PASS Protocol	
Active substance	Danicopan
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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

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder(s)	Alexion Europe SAS 103-105 rue Anatole France 92300 Levallois-Perret France
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This document has been e-signed in Alexion's electronic document management system. Please refer to last page for e-signature details.

Approved by:

PPD Epidemiology — Date

PPD
Sponsor's Responsible Medical Officer — Date

PPD
Deputy EU Qualified Person Responsible for Pharmacovigilance — Date

PASS INFORMATION

Title	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
Protocol version identifier	Original
Date of last version of protocol	Not applicable
HMA-EMA Catalogue of RWD studies number	Study to be registered prior to first data extraction
Active substance	Danicopan; ALXN2040
Medicinal product	Voydeya®
Product reference	EU/1/24/1792/001 EU/1/24/1792/002 EU/1/24/1792/003 EU/1/24/1792/004
Procedure number	EMEA/H/C/005517
Marketing authorization holder(s)	Alexion Europe SAS 103-105 rue Anatole France 92300 Levallois-Perret France
Joint PASS	No
Research question and objectives	Primary objectives: • Characterize 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 infections 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 hematologic abnormalities in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) Ultomiris or Soliris monotherapy • Characterize the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with

	PNH and with severe hepatic impairment Secondary objectives: • Characterize 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 discontinuation patterns of danicopan as add-on therapy to ravulizumab/eculizumab treatment among participants with PNH
Countries of study	Countries participating in the IPIG PNH Registry, including but not limited to: Argentina, Australia, Austria, Canada, Denmark, Finland, France, Germany, Greece, Italy, Japan, Netherlands, Norway, Saudi Arabia, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States
Author(s)	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation or Special Term	Explanation
ADR	adverse drug reaction
AE	adverse event
C3/5/5a/5b-9	complement component 3/5/5a/5b-9
C5i(s)	complement component 5 inhibitor(s)
CFR	Code of Federal Regulations
CRO	clinical research organization
CS-EVH	clinically significant EVH
DALY	disability-adjusted life year
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUROCAT	European surveillance of congenital anomalies
EVH	extravascular hemolysis
FB	Factor B
FD	Factor D
GPP	Good Pharmacoepidemiology Practice
GPS	Global Patient Safety
GVP	Good Pharmacovigilance Practices
HA	Health Authority
Hgb	hemoglobin
HMA	Heads of Medicines Agencies
HRQoL	health-related quality of life
HRU	health-resource utilization
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IPIG	International PNH Interest Group
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology

Abbreviation or Special Term	Explanation
IT	information technology
IVH	intravascular hemolysis
LDH	lactate dehydrogenase
MAC	membrane attack complex
MAH	marketing authorization holder
MAVE	major adverse vascular events
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
PAS	post-authorization studies
PASS	post-authorization safety study
PNH	paroxysmal nocturnal hemoglobinuria
pRBC	packed red blood cell(s)
PRO	participant-reported outcome
PSUR	public safety update report
Q	quarter
QALY	quality-adjusted life year
RBC	red blood cell
RMP	risk management plan
RWD	real-world data
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis Software®
ULN	upper limit of normal
WBC	white blood cell

3. RESPONSIBLE PARTIES

Table 1: Key Personnel Involved in the Study

Key Personnel	Details
Medical Affairs Lead	PPD Email address: PPD
Epidemiology Lead	PPD Email address: PPD

4. ABSTRACT

Title

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 background

PNH is an ultra-rare and life-threatening acquired hemolytic disorder caused by uncontrolled activation of the terminal complement pathway. Prevalence has been estimated to range from 1.04 to 3.81 per 100000 persons and patients typically present with PNH during adulthood. Chronic, uncontrolled C5 cleavage and release of C5a and C5b-9 lead to destruction of RBCs within blood vessels, known as IVH. The standard of care treatments for PNH currently are the C5is humanized monoclonal antibodies ravulizumab (ULTOMIRIS®) and eculizumab (SOLIRIS®), which inhibit C5 in the terminal complement pathway, prevent formation of MAC, and are effective in controlling IVH. However, a subset (approximately 20%) of patients with PNH treated with C5i may experience emergence of CS-EVH with approximately 10% of these patients requiring RBC transfusions. Therefore, there is an unmet medical need for a therapy that may adequately control EVH, while maintaining adequate IVH control.

Danicopan (tradename Voydeya®, tablet), is a first-in-class small molecule orally administered complement FD inhibitor indicated as add-on therapy to ravulizumab or eculizumab for the treatment of adult patients with PNH who have residual hemolytic anemia. It has been approved in various countries including Japan, the US, and those in the EU. Danicopan inhibits the alternative pathway mediated deposition of C3 fragments on PNH RBCs, a key cause of EVH, and improves anemia, transfusion burden, fatigue, and absolute reticulocyte count in adult patients with PNH and CS-EVH. However, there are limited data on danicopan long-term safety, including the risks of meningococcal infections and serious infections, and no data on safety in pregnant and breastfeeding women and patients with severe hepatic impairment.

Alexion Pharmaceuticals, Inc. has been the Sponsor of the International PNH Registry (M07-001) since June 2007 and has enrolled approximately 6000 patients with PNH worldwide. The primary intent of this Registry has been to characterize the long-term safety of eculizumab and ravulizumab. With the advent of additional novel therapies from various MAHs for the treatment of PNH, real world data is needed to characterize their long-term safety and effectiveness as well. IPIG, the only global professional society focusing specifically on PNH, proposed a single, unified, global registry of patients with PNH. The IPIG PNH Registry is comprised of the Core Registry and several product-specific silos initiated by IPIG on request by the respective MAHs. The IPIG PNH Registry aims to enroll patients with PNH, irrespective of the type of therapy they are receiving for PNH, to capture data on clinical outcomes, PROs, and HRU, as well as long-term safety data. Core variables will be collected in the Core Registry at enrollment and during follow-up, while specific data (eg, safety data) for participants treated with Alexion-specific therapies will be collected in the Alexion Products Silo.

This PASS, ALX-PNH-502, is an IPIG PNH Registry-based study proposed as an additional pharmacovigilance activity within the danicopan EU RMP, to characterize the long-term safety of danicopan as add-on therapy to ravulizumab or eculizumab for the treatment of adult patients with PNH who have residual hemolytic anemia.

Research question and objectives

Objectives	Outcome Measures
Primary	
Characterize the long-term safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with PNH	AEs (serious and nonserious)
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	Rate of meningococcal infection
Describe and compare the incidence of serious infections in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) Ultomiris or Soliris monotherapy	Rate of serious infections
Describe and compare the incidence of malignancies and hematologic abnormalities in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) Ultomiris or Soliris monotherapy	Rate of malignancies and hematologic abnormalities
Characterize the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with PNH and with severe hepatic impairment	AEs (serious and nonserious)
Secondary	
Characterize the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in pregnant participants, pregnant partners of participants, or participants who are breastfeeding	AEs (serious and nonserious) Pregnancy-related outcomes and infant health abnormalities up to 12 months of age in pregnant participants, pregnant partners of participants, or participants who are breastfeeding only
Describe the demographic and clinical profile at treatment initiation in participants with PNH treated with danicopan as add-on therapy to ravulizumab/eculizumab	Demographic characteristics, medical history, PNH-specific treatment history, concomitant medications, and laboratory values
Assess discontinuation patterns of danicopan as add-on therapy to ravulizumab/eculizumab treatment among participants with PNH	Number of participants who discontinue danicopan and reasons for discontinuation

Study design

The IPIG PNH Registry is a multinational, multicenter, observational registry designed to collect data on patients with PNH in a real-world clinical setting. Study ALX-PNH-502 is a noninterventional cohort study that utilizes data from the IPIG PNH Registry. In this study, data will be collected through the IPIG PNH Registry including the Alexion Products Silo.

