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Characterization of Participants Treated with Ultomiris® and Long-Term Safety Outcomes: an IPIG PNH Registry-based Study

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PASS INFORMATION

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Marketing authorisation holder(s)	Alexion Europe SAS 103 105 rue Anatole France 92300 Levallois-Perret France
Joint PASS	No
Research question and objectives	Primary: • To characterize the safety of Ultomiris in participants with PNH • To characterize the incidence of targeted clinical outcomes among participants with PNH Secondary: • To describe the demographic and clinical profile at treatment initiation for Ultomiris-treated participants with PNH • To assess Ultomiris treatment patterns among participants with PNH
Proposed Countries of study	USA, Canada, United Kingdom, France, Germany, Australia, Sweden, Netherlands, Spain, Japan, Taiwan, South Korea, China, Italy, Switzerland, Argentina, Colombia, Belgium, Turkey, Austria, Greece, and Kingdom of Saudi Arabia

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1. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
C5	complement component 5
CRO	contract research organization
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EMA	European Medicines Agency
GPS	Global Patient Safety
HCP	health care provider
HRU	health-resource utilization
ICF	informed consent form
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IPIG	International PNH Interest Group
IRB	Institutional Review Board
MAH	marketing authorisation holder(s)
MAVE	major adverse vascular event
PASS	post authorisation safety study
PNH	paroxysmal nocturnal hemoglobinuria
PRO	patient-reported outcome
SAE(s)	serious adverse event(s)

2. RESPONSIBLE PARTIES

Table 1: Key Personnel Involved in the Registry

Key Personnel	Details
Chief Investigator	Dr Richard Kelly, MBChB, PhD Consultant Hematologist PNH National Service, Leeds Teaching Hospitals NHS Trust
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3. ABSTRACT

Title

Characterization of Participants Treated with Ultomiris® and Long-Term Safety Outcomes: an IPIG PNH Registry-based Study

Rationale and background

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare and life-threatening acquired hematologic disorder caused by uncontrolled activation of the terminal complement pathway (Bektas, 2020; Brodsky, 2014; DeZern, 2015). The prevalence is estimated to be between 10 to 38 cases per million (Hansen, 2020; Jalbert, 2019; Richards, 2021). The disease has a roughly equal sex distribution and can occur at any age though is diagnosed most often in the fourth or fifth decade of life (Schrezenmeier, 2020). Prior to the availability of Soliris® (eculizumab), the estimated survival of patients with PNH after diagnosis was 50% at approximately 15 years (Hillmen, 1995; Nishimura, 2004; Socié, 1996).

Alexion Pharmaceuticals, Inc. has been the Sponsor of a global PNH Registry (M07-001) since August 2004 and has been enrolling participants with PNH worldwide, including participants treated with Soliris since its first approval (2007). The primary aim of the Alexion PNH Registry is to record the natural progression of PNH and collect and evaluate safety data specific to the use of Soliris or Ultomiris® (ravulizumab) in patients with PNH. Data from the PNH Registry are intended for health care providers (HCP) to optimize clinical decision making through enhanced understanding of the natural history of PNH with the ultimate goal of better guiding and assessing therapeutic interventions. Methods of PNH diagnosis, treatment data, clinical outcomes, and quality of life assessments are also collected. An additional objective is to increase PNH knowledge in the medical community and patient community.

In 2023, the Alexion PNH Registry will begin transitioning to the International PNH Interest Group (IPIG) PNH Registry with the objective to move from an industry-sponsored registry to an academic-led Registry database. The IPIG PNH Registry aims to enroll patients with PNH, regardless of the type of PNH-specific therapy they are receiving, to capture data on clinical outcomes, patient-reported outcomes (PROs), and health-resource utilization (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 intended to increase knowledge about PNH in the medical community and patient population.

The IPIG PNH Registry is comprised of the Core PNH disease Registry (Core Registry) and several product-specific silo protocols initiated by IPIG on request by the respective marketing authorisation holders (MAHs). Core variables will be collected in the Core Registry at enrollment and during follow-up, while specific data (eg, post authorization safety data) for participants treated with PNH-specific therapies will be collected in the silos in order to address specific objectives or requests from regulatory authorities and MAHs. Data elements previously reported to the European Medicines Agency (EMA) from the Alexion PNH Registry via interim safety reports continues to be collected via the IPIG PNH Registry.

