitor. FD inhibition is associated with an increased risk of *N meningitidis* infection, as suggested by reports in individuals with complete or near complete inhibition, with a similar infection risk as late complement inhibitors. Since the classical and lectin pathway-mediated early complement components are not inhibited by danicopan and early complement components are not inhibited by C5 inhibitors when danicopan is administered as an add-on to ravulizumab or eculizumab, the mechanism of phagocytic killing remains active and able to clear most non-*Neisseria* infections.

PNH patients receiving danicopan are often at increased risk of infection due to the underlying medical condition or its complications. Therefore, a causative link between danicopan and serious infections has not been established.

Evidence source(s) and strength of evidence:

This important potential risk is based on danicopan mode of action, experience from individuals with inherited alternative pathway deficiencies, including partial or complete FD deficiency (Biesma et al 2001, Hiemstra et al 1989, Kluin-Nelemans et al 1984, Ram et al 2010, Sprong et al 2006, Weiss et al 1998), and terminal complement inhibitors, eculizumab

and ravulizumab (Röth et al 2018), whereas a causal relationship of serious infections to ravulizumab has not yet been confirmed. Since a causal relationship of serious infections to danicopan therapy also has not been confirmed in clinical trials, this remains a potential risk.

Characterisation of the risk:

The exposure-adjusted rate of serious infections in the PNH clinical development programme for danicopan (N = 106) was 9.8 events per 100 patient-years, ie, 13 subjects (12.3%) reported 16 serious events. The serious infections reported in more than 2 subjects each included COVID-19, cystitis, and pneumonia. A serious event of *Staphylococcal* sepsis was reported in a single subject (0.9%).

In Study ALXN2040-PNH-301, during the placebo-controlled treatment period, the incidence of serious infections was similar between the add-on danicopan group and the add-on placebo group.

Most infections observed in the development programme were nonserious in nature, typical in presentation and evolution/response to treatment, and fully manageable. Additionally, most infection events were assessed as not related to danicopan treatment by the investigator and resolved without modification to danicopan treatment.

Risk factors and risk groups:

The general risk factors for development of infections include any immunodeficiency, either acquired or due to underlying condition. PNH patients are at increased risk of infections, especially those who experience bone marrow failure (aplastic anaemia, myelodysplastic syndrome).

Preventability:

The healthcare professionals and patients should be aware of the potential risk of serious infections and their signs and symptoms.

Danicopan should be administered with caution to patients with active systemic infections.

Impact on the risk-benefit balance of the product:

Danicopan is an FD inhibitor and as such, there is a plausible mechanism for the development of infections by inhibition of the alternative complement pathway. However, since danicopan does not impact the classical or lectin pathways of complement, the ability to clear most of the non-neisserial infections should remain intact.

Considering the nature and overall presentation of serious infections observed in the clinical development programme for danicopan, the impact of this risk on the benefit-risk balance of danicopan is acceptable.

Public health impact:

No impact on the public health is expected for this risk.

II.7.3.1.3 Important Potential Risk 3: Malignancies and haematologic abnormalities

Potential mechanisms:

Haematologic malignancy in PNH patients is most likely a manifestation of underlying abnormalities of haematopoietic function. Antitumor immunity is not expected to be affected by danicopan.

Evidence source(s) and strength of evidence:

Danicopan is a highly selective inhibitor of FD and does not have broad immunosuppressive effects. Danicopan's selective complement blockade preserves the activity of other immune components allowing continued immunosurveillance against cancer cells. Additionally, since tumor cells can escape the complement system and produce complement proteins, the role of the complement system in cancer surveillance and clearance is limited.

Malignancies and hematologic abnormalities are monitored as an important potential risk with C5 inhibitor ravulizumab therapy, though a causal relationship to ravulizumab has not yet been confirmed. Since a causal relationship of malignancies and hematologic abnormalities to danicopan therapy also has not been confirmed in clinical trials, this remains a potential risk. Additionally, as the natural evolution of PNH makes PNH patients more prone to development of haematologic abnormalities or malignancies (de Latour, 2008; Hillmen, 1995; Socié, 1996), the role of danicopan remains unknown.

Characterisation of the risk:

The exposure-adjusted rate of neoplasia (malignant, benign, and unspecified) in the PNH clinical development programme for danicopan (N = 106) was 4.3 events per 100 patient-years, ie, 7 subjects (6.6%) reported 7 events. Of these, only 1 event was malignant (invasive ductal breast carcinoma), and the exposure-adjusted rate of malignant neoplasm was 0.6 events per 100 patient-years. The participant had relevant risk factors of pre-existing breast nodule and a family history of breast cancer. The non-malignant neoplasia reported were events which are common in the general population, and the nature, evolution, and outcome of these events did not indicate a causal relationship with danicopan treatment.

Risk factors and risk groups:

Patients with underlying myelodysplastic syndrome or other pre-leukaemic syndromes are at risk of leukaemia acutisation.

Preventability:

There is currently no evidence of an increased risk of malignancies and haematologic abnormalities for danicopan specifically and, therefore, no requirements for prevention are needed.