All participants in the IPIG PNH Registry will be consented into the Core Registry protocol which includes the Alexion Products Silo Appendix. The Core Registry collects data on participant demographics, diagnosis information, baseline characteristics (medical and treatment history, clinical symptoms, and laboratory data), and clinical events among other data elements. Participants treated with Alexion products, Soliris, Ultomiris, and/or Voydeya add-on therapy will also have treatment specific safety-related data, collected as part of the Alexion Products Silo Appendix.

Enrolled participants will be followed for at least 5 years after their enrollment in the IPIG PNH Registry. Participants' visit schedules will follow the standard of care. Participant data are expected to be entered in the EDC system by the clinician and/or qualified designee at the time of Registry enrollment and approximately every 6 months (follow-up) thereafter. Historical data from diagnosis, prior to entry into the Core Registry, will be collected for individual participants either from sites directly or by data transfer from the Alexion International PNH Registry.

Population

Adult and pediatric participants with PNH with a detected proportion of PNH cells (PNH clone), who have provided written informed consent and are not participating in an interventional clinical study specific to PNH, are eligible for participation in the IPIG PNH Registry.

Of these, adult participants aged ≥ 18 years at treatment initiation and who initiated treatment with Ultomiris, Soliris, and/or danicopan on or after IPIG or Alexion International PNH Registry enrollment are eligible for participation in this Study ALX-PNH-502. Participants without known year of birth, sex, informed consent date, or treatment status of danicopan and Ultomiris and/or Soliris will be excluded from the study.

The study population will consist of 2 treatment cohorts:

- Participants ever-treated with danicopan as add-on therapy to ravulizumab/eculizumab on or after IPIG PNH Registry enrollment.
- Participants initiating treatment with Ultomiris or Soliris on or after IPIG or Alexion International PNH Registry enrollment and without any danicopan treatment experience during follow up.

Two subpopulations of participants ever-treated with danicopan as add-on therapy to ravulizumab/eculizumab will also be established:

- Participants with severe hepatic impairment.
- Pregnant participants, pregnant partners of participants, or participants who are breastfeeding.

Variables

Variables collected at Registry enrollment include demographics, PNH/hematological history, PNH symptoms, other medical history, ongoing severe hepatic impairment as defined by Child-Pugh Class C, previous and ongoing PNH treatments, other treatment history (concomitant medications and pRBC transfusions), pregnancy status including for female partners of treated male participants, and vaccinations received (meningococcal, pneumococcal, and *Haemophilus influenzae* type B).

Variables collected at treatment initiation include weight and height, PNH treatment type (dose and frequency), clinical laboratory test results related to PNH (including, but not limited to PNH clone size, Hgb, absolute reticulocyte count, LDH) in the 6 months prior to treatment initiation, and vaccination status (meningococcal, pneumococcal, and *H influenzae* type B).

Main data variables collected during follow-up will be PNH treatment information, safety events, and clinical events and outcomes (MAVE; serious infections with encapsulated bacteria, hematological abnormalities, malignancies; severe hepatic impairment; deaths; pregnancy outcomes).

Data sources

Sources will be data from the IPIG PNH Registry which also consists of retrospective data from the Alexion International PNH Registry that is transferred to the IPIG PNH Registry.

Study size

In this study, approximately 50 participants who are ever-treated with danicopan add-on therapy to ravulizumab/eculizumab and at least 300 participants treated with Ultomiris and/or Soliris monotherapy will be included.

Data analysis

Participant demographics, medical history, clinical events and conditions including presence of severe hepatic impairment and pregnancy status, laboratory values, PNH-specific treatment history and concomitant medication will be summarized at initiation of danicopan as add-on therapy to ravulizumab/eculizumab using descriptive analyses.

The following variables will be summarized by frequency during the follow-up period for participants treated in the danicopan as add-on therapy to ravulizumab/eculizumab cohort: number of participants who discontinue danicopan treatment and the reasons for the treatment discontinuation, AEs (nonserious and serious), special situations, and causes of death. For pregnant participants, pregnant partners of participants, or participants who are breastfeeding, pregnancy outcomes (maternal and fetal events) and infant health up to 12 months of age will be assessed.

Continuous variables will be characterized with number of nonmissing observations, mean and standard deviation, median and interquartile range, minimum and maximum, and number of missing data. Categorical variables will be characterized by the frequency and percent distribution in each category for nonmissing data and missing data, as appropriate. The analysis will include 95% confidence intervals of means and percentages, as appropriate.

Incidence of meningococcal infections, serious infections, and malignancies and hematological abnormalities (including aplastic anemia and myelodysplastic syndrome) will be measured by event rates for participants in the danicopan as add-on therapy to ravulizumab/eculizumab and Ultomiris/Soliris monotherapy cohorts (treated exposure period only).

Danicopan treated participants will further contribute person-years to the following exposure periods during Registry follow-up: untreated exposure period, ravulizumab/eculizumab monotherapy exposure period, and danicopan add-on therapy exposure period. Incidence of meningococcal infections, serious infections, and malignances and hematological abnormalities will also be assessed in danicopan-treated participants by exposure period pending feasibility.

The total number of events and the total person-years during the follow-up period of interest will be determined. The event rate will be the number of events divided by the person-years. Person years are calculated per the definition of exposure period for all participants included in the study population, regardless of whether they had an event. Incidence rates are calculated by the total number of events divided by the total person-years during the exposure period of interest. The event rate will be calculated using Poisson regression with over-dispersion or generalized estimating equations with a log link, as appropriate.

Milestones

Milestone	Planned Dates [a]
Registration in the HMA-EMA Catalogue of RWD studies	Prior to first data extraction
First data extraction	Jan 2026
Final data extraction	Jan 2030
Interim reports	Interim Report #1: Jul 2026 Interim Report #2: Jul 2028
Study progression reports	With PSUR submission
Final report of study results	Jul 2030

[a] First data extraction is inclusive of all data accumulated from FPI in May 2024 to date of IPIG data download planned for Jan 2026.

5. AMENDMENTS AND UPDATES

Protocol Version History: Original version dated 24 May 2024; Amendment 1 dated 12 Dec 2024; Amendment 2.0 dated 11 Jun 2025; and Amendment 3.0 dated 22 Aug 2025. Amendment 3.0 incorporates revisions addressing EMA queries on Protocol Amendment 2.0.

Section Number	Description of Changes	Rationale
4 Abstract (Milestones) and 6 Milestones (Table 2)	Updated planned IPIG data download date from Jan 2025 to Jan 2026.	Based on updates made due to EMA feedback.
9.7.1 Descriptive Analysis (bullet point 2)	Added "and exposure period." Updated sentence: "AEs (nonserious and serious). AEs will be further characterized by relatedness **and exposure period**."	Based on EMA feedback.
9.7.2.1 Event Rates	• Paragraph 1, point 1: Added "cohort". Updated sentence: "the danicopan as add-on therapy to ravulizumab/eculizumab **cohort**." • Paragraph 2: Added "**Specific to the characterization of clinical events with bone marrow pathology or other hematological disorders, an ever-exposed analysis will also be performed in the danicopan as add-on therapy to ravulizumab/eculizumab cohort and the IPIG Registry Ultomiris/Soliris monotherapy cohort.**"	
9.7.5 Subgroup and Sensitivity Analyses	• Paragraph 1: Deleted "if feasible" and added points 1 and 2. Updated content: "**1)** participants treated with Ultomiris only and ~~if~~	

Section Number	Description of Changes	Rationale
	~~feasible~~ **2)** participants treated with Soliris only." • Bullet point 3: Added "**Inclusion of person-time following treatment discontinuation up to 3 months for infection rate analyses.**" • Last paragraph: Added "**The SAP will describe handling of subgroup analyses in instances where sample size is limited.**"	
Throughout the document	Changed document version and date.	Administrative.