Research question and objectives

Objectives	Endpoints
Primary	
To characterize the safety of Ultomiris in participants with PNH	Incidence of reported SAEs and special events
To characterize the incidence of targeted clinical outcomes among participants with PNH	Incidence rate of MAVE, TE, malignancy, serious infection, impaired renal function, impaired hepatic function, hemolysis, mortality, and bone marrow transplant. Incidence of pregnancy outcome (both maternal and fetal events)
Secondary	
Describe the demographic and clinical profile at treatment initiation for Ultomiris-treated participants with PNH	Frequency and univariate statistics of demographic characteristics, medical history, comedications, and laboratory measures
Assess Ultomiris treatment patterns among participants with PNH	Initiation dose and average dose patterns Number of participants who discontinue Ultomiris and reasons for discontinuation

Abbreviations: MAVE = major adverse vascular event; PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; TE = thrombotic event

Study design

This noninterventional cohort study utilizes data from the IPIG PNH Registry. Data within the IPIG PNH Registry consists of retrospective data collected prior to registry enrollment (eg, from the Alexion PNH Registry) and data collected prospectively beginning at IPIG PNH Registry enrollment and through follow-up.

The IPIG PNH Registry is a multinational, multicenter, observational registry designed to collect data on patients with PNH in a real-world clinical setting.

All participants in the IPIG PNH Registry will be consented into the Core Registry protocol, which includes the Alexion Products Silo protocol as an appendix. The Core Registry protocol 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 and/or Ultomiris, will also have treatment-specific data, including serious adverse events (SAEs), collected as part of the Alexion Products Silo protocol. The necessary data to complete the objectives of this post authorisation safety study (PASS) from both the Core Registry and Alexion Products Silo protocols will be provided by IPIG to Alexion for participants eligible for this PASS.

Regardless of Alexion's commitment to provide interim safety analysis reporting, enrolled participants will be followed in the IPIG PNH Registry for at least 5 years after their enrollment. Participants' visit schedules will follow the standard of care. Participant data are expected to be entered in the electronic data capture (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 IPIG PNH Registry, will be collected for

individual participants either from sites directly or by transfer of data from the global Alexion PNH Registry (when a participant was part of the Alexion PNH Registry and after signing a consent).

Population

Adult and pediatric participants with PNH with a detected proportion of PNH cells (PNH clone) of at least 1% at registry enrollment, who have provided written informed consent, and who are not participating in an interventional clinical trial specific to PNH, are eligible for participation in the IPIG PNH Registry.

Participants enrolled in the IPIG PNH Registry with known year of birth, sex, informed consent date, and Ultomiris treatment status are eligible for this study.

Variables

Data variables will be collected for all participants enrolled in the IPIG PNH Registry. These include participant demographics, medical history, concomitant medication and other treatments, clinical laboratory tests results (related to PNH), proportion of PNH cells (PNH clone size) as measured by flow cytometry, clinical outcome data (number of units of packed red blood cells transfused, major adverse vascular events [MAVEs] including thrombosis, morbidity including myeloproliferative disease and other malignancies, serious infections, with a particular focus on *Neisseria* infections, impaired renal function, impaired hepatic function, hemolysis, pulmonary hypertension, bone marrow transplant, and mortality).

In addition to the above listed variables, for participants being treated with Ultomiris, Ultomiris-specific data will be collected. These include SAEs, meningococcal vaccination status, reasons for discontinuation of Ultomiris, infusion reactions, dosing information (including individualized dosing adjustments), pregnancy (both maternal and fetal events), exposure during lactation, and follow-up of neonates at 12 months after delivery, especially when in utero neonatal exposure to Ultomiris has occurred through maternal or paternal exposure (via semen). Information regarding exposure of an infant to Ultomiris during breastfeeding also will be collected, as well as any adverse events (AEs) an infant may experience following breastfeeding. Any events of misuse, overdose, medication errors, occupational exposure or falsified product, and lack of therapeutic efficacy will also be collected.