Impact on the risk-benefit balance of the product:

Considering the anticipated benefits of danicopan therapy and overall characteristics of the PNH population, the impact of this risk on the benefit-risk balance of danicopan is acceptable.

Public health impact:

Not applicable.

II.7.3.2 Presentation of missing information

II.7.3.2.1 Missing information 1: Use in pregnant and breastfeeding women

Evidence source:

The non-clinical studies did not show any embryo-foetal toxicity or teratogenic effects associated with danicopan. Available pharmacodynamic/toxicological data in animals have shown excretion of danicopan and its metabolites in milk.

Pregnant and breastfeeding women were excluded from the clinical studies. There are no clinical data on use of danicopan during pregnancy, on excretion of danicopan in human breast milk, and potential effects on breast-fed child.

Population in need of further characterisation:

Use of danicopan in pregnant and breastfeeding women will be investigated through routine pharmacovigilance activities using targeted safety questionnaire. A planned post-authorisation safety study ALX-PNH-502 will further characterise the safety of danicopan in this population (refer to III.2).

II.7.3.2.2 Missing information 2: Use in patients with severe hepatic impairment

Evidence source:

Danicopan is extensively metabolised in the liver and the main route of excretion is hepatic. Although PNH patients with severe hepatic impairment were not excluded from the clinical programme, no patients fitting this criterion were enrolled.

Patients with PNH may experience venous or arterial thrombosis in diverse sites including intra-abdominal and hepatic veins (e.g. Budd-Chiari syndrome, mesenteric veins, the splenic vein) (Hill et al 2013, Hill et al 2012, Hillmen et al 2010, Plessier et al 2022). Results from the single-dose hepatic impairment study in otherwise healthy subjects indicated no clinically significant difference in pharmacokinetics of danicopan in the presence of moderate hepatic impairment (Child-Pugh Class B). However, no data were generated in subjects with severe hepatic impairment (Child-Pugh Class C) and results from the hepatic impairment study cannot be extrapolated to predict outcomes in patients with severe hepatic impairment.

Population in need of further characterisation:

The pharmacokinetics and safety of danicopan in subjects with severe hepatic impairment require further investigation. A planned post-authorisation safety study ALX-PNH-502 will further characterise the safety of danicopan in this population (refer to III.2).

II.7.3.2.3 Missing information 3: Long-term safety

Evidence source:

There are limited data on long-term exposure to danicopan in clinical trials. However, there is no scientific rationale to suspect that the safety profile of danicopan in patients with a longer duration of treatment would differ to that characterised so far based on short-term clinical trial exposure.

Population in need of further characterisation:

The typical clinical development programme is not designed to detect all adverse effects with long latency or those that are infrequent. As such, data on long-term safety of danicopan use are needed. A planned post-authorisation safety study ALX-PNH-502 and 2 ongoing studies ALXN2040-PNH-301 and ALXN2040-PNH-303 will further characterise the long-term safety of danicopan in PNH patients (refer to III.2).

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the safety concerns

Table II-5 Summary of safety concerns

Important identified risks	None
Important potential risks	Meningococcal infection Serious infections Malignancies and haematologic abnormalities
Missing information	Use in pregnant and breastfeeding women Use in patients with severe hepatic impairment Long-term safety

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaire for meningococcal infection:

This structured follow-up form is designed to optimise collection of all relevant information associated with the case reports of meningococcal infection to deepen the understanding of the factors leading to this risk associated with danicopan.

This form aims to collect detailed information about the patient, concerned medicinal product, patient's history with meningococcal infections and information about past vaccination and ongoing antibiotic prophylaxis. It further collects information on laboratory findings (bacteriology, serology, biopsy) and clinical presentation of the event. Finally, information about treatment and outcome of the event are collected.

Specific adverse reaction follow-up questionnaire for use in pregnant and breastfeeding women:

This follow-up form is designed to collect information on pregnancy, newborns/infants exposed to danicopan during pregnancy (up to 3 months after date of birth), and breastfeeding.

It aims to collect general information on the course of pregnancy and delivery together with the outcomes for the newborn as well as on breastfeeding and outcomes for the breast-fed children.

The follow-up forms are provided in full in Annex 4.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Post-authorisation safety study summary

Study short name and title:

ALX-PNH-502 - An Observational Cohort Study to Assess Long-Term Safety of Danicopan Add-on Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria: Analysis of IPIG-Registry Data

Rationale and study objectives:

This is a post-authorisation non-interventional cohort study to evaluate the safety of danicopan as an add-on to ravulizumab or eculizumab in adult patients with PNH who have residual haemolytic anaemia.

There are limited data on danicopan long-term safety and the safety of danicopan in pregnant and breastfeeding women and patients with severe hepatic impairment. Further, the safety

profile of danicopan including the risks of meningococcal infection and serious infections in treated patients has not been characterised in real-world settings.