6. MILESTONES

Table 2: Study Milestones

Milestone	Planned Dates[a]
Registration in the HMA-EMA Catalogue of RWD studies	Prior to first data extraction
First data extraction	Jan 2026
Final data extraction	Jan 2030
Interim reports	Interim Report #1: Jul 2026 Interim Report #2: Jul 2028
Study progression reports	With PSUR submission
Final report of study results	Jul 2030

[a] First data extraction is inclusive of all data accumulated from FPI in May 2024 to date of IPIG data download planned for Jan 2026.

7. RATIONALE AND BACKGROUND

7.1. Overview of PNH

PNH is an ultra-rare and life-threatening acquired hemolytic disorder caused by uncontrolled activation of the terminal complement pathway (Bektas, 2020; Hochsmann, 2023; Schmidt, 2024). Chronic, uncontrolled C5 cleavage and release of C5a and C5b-9 lead to destruction of RBCs within blood vessels, known as IVH. IVH results in the release of intracellular free Hgb and LDH into circulation, irreversible binding to and inactivation of nitric oxide by Hgb, and inhibition of nitric oxide synthesis. IVH also leads to vasoconstriction and tissue-bed ischemia due to absence of vasodilatory nitric oxide; possible microthrombi manifesting as abdominal pain, dysphagia, and erectile dysfunction; WBC and platelet activation; and a proinflammatory and prothrombotic state (Hill, 2013; Hochsmann, 2023).

A substantial proportion of patients with PNH experience renal dysfunction and pulmonary hypertension (Hill, 2013; Hill, 2012; Hillmen, 2010; Hochsmann, 2023). In addition to anemia that can require frequent RBC transfusions, patients with PNH are at high risk for thrombotic events, which can be life-threatening and are the major cause of morbidity and mortality in untreated patients. Patients can experience venous or arterial thrombosis in diverse sites, including the abdomen or central nervous system (Hochsmann, 2023). Secondary effects in addition to the risk of major end organ damage from thrombosis, include abdominal pain, extreme or unrelenting fatigue, difficulties in concentrating or thinking, and lower quality of life.

Prevalence has been estimated to range from 1.04 to 3.81 per 100000 persons (Hansen, 2020; Richards, 2021) and patients typically present with PNH during adulthood.

7.2. Treatments and Unmet Medical Need

The main objective of effective PNH treatment with targeted therapy is to provide immediate, complete, and sustained inhibition of terminal complement activity to block IVH and thereby prevent thrombosis. The standard of care treatments for PNH currently are the C5is humanized monoclonal antibodies ravulizumab (ULTOMIRIS) and eculizumab (SOLIRIS), which inhibit C5 in the terminal complement pathway, prevent formation of MAC, and are effective in controlling IVH (Oliver, 2023).

Pegcetacoplan is a C3 inhibitor currently approved for the treatment of adult patients with PNH who have hemolytic anemia. Data from the Phase 3 clinical study “PEGASUS” have shown that sustained control of IVH is suboptimal following pegcetacoplan treatment (Notaro, 2022). In particular, over 48 weeks of pegcetacoplan treatment, 24% of patients experienced hemolysis requiring discontinuation, dose adjustment and/or rescue treatment with C5 inhibitors (de Latour, 2022; Gerber, 2022).

Iptacopan is a FB inhibitor that was approved more recently in December 2023 for the treatment of adult patients who have hemolytic anemia. However, iptacopan has been noted to increase total cholesterol, low density lipoprotein-cholesterol, and serum triglycerides such that close monitoring of lipid parameters and initiation of cholesterol-lowering medication may be needed (Fabhalta-PI, 2023). Alternative treatment options are needed for patients with CS-EVH to effectively manage both IVH and EVH.

Crovalimab-akkz, a C5i indicated for the treatment of adult and pediatric patients with PNH 13 years and older with body weight of at least 40 kg, was approved in the US and EU in 2024.

A subset of patients with PNH who have achieved durable IVH control and associated disease control with ravulizumab or eculizumab may experience emergence of CS-EVH and some of these patients require transfusions (Hill, 2010; McKinley, 2017; Notaro, 2022; Notaro, 2018; Risitano, 2019). CS-EVH occurs in approximately 20% of C5i-treated patients, with approximately half of this subset of patients requiring RBC transfusions (Kulasekararaj, 2023; Kulasekararaj, 2022). Therefore, there is an unmet medical need for a therapy that may adequately control EVH while maintaining adequate IVH control.

7.3. Danicopan (Voydeya®)

Danicopan is a first-in-class small molecule orally administered complement FD inhibitor indicated as add-on therapy to ravulizumab or eculizumab for the treatment of adult patients with PNH who have residual hemolytic anemia. Danicopan inhibits the alternative pathway mediated deposition of C3 fragments on PNH RBCs which is a key cause of EVH.

In adult patients with PNH and CS-EVH, danicopan add-on therapy to ravulizumab or eculizumab improves anemia, transfusion burden, fatigue, and absolute reticulocyte count as shown in a randomized, double-blind, placebo-controlled study (Lee, 2023).

Danicopan (tradename Voydeya®, tablet) has been approved in various countries including Japan, the US, and those in the EU.

7.4. IPIG PNH Registry and Rationale for this Study

Alexion Pharmaceuticals, Inc. has been the Sponsor of the International PNH Registry (M07-001) since June 2007 and has enrolled approximately 6000 patients with PNH worldwide. The primary intent of the Alexion International PNH Registry has been to characterize the long-term safety of eculizumab and ravulizumab.

With the advent of additional novel therapies from various MAHs for the treatment of PNH, real world data is needed to characterize their long-term safety and effectiveness. In the setting of a rare disease with multiple therapies from different MAHs, a single, unified, global registry of patients with PNH was proposed by IPIG, the only global professional society focusing specifically on PNH, to increase knowledge about PNH and its therapies in the medical community and patient population.

In 2022, Alexion formally entered into an agreement with IPIG and informed participating sites in the Alexion International PNH Registry of the intent to transition to the IPIG PNH Registry. The IPIG PNH Registry is a multinational, multicenter, observational registry designed to collect data on patients with PNH in a real-world clinical setting (The IPIG PNH Registry; Protocol Number: 5674-0001). The IPIG PNH Registry aims to enroll patients with PNH, irrespective of the type of therapy they are receiving for PNH, to capture data on clinical outcomes, PROs, and HRU on all enrolled patients, as well as long-term safety data of PNH-specific treatments. In addition, information on the progression of disease in the PNH population will be collected.

The IPIG PNH Registry is comprised of the Core PNH Disease Registry (Core Registry) and several product-specific silos initiated by IPIG on request by the respective MAHs. Core

variables will be collected in the Core Registry at enrollment and during follow-up, while specific data (eg, safety data) for participants treated with Alexion-specific therapies will be collected in the Alexion Products Silo.

There are limited data on danicopan long-term safety and no data on 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 infections and serious infections in treated patients has not been characterized in real world settings.

This PASS, ALX-PNH-502, is an IPIG PNH Registry based study proposed as an additional pharmacovigilance activity within the danicopan EU RMP, to characterize the long-term safety of danicopan as add-on therapy to ravulizumab or eculizumab for the treatment of adult patients with PNH who have residual hemolytic anemia.