Data sources

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

Participant data will be collected at the time of registry enrollment and throughout the follow-up period, and entered into the EDC system by the clinician and/or qualified designee.

Retrospective data from the Alexion 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.

Study size

Open-ended. All participants who fulfill the inclusion/exclusion criteria are eligible to be included in the IPIG PNH Registry. At least 300 participants are anticipated.

Data analysis

Participant demographics, medical history, clinical events, laboratory values, concomitant medication, prior treatment with Soliris, and Ultomiris dose will be summarized at initiation of Ultomiris using descriptive analyses.

Participants may contribute person-time to the following exposure periods during registry follow-up:

- Untreated period
  - Defined as time where a patient is not treated with a PNH-specific therapy until their last untreated follow-up date
- Treated with Soliris (prior to Ultomiris switch) (Soliris exposure period)
  - Defined as time treated with Soliris until the last Soliris treated follow-up date
- Treated with Ultomiris (Ultomiris exposure period)
  - Defined as time from Ultomiris initiation to last Ultomiris treated follow-up date

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

- Registry discontinuation and the reasons for last registry follow-up
- Ultomiris average dose, number of participants who discontinue treatment and the reasons for the treatment discontinuation
- SAEs
- Causes of death
- Clinical events, including number of units of packed red blood cells transfused, MAVEs (including thrombosis), morbidity including myeloproliferative disease and other malignancies (solid as well as hematologic malignancies), serious infections (with a particular focus on *Neisseria* infections), impaired renal function, impaired hepatic function, hemolysis, pulmonary hypertension, bone marrow transplant, and mortality, will be summarized by event rates based on exposure period. Pregnancy outcomes (both maternal and fetal events) will also be summarized by exposure at the time of the outcome.

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

Participants will be stratified by prior Soliris treatment status:

- Prior Soliris treatment
- Without prior Soliris treatment
- Unknown prior Soliris treatment

Study milestones

Milestone	Planned date
Start of data collection	To be determined, Q3 2023
Interim report 1	July 2025
Registration in the EU PAS register	Prior to study initiation
Final report of study results	As applicable, based on agreed regulatory requirements

4. AMENDMENTS AND UPDATES

Not applicable

5. MILESTONES

An interim analysis report is planned for July 2025.

Table 2: Study Milestones

Milestone	Planned date
Start of data collection	To be determined, Q3 2023
Interim report 1	July 2025
Registration in the EU PAS register	Prior to study initiation
Final report of study results	As applicable, based on agreed regulatory requirements

6. INTRODUCTION

6.1. Overview of Paroxysmal Nocturnal Hemoglobinuria (PNH) Disease

PNH is an ultra-rare and life-threatening acquired hemolytic disorder caused by uncontrolled activation of the terminal complement pathway (Bektas, 2020; Brodsky, 2014; DeZern, 2015). The prevalence is estimated to be between 10 to 38 cases per million (Hansen, 2020; Jalbert, 2019; Richards, 2021). The disease has a roughly equal sex distribution and can occur at any age though is diagnosed most often in the fourth or fifth decade of life (Schrezenmeier, 2020). Prior to the availability of Soliris®, the estimated survival of patients with PNH after diagnosis was 50% at approximately 15 years (Hillmen, 1995; Nishimura, 2004; Socié, 1996).

Chronic, uncontrolled complement component 5 (C5) cleavage and formation of C5a and C5b-9 lead to inflammation, platelet activation, and red blood cell intravascular hemolysis. Intravascular hemolysis results in the release of intracellular free hemoglobin and lactate dehydrogenase into circulation; irreversible binding to and inactivation of nitric oxide by hemoglobin and inhibition of nitric oxide synthesis; vasoconstriction and tissue-bed ischemia due to absence of vasodilatory nitric oxide, as well as possible microthrombi (Brodsky, 2014; Hill, 2013).

The resulting clinical manifestations include venous or arterial thrombosis, which may be in diverse sites including the abdomen or central nervous system, as well as renal dysfunction and pulmonary hypertension (Brodsky, 2014; Hill, 2017). Secondary effects, in addition to the risk of major organ damage from thrombosis, include abdominal pain, shortness of breath, dysphagia, erectile dysfunction, platelet activation, a proinflammatory and prothrombotic state, fatigue, difficulties in concentrating or thinking, and lower quality of life (Hill, 2017).