This study seeks to characterise the safety profile of danicopan as an add-on to ravulizumab or eculizumab in adult participants with PNH. The study's primary objectives are to:

- Characterise the long-term safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with PNH
- Describe and compare the incidence of meningococcal infection in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy
- Describe and compare the incidence of serious infection in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy
- Describe and compare the incidence of malignancies and haematologic abnormalities in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy
- Characterise the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with severe hepatic impairment

The study's secondary objectives are to:

- Characterise the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in pregnant participants, pregnant partners of participants, or participants who are breastfeeding
- Describe the demographic and clinical profile at treatment initiation in participants with PNH treated with danicopan as add-on therapy to ravulizumab/eculizumab
- Assess danicopan as add-on therapy to ravulizumab/eculizumab treatment discontinuation patterns among participants with PNH

List of addressed safety concerns:

- Meningococcal infection
- Serious infections

- Malignancies and haematologic abnormalities
- Use in pregnant and breastfeeding women
- Use in patients with severe hepatic impairment
- Long-term safety

Study design:

Non-interventional International PNH Interest Group (IPIG) PNH registry-based cohort study.

Study population:

Adult patients enrolled in the IPIG PNH Registry ≥ 18 years of age at treatment initiation with known year of birth, sex, informed consent date, and danicopan and ULTOMIRIS (ravulizumab) and/or SOLIRIS (eculizumab) treatment status will be eligible for inclusion in the study.

Milestones:

- Draft study protocol submission: 3 months post-approval
- First data extraction: Q4 2024
- Interim study reports: every 2 years throughout study conduct
- Final study report submission: Q3 2031

Extension period of pivotal study in patients treated with danicopan summary

Study short name and title:

ALXN2040-PNH-301 - A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Clinically Evident Extravascular Hemolysis (EVH)

Rationale and study objectives:

This pivotal Phase 3 study aims to evaluate the efficacy and safety of danicopan as an add-on therapy to a C5 inhibitor (eculizumab or ravulizumab) to treat clinically-evident EVH.

Additionally, the study aims to evaluate the safety of danicopan as add-on therapy to a C5 inhibitor during the long-term extension (LTE) period.

List of addressed safety concerns:

- Long-term safety

Study design:

This is a multiple-region, randomised, double-blind, placebo controlled, multiple-dose, Phase 3 study in patients with PNH who have clinically evident EVH on a C5 inhibitor (eculizumab or ravulizumab).

Study population:

This study has enrolled 86 patients who are receiving C5 inhibitor therapy according to the usual dose and schedule and continue to experience anaemia with or without the need of transfusion support.

Milestones:

Final clinical study report submission: Q1 2026

Long-term extension study in patients treated with danicopan summary

Study short name and title:

ALXN2040-PNH-303 - A Long-term Extension (LTE) Study to Characterize the Safety and Efficacy of Danicopan as an Add-on Therapy to a Complement Component 5 Inhibitor (C5i) in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Previously Treated with Danicopan in an Alexion-sponsored Clinical Study

Rationale and study objectives:

The purpose of this LTE study is to characterise the long-term safety and efficacy of danicopan as an add-on therapy to C5 inhibitor in patients with PNH who were previously treated with danicopan in an Alexion-sponsored clinical study.

List of addressed safety concerns:

- Long-term safety

Study design:

This is a single arm LTE study.

Study population:

This study will enrol patients with PNH who have completed participation in Alexion-sponsored clinical studies with danicopan as an add-on therapy to a C5 inhibitor.

Approximately 90 patients will be enrolled in this study.

Milestones:

Final clinical study report submission: Q1 2029

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 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				
"An Observational Cohort Study to Assess Long-Term Safety of Danicopan Add-on Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria: Analysis of IPIG-Registry Data" (ALX-PNH-502) Planned	Primary objectives: - Characterise the long-term safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with PNH - Describe and compare the incidence of meningococcal infection in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy - Describe and compare the incidence of serious infection in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy - Describe and compare the incidence of malignancies	- Meningococcal infection - Serious infections - Malignancies and haematologic abnormalities - Use in pregnant and breastfeeding women - Use in patients with severe hepatic impairment - Long-term safety	Draft study protocol submission	3 months post-approval
			First data extraction	Q4 2024
			Interim study reports	Every 2 years throughout study conduct
			Final CSR submission	Q3 2031

Table III-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	and haematologic abnormalities in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy - Characterise the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with severe hepatic impairment Secondary objectives: - Characterise the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in pregnant participants, pregnant partners of participants, or participants who are breastfeeding - Describe the demographic and clinical profile at treatment initiation in participants with PNH treated with danicopan as			

Table III-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	add-on therapy to ravulizumab/eculizumab - Assess danicopan as add-on therapy to ravulizumab/eculizumab treatment discontinuation patterns among participants with PNH			
"A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Clinically Evident Extravascular Hemolysis (EVH)" (ALXN2040-PNH-301) Ongoing	Primary objective: - To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor at 12 weeks Safety objectives: - To evaluate the safety and tolerability of 24 weeks of treatment with danicopan as add-on therapy to a C5 inhibitor - To evaluate the safety and tolerability of danicopan as add-on therapy to a C5 inhibitor during the LTE period	- Long-term safety	Final CSR submission	Q1 2026
"A Long-term Extension (LTE) Study to Characterize the Safety and Efficacy of	Primary objective: - To characterise the long-term safety of treatment	- Long-term safety	Final CSR submission	Q1 2029

Table III-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Danicopan as an Add-on Therapy to a Complement Component 5 Inhibitor (C5i) in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Previously Treated with Danicopan in an Alexion-sponsored Clinical Study" (ALXN2040-PNH-303) Ongoing	with danicopan as an add-on therapy to a C5 inhibitor Secondary objectives: - To characterise long-term efficacy of danicopan as an add-on therapy to a C5 inhibitor - To characterise the long-term effect of treatment with danicopan as an add on therapy to a C5 inhibitor on FACIT-Fatigue scores and on European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 Scale scores - To further characterise the safety of danicopan as an add-on therapy to a C5 inhibitor			

C5, complement component 5; CSR, clinical study report; FACIT, Functional Assessment of Chronic Illness Therapy; IPIG, International PNH Interest Group; LTE, long-term extension; PNH, paroxysmal nocturnal haemoglobinuria; Q, quarter.