8. RESEARCH QUESTION AND OBJECTIVES

The primary and secondary objectives and outcome measures of this study are described in the table below:

Objectives	Outcome Measures
Primary	
Characterize the long-term safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with PNH.	AEs (serious and nonserious)
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	Rate of meningococcal infection
Describe and compare the incidence of serious infections in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) Ultomiris or Soliris monotherapy	Rate of serious infections
Describe and compare the incidence of malignancies and hematologic abnormalities in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) Ultomiris or Soliris monotherapy	Rate of malignancies and hematologic abnormalities
Characterize the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with PNH and with severe hepatic impairment	AEs (serious and nonserious)
Secondary	
Characterize the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in pregnant participants, pregnant partners of participants, or participants who are breastfeeding	AEs (serious and nonserious) Pregnancy-related outcomes and infant health abnormalities up to 12 months of age in pregnant participants, pregnant partners of participants, or participants who are breastfeeding only
Describe the demographic and clinical profile at treatment initiation in participants with PNH treated with danicopan as add-on therapy to ravulizumab/eculizumab	Demographic characteristics, medical history, PNH-specific treatment history, concomitant medications, and laboratory values
Assess discontinuation patterns of danicopan as add-on therapy to ravulizumab/eculizumab treatment among participants with PNH	Number of participants who discontinue danicopan and reasons for discontinuation

9. RESEARCH METHODS

9.1. Study Design

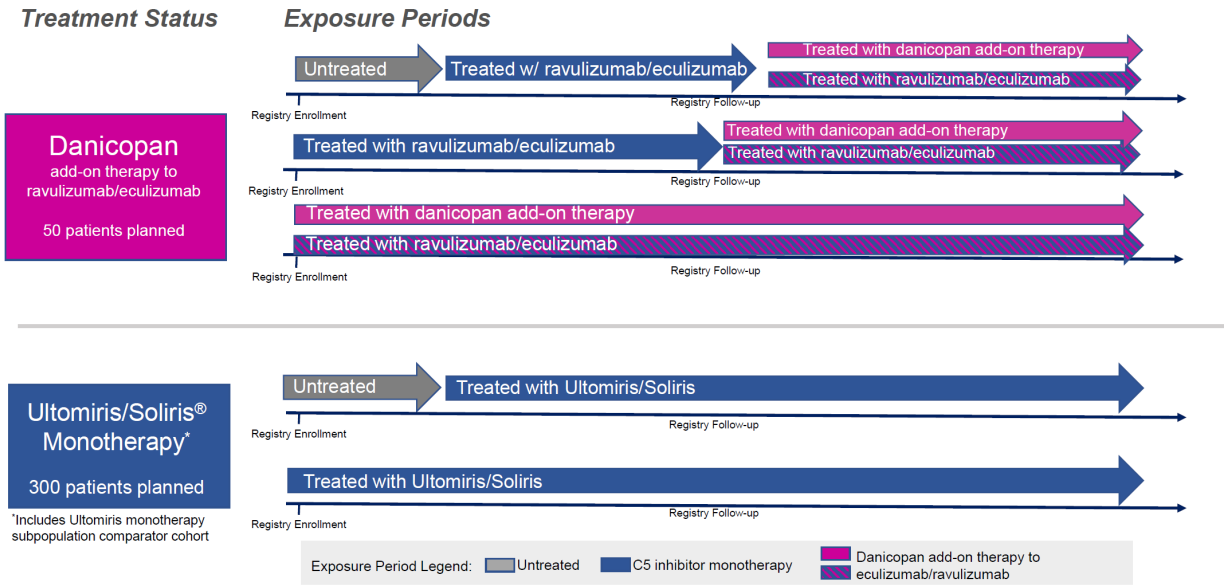
Prospective collection of safety data offers one of the strongest observational study designs as it minimizes recall bias; further selection bias is minimized given the single, unified registry and broad inclusion criteria.

For this Study ALX-PNH-502, data will be collected through the IPIG PNH Registry including the Alexion Products Silo.

This noninterventional cohort study utilizes both primary and secondary data from the IPIG PNH Registry collected retrospectively and prospectively. Primary data collected specifically for this study include AEs. All other data are considered secondary as they are collected for the purpose of fulfilling IPIG PNH Registry objectives.

The overview of the study design is presented in Figure 1.

Figure 1: Study Design Schematic



All participants in the IPIG PNH Registry will be consented into the Core Registry protocol which includes the Alexion Products Silo Appendix. The Core Registry collects data on participant demographics, diagnosis information, baseline characteristics (medical and treatment history, clinical symptoms, and laboratory data), and clinical events among other data elements. Participants treated with Alexion products, Soliris, Ultomiris, and/or Voydeya add-on therapy will also have treatment specific safety-related data, collected as part of the Alexion Products Silo Appendix.

The necessary data to complete the objectives of this PASS from both the Core Registry and Alexion Products Silo will be provided by IPIG to Alexion for participants eligible for this PASS. Primary data are specific to safety-related events.

This study intends to extract data from the IPIG PNH Registry beginning at least 6 months from first participant enrolled into the Alexion Products Silo and continue routine data extraction for 6 years. The data collection period will be defined as earliest date of C5i treatment initiation for participants enrolled in the IPIG PNH Registry until projected last data extraction.

The study population will consist of participants treated with danicopan as add-on therapy compared with participants treated with Soliris/Ultomiris monotherapy (details provided in Figure 1 and Section 9.2). Enrolled participants will be followed for at least 5 years after their enrollment in the IPIG PNH Registry including treated time in the Alexion International PNH Registry. Participants' visit schedules will follow the standard of care. Participant data are expected to be entered in the EDC system by the clinician and/or qualified designee at the time of Registry enrollment and approximately every 6 months (follow-up) thereafter. Historical data from diagnosis, prior to entry into the Core Registry, will be collected for individual participants either from sites directly or by data transfer from the Alexion International PNH Registry.

9.2. Setting

Adult and pediatric participants with PNH with a detected proportion of PNH cells (PNH clone), who have provided written informed consent and are not participating in an interventional clinical study specific to PNH, are eligible for participation in the IPIG PNH Registry. Participants currently enrolled/participating in an interventional clinical study for treatment of PNH cannot be enrolled in the IPIG PNH Registry.

Study ALX-PNH-502 participants may be from countries throughout North America, South America, Europe, Asia, and inclusive of Australia.

The study population will consist of 2 treatment cohorts:

- Participants ever-treated with danicopan as add-on therapy to ravulizumab/eculizumab on or after IPIG PNH Registry enrollment.
- Participants initiating treatment with Ultomiris or Soliris on or after IPIG or Alexion International PNH Registry enrollment and without any danicopan treatment experience during follow-up.

Two subpopulations of participants ever-treated with danicopan as add-on therapy to ravulizumab/eculizumab will also be established:

- Participants with severe hepatic impairment.
- Pregnant participants, pregnant partners of participants, or participants who are breastfeeding.

The following inclusion and exclusion criteria should be used to identify participants from the IPIG PNH Registry for Study ALX-PNH-502.

9.2.1. Inclusion Criteria

1. Adult participants aged ≥ 18 years at treatment initiation.
2. Initiated treatment with Ultomiris, Soliris, and/or danicopan on or after IPIG or Alexion International PNH Registry enrollment.

9.2.2. Exclusion Criteria

1. Participants without known year of birth, sex, informed consent date, or treatment status of danicopan and Ultomiris and/or Soliris.

9.2.3. Participant and/or Registry Discontinuation

Participation in the IPIG PNH Registry is voluntary. Participants may decline to participate or withdraw their consent at any time. In the event of a discontinuation, previously collected data will continue to be used for analyses.

For participants who discontinue treatment with danicopan after enrollment, Registry participation may be continued.

Information should continue to be submitted to the Registry for all ongoing SAEs (until resolution). Any new SAEs identified after discontinuation of danicopan, assessed by the clinician as treatment-related, will be followed up until resolution.