7. RATIONALE AND BACKGROUND

Alexion Pharmaceuticals, Inc. has been the Sponsor of a global PNH Registry (M07-001) since August 2004 and has been enrolling participants with PNH worldwide, including participants treated with Soliris since its first approval (2007). The primary aim of this Registry is to record the natural progression of PNH and collect and evaluate safety data specific to the use of Soliris or Ultomiris in patients with PNH. Data from the Alexion PNH Registry are intended for HCP to optimize clinical decision making through enhanced understanding of the natural history of PNH with the ultimate goal of better guiding and assessing therapeutic interventions. Methods of PNH diagnosis, treatment data, clinical outcomes, and quality of life assessments are also collected. An additional objective is to increase PNH knowledge in the medical community and patient community.

With the approvals of Soliris (first approval, 2007) and Ultomiris (first approval, 2018), which are both indicated for the treatment of patients with PNH, the Alexion PNH Registry had the ability to actively collect long-term clinical outcomes and safety data related to the treatment of PNH with Soliris or Ultomiris to characterize the long-term safety profile of both therapies.

In 2023, the Alexion PNH Registry will begin transitioning to the IPIG PNH Registry with the objective to move from an industry-sponsored registry to an academic-led registry database. The IPIG PNH Registry aims to enroll patients with PNH, regardless of the type of PNH-specific therapy they are receiving, 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 intended to increase knowledge about PNH in the medical community and patient population.

The IPIG PNH Registry is comprised of the Core PNH disease registry (Core Registry) and several product-specific silo protocols initiated by IPIG on request by the respective MAH. Core variables will be collected in the Core Registry at enrollment and during follow-up, while specific data (eg, post authorization safety data) for participants treated with Alexion-specific therapies will be collected in the Alexion Products Silo in order to address specific objectives or requests from regulatory authorities and MAHs.

This PASS sponsored by Alexion MAH addresses specific objectives agreed with EMA regarding Ultomiris treatment in PNH. It covers the safety concerns in the Ultomiris EU Risk Management Plan, which include the important identified risk of meningococcal infection, important potential risks of serious hemolysis after drug discontinuation in patients with PNH, serious infections, malignancies and hematologic abnormalities in patients with PNH and missing information with the use of Ultomiris in pregnant and breastfeeding women. Further, Alexion has performed an assessment of the Core Registry and Alexion Products Silo protocols to confirm that data collected aligns with those collected in the Alexion PNH Registry for the purposes of interim safety analysis reporting.

The risk of meningococcal infection is directly associated with the ravulizumab mode of action, causing deficiency in terminal complement components which is associated with an increased incidence of infections caused by *Neisseria* spp., especially *N meningitidis*. The potential risk of serious hemolysis after drug discontinuation in PNH patients is based on a theoretical possibility, associated with abrupt Ultomiris discontinuation, resulting in a so-called rebound effect. Given Ultomiris is a monoclonal antibody, potential immunogenicity is common to all biologics. As for

the potential risk of malignancies and hematologic abnormalities in patients with PNH, the natural evolution of PNH disease makes patients with PNH more prone to development of hematologic abnormalities or malignancies as approximately 30% to 70% of patients with PNH eventually develop aplastic anemia or myelodysplastic syndrome (de Latour, 2008; Hillmen, 1995; Socié, 1996). The potential role of ravulizumab in such abnormalities or malignancies (if any) is unknown.

There are no human data on the use of ravulizumab during pregnancy and breastfeeding. Some immunoglobulins are known to cross placental barrier and be likely excreted into the breast milk. However, the ravulizumab heavy chain sequence was combined from human immunoglobulin G (IgG)2 and IgG4 Fc sequences to form a hybrid constant region that has minimal binding Fc gamma receptors (Alexion data on file). Considering the mode of ravulizumab action and the missing data, the benefit-risk balance of Ultomiris remains currently unknown in these patient populations.

Therefore, considering the knowledge gaps and regulatory commitments, the aims of this PASS are to address and characterize these safety concerns among real-world users of Ultomiris.