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Table V-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Meningococcal infection	Routine risk communication: SmPC sections 4.3 and 4.4 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Signs and symptoms of meningococcal infection and steps to be taken should any of these occur are detailed in SmPC section 4.4 and the PL section 2. The need for a vaccination (including the need for antibiotic prophylaxis until 2 weeks after vaccination) is stated in SmPC section 4.4. and PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.
Serious infections	Routine risk communication: SmPC section 4.4 PL sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.
Malignancies and haematologic abnormalities	Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.

Table V-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Use in pregnant and breastfeeding women	Routine risk communication: SmPC sections 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: The recommendation for the use of effective contraception during treatment and until 3 days after discontinuation is included in SmPC section 4.6 and PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.
Use in patients with severe hepatic impairment	Routine risk communication: SmPC sections 4.2, 4.4, and 5.2 Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.
Long-term safety	Other routine risk minimisation measures beyond the Product Information: Legal status: Subject to restricted medical prescription.

PL, Package Leaflet; SmPC, Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Meningococcal infection	Routine risk minimisation measure: SmPC sections 4.3 and 4.4 PL sections 2 and 4 Signs and symptoms of meningococcal infection and steps to be taken should any of these occur are detailed in SmPC section 4.4 and the PL section 2. The need for a vaccination (including the need for antibiotic prophylaxis until 2 weeks after vaccination) is stated in SmPC section 4.4. and PL section 2. Subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: ALX-PNH-502 (final CSR: Q3 2031)
Serious infections	Routine risk minimisation measure: SmPC section 4.4 PL sections 2 and 4 Subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: ALX-PNH-502 (final CSR: Q3 2031)
Malignancies and haematologic abnormalities	Routine risk minimisation measure: Subject to restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: ALX-PNH-502 (final CSR: Q3 2031)

Table V-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnant and breastfeeding women	Routine risk minimisation measure: SmPC sections 4.6 and 5.3 PL section 2 The recommendation for the use of effective contraception during treatment and until 3 days after discontinuation is included in SmPC section 4.6 and PL section 2. Subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: ALX-PNH-502 (final CSR: Q3 2031)
Use in patients with severe hepatic impairment	Routine risk minimisation measure: SmPC sections 4.2, 4.4, and 5.2 Subject to restricted medical prescription.	Additional pharmacovigilance activities: ALX-PNH-502 (final CSR: Q3 2031)
Long-term safety	Routine risk minimisation measure: Subject to restricted medical prescription	Additional pharmacovigilance activities: ALX-PNH-502 (final CSR: Q3 2031) ALXN2040-PNH-301 (final CSR: Q1 2026) ALXN2040-PNH-303 (final CSR: Q1 2029)

CSR, clinical study report; PL, Package Leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for VOYDEYA (danicopan)

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

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

This summary of the RMP for VOYDEYA 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 VOYDEYA RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

VOYDEYA is indicated as an add-on therapy to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria who have residual haemolytic anaemia. It contains danicopan as the active substance and it is given by oral route of administration.

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

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of VOYDEYA, together with measures to minimise such risks and the proposed studies for learning more about VOYDEYA risks, are outlined below.

Measures to minimise 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 authorised 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 (eg, with or without prescription) can help to minimise its risks.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report 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 VOYDEYA is not yet available, it is listed under 'missing information' below.

VI.2.1 List of important risks and missing information

Important risks of VOYDEYA are risks that need special risk management activities to further investigate or minimise 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 VOYDEYA. 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 (eg, on the long-term use of the medicine);

Table VI-1 List of important risks and missing information

Important identified risks	None
Important potential risks	Meningococcal infection Serious infections Malignancies and haematologic abnormalities
Missing Information	Use in pregnant and breastfeeding women Use in patients with severe hepatic impairment Long-term safety