A participant may be withdrawn from the Registry by the Sponsor or participating clinician if: (1) the Registry is stopped by IPIG; (2) it is discovered that the participant did not meet the requirements for participation in the Registry; (3) the Institution and/or Registry Clinician is no longer participating in the Registry; or (4) relevant Regulatory Authorities and/or IRB/IEC decide to stop the Registry.

9.3. Variables

9.3.1. Exposure Period Definitions

The following exposure periods will be defined for participants with further specifications detailed in the SAP.

Participants treated with danicopan add-on therapy:

- Danicopan add-on therapy exposure period
  - Defined as time from danicopan initiation to last danicopan treated date plus 1 week
- Ravulizumab/eculizumab monotherapy exposure period
  - Defined as time from earliest ravulizumab or eculizumab treatment initiation date until the last ravulizumab or eculizumab treated follow-up date plus 12 weeks for ravulizumab and 4 weeks for eculizumab
- Untreated exposure period
  - Defined as time from Registry enrollment where a participant is not treated with a PNH-specific therapy until their last untreated follow-up date

Participants treated with Ultomiris/Soliris monotherapy:

- Ultomiris/Soliris monotherapy exposure period
  - Defined as time from earliest Ultomiris or Soliris treatment initiation date until the last Ultomiris or Soliris treatment follow-up date plus 12 weeks for Ultomiris and 4 weeks for Soliris.

Exposure periods will end on the date of Registry discontinuation for those participants who discontinue from the Registry.

9.3.2. Outcome Measures

The following data variables will be collected for all participants and will inform outcome/endpoint assessments.

9.3.2.1. Collected at Registry Enrollment

- Demographic data (eg, year of birth, gender, race, ethnicity)
- PNH/hematological history
  - Date of PNH diagnosis
  - PNH symptoms at diagnosis
  - History of bone marrow pathology, hematological disorders, and hematological malignancies
  - History of bone marrow transplant
  - History of MAVE, including thrombosis
  - High disease activity, ie, increased IVH (LDH $\geq 1.5 \times$ ULN) and the presence of related clinical symptom(s): fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (Hgb < 100 g/L), MAVE (including thrombosis), dysphagia, or erectile dysfunction
- Other medical history (co-morbidities including, but not limited to, serious and/or encapsulated bacterial infections, renal impairment, hepatic impairment, autoimmune diseases, pulmonary hypertension, malignancies, obstetric history and other medical conditions)
- Ongoing severe hepatic impairment as defined by Child-Pugh Class C
- Previous and ongoing PNH treatments (including start date, dosing information, date of discontinuation/switch, reason for discontinuation/switch)
- Other treatment history (concomitant medications [eg, anticoagulants, erythropoiesis stimulating agents, corticosteroids, other immunosuppressive therapies, analgesics, antibiotic prophylaxis] and pRBC transfusions in the 6 months prior to enrollment, including start/end date and dosing/unit information)
- Meningococcal, pneumococcal, and *H influenzae* type B vaccinations received and date of administration

- PNH symptoms
- Pregnancy status including for female partners of treated male participants

9.3.2.2. Collected at Treatment Initiation

- Weight and height
- PNH treatments (including start date, dosing information)
- Concomitant medications and treatments including start/end date and dosing/unit information
- Clinical laboratory test results related to PNH (including, but not limited to PNH clone size, Hgb, absolute reticulocyte count, LDH, LDH ULN, LDH ratio, haptoglobin, indirect and total bilirubin, direct antiglobulin test) in the 6 months prior to treatment initiation
- Presence of severe hepatic impairment
- Meningococcal, pneumococcal, and *H influenzae* type B vaccination status
- SAEs
- Meningococcal infections
- Pregnancies (both maternal and fetal events)

For patients initiating danicopan after registry enrollment, clinical laboratory results, concomitant medication, PNH treatment information, and vaccination status at treatment initiation will be collected as part of registry follow-up.

9.3.2.3. Collected During Follow-up

The following data (as available) will be collected during follow-up approximately every 6 months post-enrollment:

- PNH treatments (including start date, dosing information, date of discontinuation/switch, reason for discontinuation/switch)
- Clinical events and outcomes:
  - MAVE, including thrombosis
  - Infections, including but not limited to *Neisseria meningitidis, Streptococcus pneumoniae*, and *H influenzae* type B
    - Infections are considered serious if they result in a medically important event or reaction, need for or prolongation of hospitalization, persistent or significant disability or incapacity, life-threatening status, or death
  - Bone marrow pathology including, but not limited to myeloproliferative disease and malignancies
  - Other hematological disorders
  - Malignancies

  - Severe hepatic impairment as defined by Child-Pugh Class C
  - Deaths (including cause of death)
  - Pregnancies: information on pregnancy outcome in female participants and female partners of treated male participants. Follow-up of child at the age of 12 months if born during the Registry follow-up. Where feasible, birth defects will be categorized using EUROCAT classifications for stillbirth, neonatal cause of death, spontaneous/elective abortion, termination of pregnancy for fetal anomaly, major congenital malformations, preterm delivery, low birth weight, and small for gestational age infants. When categorization to a EUROCAT classification is not possible, information on pregnancy outcome will be recorded as 'other' and further described in written narratives.

- AEs and special situations

9.3.3. Other Variables

The following data variables will be collected for all participants.

9.3.3.1. Collected at Registry Enrollment

- Weight and height
- Proportion of PNH cells (PNH clone size) as measured by flow cytometry of granulocytes, monocytes, and erythrocytes at diagnosis and enrollment
- Clinical laboratory test results related to PNH (including, but not limited to, Hgb, absolute reticulocyte count, LDH, LDH ULN, LDH ratio, haptoglobin, indirect and total bilirubin, direct antiglobulin test) at diagnosis and enrollment

9.3.3.2. Collected During Follow-up

- PNH symptoms
- Clinical laboratory test results related to PNH (including, but not limited to, Hgb, absolute reticulocyte count, LDH, LDH ULN, LDH ratio, haptoglobin, indirect and total bilirubin, direct antiglobulin test)
- Proportion of PNH cells (PNH clone size) as measured by flow cytometry of granulocytes, monocytes, and erythrocytes
- Concomitant medications and treatments (eg, RBC transfusions, anticoagulants, erythropoiesis stimulating agents, corticosteroids, other immunosuppressive therapies, analgesics, antibiotic prophylaxis), including start/end date and dosing/unit information
- Meningococcal, pneumococcal, and *H influenzae* type B vaccination status
- Clinical events and outcomes:
  - Breakthrough hemolysis, ie, ≥ 1 new or worsening sign or symptom of IVH (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [Hgb < 100 g/L],

MAVE [including thrombosis], dysphagia, or erectile dysfunction) and elevated LDH (≥ 2 × ULN) after prior LDH reduction to < 1.5 × ULN on therapy

- Development or worsening of autoimmune disease
- Medical conditions (eg, diabetes, hypertension, ischemic heart disease)
- Impaired renal function
- Impaired hepatic function
- Pulmonary hypertension
- Bone marrow transplant

9.3.4. Data Collection Schedule

Data will be collected by participating clinicians in the IPIG PNH Registry via eCRF at specified data entry timepoints including at enrollment, Month 6, and then every 6 months thereafter. Data associated with treatment initiation will be collected at enrollment for participants commencing treatment at enrollment or the closest follow-up visit after treatment initiation if occurring during follow-up. Therefore, for participants initiating treatment after registry enrollment, clinical outcomes and treatment information collected as part of registry follow-up will contribute to a participant's medical history at treatment initiation.