8. RESEARCH QUESTION AND OBJECTIVES

The objectives of this IPIG PNH Registry-based study are as follows:

8.1. Primary Objectives

- To characterize the safety of Ultomiris in participants with PNH
- To characterize the incidence of targeted clinical outcomes among participants with PNH

8.2. Secondary Objectives

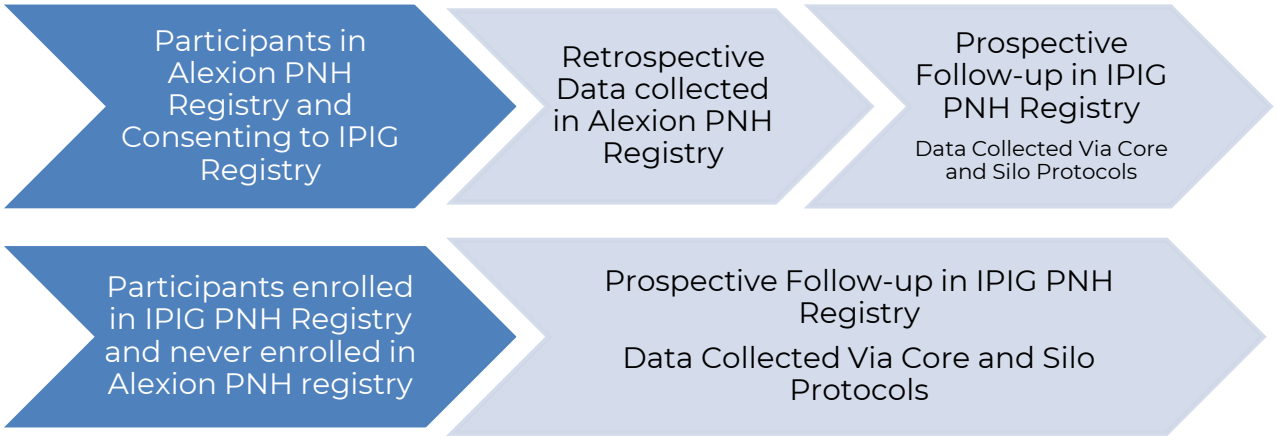
- To describe the demographic and clinical profile at treatment initiation for Ultomiris treated participants with PNH
- To assess Ultomiris treatment patterns among participants with PNH

9. RESEARCH METHODS

9.1. Study Design

The data for this study will be collected through the IPIG PNH Registry and the Alexion Products Silo. Figure 1 presents the overview of the study design.

Figure 1: Study Design Schematic



Abbreviations: IPIG = International PNH Interest Group; PNH = paroxysmal nocturnal hemoglobinuria

This noninterventional cohort study utilizes data from the IPIG PNH Registry. Data within the IPIG PNH Registry consists of retrospective data collected prior to registry enrollment (eg, from the Alexion PNH Registry) and data collected prospectively beginning at IPIG PNH Registry enrollment and through follow-up.

The IPIG PNH Registry is a multinational, multicenter, observational registry designed to collect data on patients with PNH in a real-world clinical setting.

Participants (adult and pediatric) with PNH diagnosis confirmed by flow cytometry and who meet the inclusion/exclusion criteria will be invited to participate in the IPIG PNH Registry. All participants with PNH will be eligible, regardless of whether they are receiving PNH-specific therapy and regardless of what type of therapy they are receiving.

Each participant (or parent/legally authorized representative) will sign an informed consent form (ICF) indicating their consent to participate in the IPIG PNH Registry prior to any registry related data collection. If applicable, minor participants will be given an assent form and be asked to sign it to confirm their agreement to participate. Minor participants who reach the age of consent during the study period must sign an Adult Patient/Parent ICF at their next visit to confirm their consent to continue participation in the Registry.

All participants in the IPIG PNH Registry will give consent for the Core Registry protocol, which includes the Alexion Products Silo protocol as an appendix. The Core Registry protocol 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 (ie, Soliris and/or

Ultomiris) will also have treatment-specific data, including SAEs, collected as part of the Alexion Products Silo protocol. The necessary data to complete the objectives of this PASS from both the Core Registry and Alexion Products Silo protocols will be provided by IPIG to Alexion for participants eligible for this PASS.