VI.2.2 Summary of important risks

Table VI-2 Important potential risk: Meningococcal infection

Evidence for linking the risk to the medicine	This important potential risk is based on danicopan mode of action, experience from individuals with complement deficiencies (Biesma et al 2001, Figueroa and Densen 1991, Hiemstra et al 1989, Sprong et al 2006), and terminal complement inhibitors, eculizumab and ravulizumab (Röth et al 2018). The link between terminal complement components deficiency states and (serious) infections caused by *Neisseria meningitidis* is firmly established and evidenced by the scientific literature (Figueroa and Densen 1991, Lewis and Ram 2014, Ram et al 2010, Ross and Densen 1984). However, this risk remains potential for FD inhibitors since classical and lectin pathways of complement are not inhibited by FD blockade.
Risk factors and risk groups	No risk factors specific to danicopan were identified. General risk factors for meningococcal infection include the following: • Underlying disease (eg, splenectomised patients with sickle cell disease), genetic complement deficiency or therapeutic inhibition of complement (eg, C5 inhibitors eculizumab and ravulizumab) • Lack of commercially available vaccine against certain meningococcus serogroup • (Partial) resistance of meningococcal strain to prophylactic antibiotics • Professionals who are exposed to environments of greater risk for meningococcal disease • Research, industrial, and clinical laboratory personnel who are routinely exposed to *N meningitidis* • Military personnel during recruit training (military personnel may be at increased risk of meningococcal infection when accommodated in close quarters) • Day-care centre workers • Living on a college or university campus • Travelling to endemic areas for meningococcal meningitis (eg, India, Sub Saharan Africa, pilgrimage to Saudi Arabia for Hajj).
Risk minimisation measures	Routine risk minimisation measure: SmPC sections 4.3 and 4.4 PL sections 2 and 4 Signs and symptoms of meningococcal infection and steps to be taken should any of these occur are detailed in SmPC section 4.4 and the PL section 2. The need for a vaccination (including the need for antibiotic prophylaxis until 2 weeks after vaccination) is stated in SmPC section 4.4. and PL section 2. Subject to restricted medical prescription

Table VI-2 Important potential risk: Meningococcal infection

Additional pharmacovigilance activities	Additional pharmacovigilance activities: ALX-PNH-502 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

C5, complement component 5; FD, factor D; PL, Package Leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

Table VI-3 Important potential risk: Serious infections

Evidence for linking the risk to the medicine	This important potential risk is based on danicopan mode of action, experience from individuals with inherited alternative pathway deficiencies, including partial or complete FD deficiency (Biesma et al 2001, Hiemstra et al 1989, Kluin-Nelemans et al 1984, Ram et al 2010, Sprong et al 2006, Weiss et al 1998), and terminal complement inhibitors, eculizumab and ravulizumab (Röth et al 2018). Since a causal relationship of serious infections to danicopan therapy has not been confirmed in clinical trials, this remains a potential risk.
Risk factors and risk groups	The general risk factors for development of infections include any immunodeficiency, either acquired or due to underlying condition. PNH patients are at increased risk of infections, especially those who experience bone marrow failure (aplastic anaemia, myelodysplastic syndrome).
Risk minimisation measures	Routine risk minimisation measure: SmPC section 4.4 PL sections 2 and 4 Subject to restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: ALX-PNH-502 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

FD, factor D; PL, Package Leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

Table VI-4 Important potential risk: Malignancies and haematologic abnormalities

Evidence for linking the risk to the medicine	Malignancies and hematologic abnormalities are monitored as an important potential risk with C5 inhibitor ravulizumab therapy, though a causal relationship to ravulizumab has not yet been confirmed. Since a causal relationship of malignancies and hematologic abnormalities to danicopan therapy also has not been confirmed in clinical trials, this remains a potential risk. Additionally, as the natural evolution of PNH makes PNH patients more prone to development of haematologic abnormalities or malignancies (de Latour, 2008; Hillmen, 1995; Socié, 1996), the role of danicopan remains unknown.
Risk factors and risk groups	Patients with underlying myelodysplastic syndrome or other pre-leukaemic syndromes are at risk of leukaemia acutisation.

Table VI-4 Important potential risk: Malignancies and haematologic abnormalities

Risk minimisation measures	Routine risk minimisation measure: Subject to restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: ALX-PNH-502 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

C5, complement component 5; PNH, paroxysmal nocturnal haemoglobinuria

Table VI-5 Missing information: Use in pregnant and breastfeeding women

Risk minimisation measures	Routine risk minimisation measure: SmPC sections 4.6 and 5.3 PL section 2 The recommendation for the use of effective contraception during treatment and until 3 days after discontinuation is included in SmPC section 4.6 and PL section 2. Subject to restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: ALX-PNH-502 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

PL, Package Leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

Table VI-6 Missing information: Use in patients with severe hepatic impairment

Risk minimisation measures	Routine risk minimisation measure: SmPC sections 4.2, 4.4, and 5.2 Subject to restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: ALX-PNH-502 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

Table VI-7 Missing information: Long-term safety

Risk minimisation measures	Routine risk minimisation measure: Subject to restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: ALX-PNH-502 ALXN2040-PNH-301 ALXN2040-PNH-303 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

PNH, paroxysmal nocturnal haemoglobinuria.

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of VOYDEYA.

VI.2.3.2 Other studies in post-authorisation development plan

ALX-PNH-502

Purpose of the study: This is a post-authorisation non-interventional cohort study to evaluate the safety of danicopan as an add-on to ravulizumab or eculizumab in adult patients with PNH who have residual haemolytic anaemia.

There are limited data on danicopan long-term safety and the safety of danicopan in pregnant and breastfeeding women and patients with severe hepatic impairment. Further, the safety profile of danicopan including the risk of meningococcal infection in treated patients has not been characterised in real-world settings.