Table 3: Data Collection Schedule

Data	Enrollment Visit	Treatment Initiation*	Follow-up Every 6 Months
Demographics	X		
Weight/height	X	X	
PNH/hematological history	X		
Severe hepatic impairment assessment	X	X	X
Other medical history and comorbidities	X		X (only comorbidities)
PNH treatment information	X (including history)	X	X
Concomitant medications and treatments	X	X	X
Vaccination status	X	X	X
PNH symptoms	X		X
Clinical laboratory test results related to PNH	X	X	X

Table 3: Data Collection Schedule

Data	Enrollment Visit	Treatment Initiation*	Follow-up Every 6 Months
Clinical events and outcomes			X
Pregnancy status and outcome	X	X	X
AEs and special situations		X	X

*The IPIG Core Registry Protocol does not include a specific visit for treatment initiation data collection. This information is gathered either through 24-hour SAE/Special Situation reporting or via dedicated eCRF questions during follow-up visits.

9.4. Data Sources

Participants enrolled in the IPIG PNH Registry, who are treated with danicopan, Ultomiris, and Soliris, will have additional data collected in the Alexion Products Silo to the already collected data in the Core Registry.

Participant data will be collected by the clinician and/or qualified designee at the time of Registry enrollment and throughout the follow-up period, in accordance with the natural course of participant healthcare. Collected data will be entered into the EDC system by the clinician and/or qualified designee.

Retrospective data from the Alexion International PNH Registry will be transferred to the IPIG PNH Registry for consenting participants and all common data elements will be linked in the analysis dataset.

Data from the Global Drug Safety database will also be reviewed to identify adverse events reported directly to the Safety Database with a notation to ALX-PNH-502 or the IPIG registry. Additionally, supplemental safety information on meningococcal infections and pregnancy will be collected using the Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire and Pregnancy/Breastfeeding Reporting and Outcome Form.

9.5. Study Size

In this study, approximately 50 participants who are ever-treated with danicopan add-on therapy to ravulizumab/eculizumab and at least 300 participants treated with Ultomiris and/or Soliris monotherapy will be included. The monotherapy cohort estimate is inclusive of participants initiating treatment in the Alexion International PNH Registry.

The anticipated number of participants were estimated on the basis of the active participants treated with Ultomiris and/or Soliris in the Alexion International PNH Registry prior to closure and accounting for declines in patient enrollment within the Alexion Products Silo due to competitor therapies and consideration that not all participants initiate treatment on/after registry enrollment. Assuming 2% of participants experience an outcome of interest (eg, infection, malignancy), the enrollment of 50 danicopan patients results in an absolute precision of approximately 4% with 95% confidence using an exact method.

Leveraging data from the Alexion International PNH Registry and conservatively estimating that on average each of the projected 50 participants will contribute 2.5 person-years of follow-up, it is estimated that the resulting event rate for infection and malignancy will result in an absolute precision ranging between 0 – 5% with a 95% confidence interval depending on event rate and population size assumptions employed.

Table 4: Estimate of Precision for Absolute Proportion by Study Size

Study Sample Size	Half Width of 95% CI
30	5%
40	4%
50	4%
60	4%
70	3%

Table 5: CCI [redacted]

CCI [redacted]

9.6. Data Management

IPIG PNH Registry data collection will be performed at participating sites using eCRFs. Data will be entered into a central database that will be managed by a CRO. Common data elements from the Alexion International PNH Registry and IPIG PNH Registry will be linked in the

analysis dataset. The IPIG PNH Registry Core Registry and Alexion Products Silo Appendix Data Management Plans further detail the data management activities. Study data will be retained for up to 15 years or in accordance with applicable regulations after termination of the study.

9.7. Data Analysis

All analyses will be carried out using SAS® version 9.4 or higher. Statistical analysis will be descriptive only. No formal hypothesis testing will be performed. A SAP will detail the proposed analyses and handling of missing data in full.

9.7.1. Descriptive Analysis

Participant demographics, medical history, clinical events and conditions including presence of severe hepatic impairment and pregnancy status, laboratory values, PNH-specific treatment history and concomitant medication will be summarized at initiation of danicopan as add-on therapy to ravulizumab/eculizumab using descriptive analyses.

The following variables will be summarized by frequency during the follow-up period:

- Number of participants who discontinue treatment and the reasons for the treatment discontinuation
- AEs (nonserious and serious). AEs will be further characterized by relatedness and exposure period
- Special situations
- Causes of death

Additionally, for pregnant participants, pregnant partners of participants, or participants who are breastfeeding, pregnancy outcomes (maternal and fetal events) and infant health up to 12 months of age will be assessed.

Continuous variables will be characterized with number of nonmissing observations, mean and standard deviation, median and interquartile range, minimum and maximum, and number of missing data. Categorical variables will be characterized by the frequency and percent distribution in each category for nonmissing data and missing data, as appropriate. The analysis will include 95% confidence intervals of means and percentages, as appropriate.

9.7.2. Outcome Measures Analysis

9.7.2.1. Event Rates

Incidence of meningococcal infections, serious infections, and malignancies and hematological abnormalities (including aplastic anemia and myelodysplastic syndrome) will be measured by event rates for participants in 1) the danicopan as add-on therapy to ravulizumab/eculizumab cohort, 2) IPIG Registry Ultomiris/Soliris monotherapy cohorts (treated exposure period only), and 3) Ultomiris/Soliris monotherapy cohorts (treated exposure period only). The event rate for the Ultomiris/Soliris monotherapy cohort inclusive of events recorded in the Alexion PNH registry will be presented in the final PASS report.

Danicopan treated participants will further contribute person-years to the following exposure periods during Registry follow-up: untreated exposure period, ravulizumab/eculizumab monotherapy exposure period, and danicopan add-on therapy exposure period.

Incidence of meningococcal infections, serious infections, and malignancies and hematological abnormalities will also be assessed in danicopan-treated participants by exposure period pending feasibility. Specific to the characterization of clinical events with bone marrow pathology or other hematological disorders, an ever-exposed analysis will also be performed in the danicopan as add-on therapy to ravulizumab/eculizumab cohort and the IPIG Registry Ultomiris/Soliris monotherapy cohort.

The total number of events and the total person-years during the follow-up period of interest will be determined. The event rate will be the number of events divided by the person-years. Person-years are calculated per the definition of exposure period in Section 9.3.1 for all participants included in the study population, regardless of whether they had an event. Incidence rates are calculated by the total number of events divided by the total person-years during the exposure period of interest. The event rate will be calculated using Poisson regression with over-dispersion or generalized estimating equations with a log link, as appropriate.

9.7.2.2. Treatment Groups

The study population will consist of 2 treatment cohorts:

- Participants ever-treated with danicopan as add-on therapy to ravulizumab/eculizumab on or after IPIG PNH Registry enrollment.
- Participants initiating treatment with Ultomiris or Soliris on or after IPIG or Alexion International PNH Registry enrollment and without any danicopan treatment experience during follow-up. This cohort will further be divided into participants who initiate treatment with Ultomiris or Soliris on or after IPIG Registry enrollment (IPIG Registry Ultomiris/Soliris monotherapy cohort).

Two subpopulations of participants ever-treated with danicopan as add-on therapy to ravulizumab/eculizumab will also be established:

- Participants with severe hepatic impairment.
- Pregnant participants, pregnant partners of participants, or participants who are breastfeeding.

9.7.3. Methods to Address Bias

Confounding by indication bias will be assessed via descriptive analysis of participants in the 2 treatment cohorts, ie, participants ever-treated with danicopan as add-on therapy to ravulizumab/eculizumab, participants initiating treatment with Ultomiris/Soliris and never -treated with danicopan. Any confounding will subsequently be addressed using appropriate statistical techniques such as multivariable analysis or stratified analyses, as sample size and data permit. Examples of covariates which may be considered are LDH, bilirubin, reticulocyte count, history of breakthrough hemolysis, and presence of anemia at the closest timepoint preceding an outcome of interest. Additional covariates may be considered based on outcome assessed and review of data.