Regardless of Alexion's commitment to provide interim safety analysis reporting, enrolled participants will be followed in the IPIG PNH Registry for at least 5 years after their enrollment. 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 IPIG PNH Registry, will be collected for individual participants either from sites directly or by transfer of data from the global Alexion PNH Registry (when a participant was part of the Alexion PNH Registry and after signing a consent).

Participants enrolled in the Alexion Products Silo, who are treated with Ultomiris, will have additional data collected further to the data already collected in the Core Registry protocol.

Clinicians will be encouraged to enter all available data for enrolled participants treated with Ultomiris into the Alexion Products Silo at the time of registry enrollment and consistent with the Core Registry protocol, every 6 months thereafter. Additionally, participants who discontinue Ultomiris will be followed for 12 weeks.

To preserve the integrity of data collected for any interventional therapy for PNH in clinical studies, as well as to avoid duplicate safety reporting, participants should be discontinued from the IPIG PNH Registry including the Alexion Product Silo if applicable, when they enroll in an interventional clinical study for a PNH therapy.

9.2. Setting

The following criteria should be used to identify participants for Study ALX-PNH-501.

9.2.1. Inclusion Criteria

1. Participants of any age and sex, with PNH with a detected proportion of PNH cells (PNH clone) of at least 1% at registry enrollment, initiating Ultomiris on or after enrollment into the Alexion or IPIG PNH Registries.

2. Ability to comprehend and sign consent or able to give assent to have data entered in the IPIG PNH Registry. Participants who are minors must have parent/legal guardian consent. Participants who are minors must be willing and able to give assent, if applicable as determined by the Ethics Committees/Institutional Review Boards (IECs/IRBs). Upon attaining adulthood, these participants must be re-consented.

9.2.2. Exclusion Criteria

1. Participants currently enrolled in an interventional clinical study for treatment of PNH cannot be enrolled in the IPIG PNH Registry while enrolled/participating in the clinical study for PNH therapy.

2. Participants without known year of birth, sex, Ultomiris treatment status, or informed consent date.

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 Ultomiris 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 Ultomiris, assessed by the clinician as treatment-related should be reported during the 12-week follow-up period, and followed up until resolution.

Following the fulfillment of any regulatory or other legal obligation, the Registry may be stopped by the Sponsor for any reason. A participant may be withdrawn from the Registry by Sponsor or the participating clinician if: (1) the Registry is stopped by Sponsor; (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. Data Variables

The following data variables will be collected for all participants enrolled in the IPIG PNH Registry (as applicable to the specific participant and the standard management practices at a given institution):

- Participant demographics
- Medical history, PNH treatment, and concomitant medication (eg, anticoagulants, erythropoiesis stimulating agents, steroids, other immunosuppressive therapies, and analgesics)
- Clinical laboratory tests results related to PNH, including lactate dehydrogenase levels
- Proportion of PNH cells (PNH clone size) as measured by flow cytometry
- Clinical outcome data including:
  - number of units of packed red blood cells transfused
  - MAVEs, including thrombosis
  - morbidity including myeloproliferative disease and other malignancies (solid as well as hematologic malignancies)
  - serious infections, with a particular focus on *Neisseria* infections
  - impaired renal function
  - impaired hepatic function

  - hemolysis
  - bone marrow transplant
  - pulmonary hypertension
  - mortality
- Pregnancy and lactation status
- Registry discontinuation and reasons

For participants being treated with Ultomiris, in addition to the items listed above, the following Ultomiris-specific data will be collected:

- Pregnancy (both maternal and fetal events), exposure during lactation, and follow-up of neonates at12 months after delivery, especially when the neonate has experienced Ultomiris exposure in utero (EIU)
  - Exposure during pregnancy also called EIU can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. Information regarding exposure of an infant to Ultomiris during breastfeeding also will be collected, as well as any AEs an infant may experience following breastfeeding.
- SAEs (an SAE is defined as any AE that results in death, or is life-threatening, or requires inpatient hospitalization or prolongation of existing hospitalization, or is an important medical event, or results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect)
- Meningococcal vaccination status
- Reasons for discontinuation of Ultomiris
- Infusion reactions, specifically those adverse reactions identified by: anaphylaxis, anaphylactoid reaction, infusion-related reaction, infection site irritation, pruritus, rash, pruritus generalized, rash pruritic, urticaria, hypotension, drug hypersensitivity
- Dosing information including the reason for individualized dosing adjustments outside the 8 weeks ± 7 days for Ultomiris
- Special events regarding the use of Ultomiris including any events of misuse, overdose, medication errors, occupational exposure or falsified product, and lack of therapeutic efficacy will also be reported

9.3.2. Exposure Period During Registry Follow-up

Participants may contribute person-time to the following exposure periods during registry follow-up:

- Untreated period
  - Defined as time where a patient is not treated with a PNH-specific therapy until their last untreated follow-up date
- Treated with Soliris (prior to Ultomiris switch) (Soliris exposure period)

  - Defined as time treated with Soliris until the last Soliris treated follow-up date
- Treated with Ultomiris (Ultomiris exposure period)
  - Defined as time from Ultomiris initiation to last Ultomiris treated follow-up date

9.3.3. Data Collection Frequency

Participating physicians will be prompted to complete the IPIG PNH Registry electronic case report form (eCRF) at specified data entry time points (Baseline, Month 6 and then every 6 months thereafter). See Table 3 below.

Table 3: IPIG PNH Registry Data Entry Time Points

Visit Type	All Registry Participants	Ultomiris Treated Registry Participants
Enrollment	X	X
Month 6	X	X
Every 6 months	X	X
Ultomiris discontinuation follow-up (12 weeks post discontinuation of Ultomiris)		X
IPIG PNH Registry discontinuation	X	X

Abbreviations: IPIG = International PNH Interest Group; PNH = paroxysmal nocturnal hemoglobinuria

Data will be collected on an ongoing basis for all actively enrolled participants in the IPIG PNH Registry as outlined in Section 9.1, as well as during the 12-week follow-up period should a participant discontinue Ultomiris. Participants who discontinue Ultomiris are encouraged to remain in the IPIG PNH Registry.

9.4. Data Sources

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

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 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.

9.5. Study Size

The study size for this Registry is open-ended. All participants who fulfill the inclusion/exclusion criteria are eligible and will be included in the study. At least 300 participants are anticipated.

9.6. Data Management

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

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.

9.7.1. Descriptive Analyses

Participant demographics, medical history, clinical events, laboratory values, concomitant medication, prior treatment with Soliris, and Ultomiris dose will be summarized at initiation of Ultomiris using descriptive analyses. Treatment and registry discontinuation along with associated reasons, pregnancy and fetal outcomes, and SAEs collected during registry follow-up will also be summarized.

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. Endpoint Analyses

9.7.2.1. Event Rates

Clinical events, including death, MAVEs (including thrombosis), infection, malignancy, impaired renal function, impaired hepatic function, Ultomiris infusion reactions, hemolysis, pulmonary hypertension, and bone marrow transplant, will be summarized by event rates based on the exposure period defined below.

Event rates are calculated by:

- 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. The event rate will be calculated using Poisson regression with over-dispersion or generalized estimating equations with a log link, as is appropriate.

9.7.2.2. Treatment Groups

Participants will be categorized into treatment groups by prior Soliris treatment status:

- Prior Soliris treatment
- Without prior Soliris treatment
- Unknown prior Soliris treatment

Pregnancy outcomes (both maternal and fetal events) will also be summarized by exposure (defined in Section 9.3.2) at the time of the event.

9.8. Quality Control

- Alexion assumes accountability for actions delegated to other individuals (eg, IPIG, CROs).
- 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.
- 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 Soliris or Ultomiris 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.
  - Similarly, symptom history reported will reflect symptomatology at any time prior to Ultomiris initiation due to the manner in which symptom history is collected. Participants with prior Soliris treatment may have had greater reported symptoms when compared with participants without prior Soliris treatment as the duration of follow-up is longer.