This study seeks to characterise the safety profile of danicopan as an add-on to ravulizumab or eculizumab in adult participants with PNH. The study's primary objectives are to:

- Characterise the long-term safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with PNH
- Describe and compare the incidence of meningococcal infection in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy
- Describe and compare the incidence of serious infection in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy

- Describe and compare the incidence of malignancies and haematologic abnormalities in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy

- Characterise the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with severe hepatic impairment

The study's secondary objectives are to:

- Characterise the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in pregnant participants, pregnant partners of participants, or participants who are breastfeeding

- Describe the demographic and clinical profile at treatment initiation in participants with PNH treated with danicopan as add-on therapy to ravulizumab/eculizumab

- Assess danicopan as add-on therapy to ravulizumab/eculizumab treatment discontinuation patterns among participants with PNH

ALXN2040-PNH-301

Purpose of the study: This pivotal Phase 3 study aims to evaluate the efficacy and safety of danicopan as an add-on therapy to a C5 inhibitor (eculizumab or ravulizumab) to treat clinically-evident EVH.

Additionally, the study aims to evaluate the safety of danicopan as add-on therapy to a C5 inhibitor during the long-term extension (LTE) period.

ALXN2040-PNH-303

Purpose of the study: The purpose of this LTE study is to characterise the long-term safety and efficacy of danicopan as an add-on therapy to C5 inhibitor in patients with PNH who were previously treated with danicopan in an Alexion-sponsored clinical study.

VII. PART VII: ANNEXES

VII.1 ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

- *Global Pharmacovigilance Suspected/Confirmed Meningococcal Case Questionnaire*
- *Pregnancy Reporting and Outcome Form/Breast Feeding*

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

Alexion Manufacturer Number:	

Date of Birth: *(DD/MMM/YYYY)*

Age (if known):

Or Age Category:

☐ Child (<12 years) ☐ Adolescent (12-17 years) ☐ Adults (18-65 years) ☐ Elderly (>65 years)

Gender:

☐ Female ☐ Male ☐ Prefer not to disclose

☐ Intersex ☐ Transgender

Weight: ☐ lbs. ☐ kgs.

Height: ☐ cm. ☐ in.

Ethnicity: *(Applicable for US Only. Record only if obtained through voluntary self-identification.)*

☐ Not Hispanic or Latino ☐ Hispanic or Latino

☐ Not Reported ☐ Unknown

Race: *(Applicable for US Only. Record only if obtained through voluntary self-identification.)*

☐ Aboriginal or Torres Strait Islander ☐ Caucasian

☐ African American ☐ Native Hawaiian or Pacific Islander

☐ American Indian or Alaska Native ☐ Not Reported

☐ Asian ☐ Unknown

☐ Black

☐ Other *(Specify)*

Product Name: **Current Dosage:**

Initiation Date and Dosage: **Last dose prior to the event Date and Dosage:**

(DD/MMM/YYYY)

Action Taken with Product:

☐ No Change ☐ Temporarily withdrawn ☐ Drug Interrupted ☐ Withdrawn

☐ Dose Increased ☐ Dose Decreased ☐ Unknown ☐ Not Applicable

☐ Other *(Specify)*

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

Product Name: **Current Dosage:**

Initiation Date and Dosage: **Last dose prior to the event Date and Dosage:**

(DD/MMM/YYYY)

Action Taken with Product:

☐ No Change ☐ Temporarily withdrawn ☐ Drug Interrupted ☐ Withdrawn

☐ Dose Increased ☐ Dose Decreased ☐ Unknown ☐ Not Applicable

☐ Other *(Specify)*

Patient History

Previous history of meningococcal infection? ☐ Yes ☐ No ☐ Unknown

(please describe)

Risk factor for meningococcal infection? ☐ Yes ☐ No ☐ Unknown

(please describe)

(ex. Medical condition, exposure to laboratory, industry, close quarters, college campus, daycare workers, military, living in proximity or recent travel to endemic areas)

Meningococcal Vaccination ☐ Yes *(provide vaccine name and date below)* ☐ No ☐ Unknown

Was the patient vaccinated per Advisory Committee on Immunization Practices (ACIP) guidelines?
(Applicable for US only)

☐ Yes ☐ No ☐ Unknown

Was the patient vaccinated according to current national vaccination guidelines?
(Applicable for ex-US only)

☐ Yes ☐ No ☐ Unknown ☐ Not Applicable

Vaccine Name: ☐ Initial Vaccination date:

(DD/MMM/YYYY)

☐ Booster Vaccination date:

(DD/MMM/YYYY)

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

Vaccine Name: ☐Initial Vaccination date: *(DD/MMM/YYYY)*

☐Booster Vaccination date: *(DD/MMM/YYYY)*

Vaccine Name: ☐Initial Vaccination date: *(DD/MMM/YYYY)*

☐Booster Vaccination date: *(DD/MMM/YYYY)*

Vaccine Name: ☐Initial Vaccination date: *(DD/MMM/YYYY)*

☐Booster Vaccination date: *(DD/MMM/YYYY)*

Antibiotic prophylaxis: ☐Yes ☐No

(If yes) Antibiotic Name / Active substance: Dosage / frequency:

Start date: *(DD/MMM/YYYY)* Stop date: *(DD/MMM/YYYY)* ☐ Ongoing

Is the patient compliant with their antibiotic prophylaxis? ☐ Yes ☐ No ☐ Unknown

Bacteriological work up

CSF: *Direct Exam Results:*

CSF: *Culture Results:*

CSF: *PCR Results:*

Blood: *Direct Exam Results:*

Blood: *Culture Results:*

Blood: *PCR Results:*

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

Clinical Presentation

Description of initial clinical signs and/or symptoms patient has presented with:

Onset Date of first symptom(s) *(DD/MMM/YYYY)*

Malaise	☐ Yes ☐ No	
Myalgia	☐ Yes ☐ No	
Fever	☐ Yes ☐ No	*(If yes, please provide temp)*
Hypothermia	☐ Yes ☐ No	*(If yes, please provide temp)*
Headache	☐ Yes ☐ No	
Neck stiffness	☐ Yes ☐ No	
Photophobia	☐ Yes ☐ No	
Vomiting	☐ Yes ☐ No	
Confusion	☐ Yes ☐ No	
Chills	☐ Yes ☐ No	
Convulsions	☐ Yes ☐ No	
Rash	☐ Yes ☐ No	*(If yes, please specify type and localization)*
Other	☐ Yes ☐ No	*(Please specify)*

Patients who receive(d) Antibiotic Prophylaxis Only:
Minimum Inhibitory Concentration (MIC):

Serology

Neisseria meningitidis serogroup / serotype:

☐ A ☐ B ☐ C ☐ W135 ☐ X ☐ Y ☐ Z

Other:

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

(specify)

Neisseria meningitidis serosubtype: *(if available)*

Neisseria meningitidis Genotyping (MLST): *(if available)*

Meningococcal Antigen Typing System (MATS) assay (For serogroup B infection in patients vaccinated by 4CMenB):

Skin biopsy culture:

☐ Done
☐ Not done

If done, results:

Treatment of the event

Antibiotic Name:

Start date: *(DD/MMM/YYYY)*

Stop date: *(DD/MMM/YYYY)*

☐ Ongoing

Other medication:

Medication Name:

Start date: *(DD/MMM/YYYY)*

Stop date: *(DD/MMM/YYYY)*

☐ Ongoing

Other supportive treatment:

Was the patient admitted to the ICU? ☐ Yes ☐ No ☐ Unknown

Did the patient experience or require any of the following (select all that apply):

Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire

Please send completed form to: adverseeventreporting@alexion.com or Fax to: 1-203-439-9347 or clinicalsae@alexion.com (for clinical trials only)

☐ Any organ system failure *(specify)*

☐ Mechanical ventilation

☐ Medication (vasopressors) to support blood pressure *(specify)*

Outcome

☐ Unknown

☐ Recovered ☐ Recovered with sequelae *(specify sequelae)*

Date Recovered: (DD/MMM/YYYY)

☐ Ongoing ☐ Fatal *(Specify cause of death)*

Date of Death: (DD/MMM/YYYY)

Additional Comments:

Name of Individual Completing the Form
Designation
Contact Information
Date Form Completed

ALEXION Pregnancy/Breastfeeding Reporting and Outcome Form	FRM-0502455 v1.0

1. *Please complete and send Section I (p1-3) at start of pregnancy depending on report type to either…*
   - ☐ *Post-Marketing Email*: *AdverseEventReporting@alexion.com*
     OR
   - ☐ *Clinical Trials/Studies Email*: *ClinicalSAE@alexion.com*
2. *Please continue report both immediately post-delivery and at three months post-delivery*
3. *Please add additional notes, if necessary, into section IV at the bottom of page 4.*

I Pre-delivery

A)	**General Information**			
A0	Suspect Drug: Action taken with suspect drug in response to pregnancy: _____	Indication: _____ Dosage of drug prior to discovery of pregnancy: _____	Adjusted dosage of drug since discovery of pregnancy: _____	Date of last drug administration before pregnancy was noticed. ___/_____/_____ dd /mmm / yyyy
A1	Patient ID *(if applicable):*	Pregnant: Patient ☐ Patient's partner ☐	Date pregnancy was noticed ___/_____/_____ dd /mmm/yyyy	Estimated date of delivery ___/_____/_____ dd / mmm / yyyy
A2	Mother's date of birth or Age	___/_____/_____ or _____ dd / mmm / yyyy	Height: _____ ☐ cm ☐ ft/inches	Weight: _____ ☐ kg ☐ lbs
A3	Source of information for this report (Reporter)	☐ = (Pregnant) woman ☐ = Primary care physician/Investigator ☐ = Obstetrician ☐ = Pediatrician ☐ = Other: _____		
A4	Date of this Report (current date)	___/_____/_____ dd / mmm / yyyy		
A5	Name, Address and email of Reporter			
A6	Name, Address and email of Gynecologist- obstetrician (if applicable)			
A7	Name and address of place of planned delivery			
B)	**Maternal Information**			
Obstetrical History				
B1	Previous pregnancies	N = _____		
B2	Outcome of previous pregnancies (insert digits if multiple pregnancies)	☐ = Live birth ☐ = Miscarriage ☐ = Elective termination ☐ = Late fetal death ☐ = Ectopic pregnancy ☐ = Molar pregnancy		