9.7.4. Data Imputation

Data imputations are planned for dates except for when the year is missing. If a day is missing, it will be imputed with 15, and if a month is missing, it will be imputed with 6. Treatment dose may also be imputed in situations where follow-up dose is not reported but no change in dose or a final dose is noted, and will be detailed accordingly in the interim report SAP. Details of these imputations will be described in the SAP accompanying each analysis report.

9.7.5. Subgroup and Sensitivity Analyses

A subgroup analysis will be performed in the C5i monotherapy comparator cohort. The subgroups will consist of 1) participants treated with Ultomiris only and 2) participants treated with Soliris only.

Additional sensitivity analyses pertaining to the outcome measures analysis will include:

- Event rate analysis leveraging data from participants initiating treatment with Ultomiris/Soliris on/after IPIG registry enrollment only (ie, exclusion of prevalent users)
- Inclusion of person-time following treatment discontinuation for malignancy event rate analyses.
- Inclusion of person-time following treatment discontinuation up to 3 months for infection rate analyses.

The SAP will describe handling of subgroup analyses in instances where sample size is limited. Additional subgroup/sensitivity analyses may be proposed for interim analyses and will be appropriately described in advance within the accompanying report SAP.

9.8. Quality Control

- IPIG is responsible for the development and maintenance of eCRF completion guidelines, study-related monitoring activities and audits, data management of the IPIG PNH Registry including quality checking of the data, and retainment of records and documents pertaining to the conduct of this study according to local and institutional retention policies.
- IPIG will be reviewing data consistency, completeness and coherency and issuing data queries on at least a monthly basis as described within the IPIG Registry ClinInfo Data Management Plan.
- Alexion is responsible for the data management specific to this PASS.

9.9. Limitations of the Research Methods

The Registry is associated with some methodological limitations commonly found in observational studies:

- Selection bias
  - In order to limit bias in the selection of participants, clinicians and/or qualified designee will be asked to consecutively enroll all participants who consent and

meet the selection criteria, regardless of other considerations. However, participation in the Registry will be voluntary (for sites and participants), which represents a common nonresponse selection and participation bias for this type of observational study.

- Surveillance bias
  - The IPIG PNH Registry collects data at 6 month intervals to reflect the participants' status during the prior 6 months. This is done in lieu of requiring a fixed visit schedule for participants. It is important to consider the possibility of surveillance bias wherein participants with prior Ultomiris or Soliris treatment may have presented more often for their infusions or for regular follow-up visits than while untreated with a PNH-specific therapy. The Registry does not collect the number of times a participant was seen by the site or by other healthcare providers; however, the direction of the surveillance bias is likely to result in greater confidence in the completeness of data for the participants during their treated time.
- Missing data
  - Participant data collected in the Registry will rely on the quality of source documentation of sites. Site training and continuous monitoring will aim to minimize missing data and maintain and improve the quality of source documentation practices of sites. In addition, automated edit checks and queries implemented in the EDC system will minimize missing or incorrect data. Sensitivity analyses will be performed to assess the impact of imputing any missing data.
  - There may be some bias at the study sites for under-reporting events included as part of medical history during the period before enrollment into the Alexion or IPIG PNH Registries rather than during the period after enrollment. However, this can be expected given the limitations of retrospective data collection versus prospective data collection. With respect to collection of a participant's medical history, it is possible that more events are reported while the participant is followed during the Registry than during the period prior to Registry enrollment.
- Confounding by indication
  - Confounding by indication may be a limitation of the comparator analysis to Ultomiris/Soliris monotherapy participants and will be assessed via a descriptive analysis and appropriate statistical techniques (Section 9.7.3).
- Lost to follow-up
  - As the follow-up duration in the IPIG PNH Registry will be at least 5 years after enrollment, the proportion of discontinued participants might be important. The characteristics of these discontinued participants will be compared with the Registry completers to detect any potential bias.

9.10. Other Aspects

A review of published scientific literature, the HMA-EMA RWD Catalogue of Studies, and publicly available registry reports specific to alternative oral PNH therapies will be performed at the time of the final analysis report. Data to be extracted include demographic and clinical characteristics of treated patients on alternative PNH therapies and any reported long-term safety data for these therapies that align with the outcomes defined in this PASS. If available, this information may be used for a qualitative comparison of the PASS study findings. Due to anticipated differences in the study population, data quality, and data collection and analysis methods, any conclusions that may be drawn from this assessment should be interpreted with caution.

10. PROTECTION OF HUMAN SUBJECTS

The Registry shall be conducted in compliance with ISPE GPP guidelines, the ethical principles arising from the Declaration of Helsinki, the EU GVP, European and National laws in terms of data protection and all current local regulations.

The Registry protocol, protocol amendments, ICF, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the clinician/CRO/Alexion and reviewed and approved as appropriate by the IRB/IEC before the study is initiated.

Any amendments to the IPIG PNH Registry (Core and Alexion Products Silo Appendix) protocol will require IRB/IEC approval before implementation of changes made to the study design.

The clinician will be responsible for the following, as applicable in the IPIG PNH Registry:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures per local regulations
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations

Alexion will not have access to patient records and will receive deidentified data for analyses.

10.1. Informed Consent

In the IPIG PNH Registry, the clinician and/or qualified designee will ensure that the participant and/or their parent/legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the Registry. The participant and/or their parent/legally authorized representative must also be notified that they are free to withdraw their consent/assent at any time for any reason. The participant and/or their parent/legally authorized representative should be given the opportunity to ask questions and allowed time to consider the information provided.

Each participant, and/or their parent/legally authorized representative, must sign an ICF, approved by the IRB/IEC, indicating their consent to participate, prior to enrollment in the IPIG PNH Registry. When applicable, minor participants will be given an assent form and will be asked to sign it to confirm their agreement to participate. ICFs will also be signed by the clinician and/or qualified designee.

The original signed ICFs must remain in the participant's file in the clinic. Each participant and/or their parent/legally authorized representative will receive a copy of the signed ICF.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Alexion has a legal responsibility to report SAEs, AEs, and ADRs, as applicable. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and clinicians.

11.1. Definitions

11.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a registry participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of this medicinal product.

11.1.2. Adverse Reaction

An adverse reaction is a response to a medicinal product, which is noxious and unintended. Synonyms are ADR, suspected adverse (drug) reaction, adverse effect, and undesirable effect. Response in this context means that causal relationship between the medical product and an AE is at least a reasonable possibility.

11.1.3. Serious Adverse Events

Preamble: “Serious” and “Severe” are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious”, which is based on event outcome or action criteria usually associated with events that pose a threat to a participant’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

An SAE is an AE that meets any of the following criteria:

- Results in death of participant.
- Is life-threatening: this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization: an event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
- Results in prolongation of existing hospitalization: an event that occurs while the study participant is hospitalized and prolongs the participant's hospital stay.
- Is a congenital anomaly/birth defect: an anomaly detected at or after birth, or any anomaly that results in fetal loss.

- Results in persistent or significant disability/incapacity: an event that results in a condition that substantially interferes with the activities of daily living of a study participant. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle).
- Is a medically important event or reaction: an important medical event that may not be immediately life-threatening or result in death or hospitalization but based on medical judgment may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed above (ie, death of participant, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly/birth defect, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered as a SAE.

11.1.4. Special Situations

This is any incidence of overdose, medication error, occupational exposure, abuse, misuse or lack of therapeutic efficacy while using the medicinal product. A ‘special situation’ should be collected and followed up by the clinician and reported to the MAH whether or not these ‘special situations’ are associated with an AE.