- Data collection bias
  - 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.
  - 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. 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
  - Confounding occurs when the effects of a treatment or the exposition effect of the disease vary by presence/level of another factor. Confounding may be addressed by using stratification or subgroups in the statistical analysis.
- Lost to follow-up
  - Because 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

Not applicable

10. PROTECTION OF HUMAN PARTICIPANTS

The Registry shall be conducted in compliance with International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice (GPP) guidelines, the ethical principles arising from the Declaration of Helsinki, the European Union (EU) Good Pharmacovigilance Practices (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 Code of Federal Regulations (CFR), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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.

Participants enrolled while under the age of consent will be asked to sign an Adult Patient/Parent ICF at their next visit to confirm their consent to participate if they reach the age of consent during their participation in the IPIG PNH Registry.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Alexion has a legal responsibility to report SAEs, AEs, and adverse drug reactions (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 participant or clinical trial subject 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 Events

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

11.2. Collection and Reporting of Safety Events by Clinicians

The safety profiles of Alexion C5 inhibitors have been well characterized through clinical study and postmarketing experience in the PNH indication. Ultomiris has been approved for use since 2018 and is currently marketed in multiple indications. The primary safety risk of Alexion C5 inhibitors is related to their mechanism of action; complement inhibitors are known to increase the risk of meningococcal infections. In the context of this Ultomiris 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. As the safety profile of Ultomiris is otherwise well characterized, other nonserious AEs will not be collected for the purpose of this PASS study. However, physicians are informed of the possibility to report all other AEs for which they suspect a causal relationship with Ultomiris to Alexion Global Patient Safety (GPS) or to the concerned competent authority via the national spontaneous reporting system.

All SAEs, pregnancies (both maternal and fetal events), exposure during lactation and follow-up of neonates at 12 months after delivery from participants exposed to Ultomiris 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 Ultomiris, 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 Ultomiris, seriousness, action taken, and outcome.

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 outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, and maternal and/or newborn complications. 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, 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 Ultomiris 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 US website www.clinicaltrials.gov and in the EU ENCEEP PASS Register), 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:

- Study is still ongoing in other countries or regions
- Study is part of an ongoing review for approval by Health Authorities; study result data deferral request can be submitted.

13. REFERENCES

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APPENDIX A. LIST OF STAND-ALONE DOCUMENTS

None

APPENDIX B. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

This Checklist is developed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols (Revision 4; Doc.Ref. EMA/540136/2009).

Study title:
Characterization of Participants Treated with Ultomiris® and Long-Term Safety Outcomes: an IPIG PNH Registry-based Study

EU PAS Register® number:
Study reference number (if applicable): ALX-PNH-501

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]	☒	☐	☐	5
1.1.2 End of data collection[2]	☐	☐	☒	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

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? (e.g. 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? (e.g. 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? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. 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? (e.g. 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:				9.1, 9.2
4.2.1 Study time period	☐	☒	☐	
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? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

The beginning of the study time period is dependent on the earliest date of enrollment into the Alexion PNH Registry for an Ultomiris-treated participant who consents to participation in the IPIG PNH Registry and transfer of their data from the Alexion PNH Registry. Thus, the study period may commence as early as 2007 (accounting for Soliris treated time) and will end per agreement with regulatory authorities.

Country of origin is summarized in the PASS Summary Table.

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? (e.g. 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? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. 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?	☐	☐	☒	

Comments:

The validity of the exposure is dependent on self-report from investigators and subject to the same biases described in Section 9.9. The exposure, Ultomiris, is not categorized.

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?	☒	☐	☐	3
6.2	Does the protocol describe how the outcomes are defined and measured?	☐	☒	☐	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Information on which clinical outcomes are collected is specified in this protocol. Further information related to the definition and measurement of these outcomes is specified within the Core Registry and Alexion Products Silo protocols.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. 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? (e.g. 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? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. 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? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. 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? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

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?	☐	☐	☒	
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?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Further details on the analysis plan will be detailed in a separate Statistical Analysis Plan.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. 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?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.8
12.1.3 Residual/unmeasured confounding? (e.g. 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? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

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?	☐	☐	☒	

Comments:

No amendments/deviations at the time of this submission however this will be accounted for as the need arises.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. 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 C. ADDITIONAL INFORMATION

Not applicable