ALEXION

Pregnancy/Breastfeeding Reporting and Outcome Form	FRM-0502455 v1.0

B3	Previous pregnancy complications:	□ = None □ = _____
B4	Previous fetal / neonatal abnormalities and type	□ = Yes _____ □ = None
B5	Medical History	□ = None □ = Hypertension □ = Diabetes □ = Seizures □ = Thyroid disorder □ = Asthma □ = Allergic disease □ = Heart Disease □ = Depression □ = Other psychiatric disorder □ = Sexual transmitted disease □ = Hepatitis □ = HIV / AIDS
B6	Family history	□ = None □ = History of congenital abnormality □= Psychomotor retardation in family
B7	Consanguinity between parents	□ = None □ Degree of relationship: _____
Current Pregnancy		
B8	Date of last menstrual period (LMP*)	___/_____/_____ dd /mmm / yyyy
B9	Gestational age at the time of last study drug intake	_____weeks _____ days based on □ = Ultrasound □ = LMP*
B10	Number of fetuses	N = _____
B11	Contraceptive method(s) used before pregnancy	= None = Oral contraceptive = Other _____
B12	Recreational drug use	□ = Tobacco □ = Alcohol □ = Illicit drug (specify amount and when stopped)
B13	Positive serology tests	□ = None □ = Rubella □ = Toxoplasmosis □ = Other_____
Please fill out B14-B17 for initial and follow-up information:		
B14	Concomitant medication (including over-the-counter medication, supplements, vitamins)	Initial: Follow-up:
B15	Complications during pregnancy and date (including any adverse drug reactions) Please report further complications on page 4	Initial □ = None □ = (If any: document on last page) Follow-up □ = None □ = (If any: document on last page)

ALEXION Pregnancy/Breastfeeding Reporting and Outcome Form	FRM-0502455 v1.0

B16	Disease course(s) during pregnancy and any complications Please indicate for all complications listed in B17.	Initial □= None □= (If any: document on last page) Follow-up: □= None □= (If any: document on last page)
B17	Antenatal check-up (specify dates and results), e.g. fetal ultrasound, serum markers (AFP etc), chorionic biopsy, amniocentesis	Initial: □= No path. findings □= (document on last page) Follow-up: □= No path. findings □= (document on last page)
	___/____/_____ ____ _____ dd / mmm / yyyy Reporter's Signature Date (Initial)	___/_____/_____ _____ dd /mmm / yyyy Reporter's Signature Date (Follow Up)

II Post-delivery

C) **Delivery and Neonatal Information** (Initial) - Please also complete B14-B17 if applicable			
C1	**Source and date of information**		___/_____/_____ dd/ mmm/yyyy
C2	**Mode of delivery**	□ = Spontaneous □ = Caesarian section □ = Other ___ _____	
C3	**Labor / Delivery complications**	□ = None □ Fetal distress □ Amniotic fluid abnormal □ Abnormal placenta □ = Other _____	
C4	**Outcome of pregnancy**	□ = Live birth □ = Miscarriage □ = Elective termination □ = Late fetal death □ = Ectopic pregnancy □ = Molar pregnancy	
C5	**Date of delivery**	___/_____/_____ dd /mmm / yyyy	Gender: □ = Male □ = Female
C6	**Gestational age at birth**	_____ weeks	
C7	**Weight at birth**	_____ □kg lbs	
C8	**Length**	_____ □cm inches	
C9	**Head circumference**	_____ □cm inches	
C10	**Malformation/anomalies diagnosed at birth**	□ = None □ = Other:	
C11	**APGAR Score**	APGAR Score 1 APGAR Score 2	
C12	**Admission to intensive care unit?**	□ = No □ = Yes:	
C13	**Neonatal illness, hospitalization, drug therapies**	□ = None □ = Other:	

ALEXION Pregnancy/Breastfeeding Reporting and Outcome Form	FRM-0502455 v1.0

C14	**Breastfeeding**	□ = No □ = Yes: Start date ___/_____/_____ Stop date ___/_____/_____ dd /mmm / yyyy dd /mmm / yyyy Did the breastfed infant experience any adverse events or side effects □ = No □ = Yes (please complete an adverse event report form and send it to Alexion)

D) Fetal Information in case of elective termination, spontaneous abortion, and late fetal death			
D1	**Source and date of information**		___/_____/_____ dd/mmm/yyyy
D2	**Reason for termination (If applicable)**		
D3	**Gestational age at termination**	_____weeks	
D4	**Results of physical examination (gender, external anomalies) and pathology**	_____	

III Follow-up - Three months after birth

1	**Source and date of information**		___/_____/_____ dd/mmm/yyyy
2	**Malformation/anomalies diagnosed since initial report**	□ = None □ = Other:	
3	**Infant illnesses hospitalizations, drug therapies**	□ = None □ = Other:	
Reporter's Signature _____		___/____/____ dd/mmm/yyyy	

IV Additional Notes

VII.2 ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Not applicable.