11.1.5. Severity Assessment

The severity (intensity) of AEs will be rated by the clinician as mild, moderate, or severe using the following criteria:

- Mild: events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate: events result in a low level of inconvenience or concerns with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Severity and seriousness must be differentiated. Severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE (Section 11.1.3).

11.1.6. Relatedness Assessment

The following definitions of relationship to study drug should be used by clinicians to characterize the suspected causality of each AE, based on their consideration of all available information about the AE, including temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative etiology (eg, underlying illness, concurrent conditions, concomitant treatments):

- Related - There is a reasonable possibility that the administration of a drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.
- Not Related - A causal relationship of the AE to drug administration is unlikely, or underlying diseases, complications, concomitant drugs and concurrent treatments provide a sufficient explanation for the observed AE.

For events where a causality assessment is not entered into the EDC, a query will be issued to the site as per the IPIG Registry Data Management Plan. For queries that remain unresolved, these events will be forwarded to the safety database for company assessment. In practice, the company assesses reported adverse events without a causality assessment as related.

11.2. Collection and Reporting of Safety Events by Clinicians

The safety profile of danicopan has been well characterized through clinical studies in the PNH indication.

The primary safety risk of danicopan as an FD inhibitor is related to its mechanism of action; complement inhibitors are known to increase the risk of meningococcal infections. In the context of this Voydeya PNH PASS, SAEs, meningococcal infections, as well as pregnancy and other outcomes (as described in Section 9.3) will be collected and analyzed in order to better characterize these important risks or to address missing information. Clinicians will be informed to report all AEs (including nonserious), for which they suspect a causal relationship with Voydeya, to Alexion GPS or to the concerned competent authority via the national spontaneous reporting system.

All SAEs, meningococcal infections, pregnancies (both maternal and fetal events), exposure during lactation and follow-up of neonates at 12 months after delivery from participants exposed to Voydeya will be systematically collected within the EDC. Clinicians must report these events within 24 hours of awareness.

SAEs should be reported by the clinician to Alexion GPS within 24 hours of awareness of the event, regardless of its relationship to Voydeya, primarily via the EDC system. If the electronic system is unavailable at the time the clinician or the site becomes aware of an SAE, the site will use the or using paper AE Report Form to be emailed or faxed to:

Contact details for safety reporting:

Email: ClinicalSAE@alexion.com

Fax: +1-203-439-9347

Sufficient information should be reported to enable the event to be fully described. All reports should at a minimum include age, sex, comprehensive description of the event, event start and end dates, clinician-specified severity, relationship to Voydeya, seriousness, action taken, and outcome.

Meningococcal infections will be recorded using the Global Drug Safety Suspected / Confirmed Meningococcal Case Questionnaire.

Pregnancy will be recorded separately but must be processed similarly to SAEs. All pregnancies in female participants and female partners of male participants will be recorded. The pregnancy should be followed up to determine birth outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any major congenital abnormalities/malformations, and maternal and/or newborn complications in line with EUROCAT definitions. Pregnancy should be recorded on the Pregnancy/Breastfeeding Reporting and Outcome Form and reported by the clinician to Alexion. Pregnancy follow-up should also be recorded via the Pregnancy/Breastfeeding Reporting and Outcome Form.

The clinicians are responsible for maintaining compliance with any applicable site-specific requirements related to the reporting of SAEs or other safety information to the IRBs/IECs that approved the IPIG PNH Registry.

11.3. Case Processing and Submission to Competent Authorities

Alexion or designee will be responsible for case processing in Alexion Safety Database, quality control, query management, medical review and coding, individual case safety report submission of valid cases and aggregate reporting to Competent Authorities as appropriate in accordance with applicable local and regional regulations.

Queries and requests for additional information may be issued by GPS or designee staff; additional information (in a pseudonymized or redacted manner) must be provided to GPS without delay in order to allow submission to Competent Authorities within the regulatory reporting timeframes.

All safety reports on Voydeya, Ultomiris, and Soliris made during the course of this study will be recorded and summarized in the final study report.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the HMA-EMA Catalogue of real-world data sources and studies), as appropriate, and in accordance with national, regional, and local regulations. However, posting of study results per local regulations may be deferred to a later date for one of the following reasons:

- The study is still ongoing in other countries or regions.
- The study is part of an ongoing review for approval by HAs; study results data deferral request can be submitted.

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APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

None.

APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

This Checklist is developed in line with the ENCePP Checklist for Study Protocols (Revision 4; Doc.Ref. EMA/540136/2009).

Study title:
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

HMA-EMA Catalogue of RWD studies number: To be determined
Study reference number (if applicable): ALX-PNH-502

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☐	☐	☒	
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the HMA-EMA Catalogue of RWD studies	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Study will be registered in HMA-EMA Catalogue of RWD studies prior to first data extraction.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7, 8
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9.3, 11.2, 11.3

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1, 9.2
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.5 and 9.7.5
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☒	☐	☐	9.9
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Additional information on the data source and variables can be located in the International PNH Interest Group PNH Registry Core PNH Registry Protocol and the Alexion Products Silo Appendix. MedDRA will be used to code AEs as part of Case Processing activities (Section 11.3).

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Further details on the analysis plan including handling of missing data will be detailed in a separate Statistical Analysis Plan. Should sensitivity analyses be required, they will be discussed in the SAP.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6, 9.7
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Study size and duration has been agreed to with the EMA. Prior discussions with the agency have described the rationale for proposed study size based on experience with Alexion International PNH Registry.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

This protocol uses secondary data and thus pertaining to 13.2, outcomes of such review procedures will be addressed by IPIG or their designee.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

One amendment was prepared at the time of this submission.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

APPENDIX 3. GLOBAL DRUG SAFETY SUSPECTED / CONFIRMED MENINGOCOCCAL CASE QUESTIONNAIRE

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
☐ African American
☐ American Indian or Alaska Native
☐ Asian
☐ Black
☐ Other *(Specify)*
☐ Caucasian
☐ Native Hawaiian or Pacific Islander
☐ Not Reported
☐ Unknown

Product Name: **Current Dosage:**

Initiation **Last dose**

Date and Dosage:		**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)*

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)

(e.g., 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)*
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:*

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:
(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 If done, results:
☐ Not done

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):

☐ 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 Date of Death:

(Specify cause of death) (DD/MMM/YYYY)

Additional Comments:

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

Revision History

Version Number	Change Type (New, Revised or Admin)	Revision Summary	Justification
1.0	New	Initial Release	N/A
2.0	Revised	Form Updated	Additional fields added
3.0	Revised	Form Updated	Due to Danicopan approval, form updated to include multiple product entries

APPENDIX 4. PREGNANCY / BREASTFEEDING REPORTING AND OUTCOME FORM

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 to 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			

A) General Information		
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
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)

B) Maternal Information		
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)
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
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 _____	

C) **Delivery and Neonatal Information** (Initial) - Please also complete B14-B17 if applicable			
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	☐ = None ☐ = Other:	
C14	Breastfeeding	☐ = No ☐ = Yes: Start date ____/_____/_____ dd /mmm / yyyy Stop date ____/_____/_____ 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			
D1	Source and date of information		____/_____/_____ dd/mmm/yyyy
D2	Reason for termination (If applicable)		
D3	Gestational age at termination	_____weeks	

D) Fetal Information in case of elective termination, spontaneous abortion, and late fetal		
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

Document History

Version Number	Change Type *(New, Revised or Admin)*	Revision Summary	Justification
2.0	Revised	ALXN-SOP-0003874 removed from title and replaced with ALXN-SOP-0003872	ALXN-SOP-0003874 Obsolescence
3.0	Admin	To correct the viewable rendition	Deviation PR#156705

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