PROTOCOL NUMBER:

M07-001

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) REGISTRY

Sponsor:	Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard Boston, MA 02210
Sponsor Contact:	Email: Clinicaltrials@alexion.com
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Proprietary Notice:

SPONSOR SIGNATURE PAGE

REGISTRY PROTOCOL TITLE: **PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) Registry**

PROTOCOL NUMBER: M07-001

Reviewed and Approved by:

[redacted]

21 JAN 2019

Sponsor S[redacted] Date

[redacted]
Alexion Pharma GmbH
Executive Director, Global Medical Affairs
Giesshübelstrasse 30, Zürich 8045, Switzerland

[redacted]

Sponsor Signatory Date

[redacted], QPPV
Alexion Europe SAS
1-15, avenue Edouard Belin
92500 Rueil-Malmaison, France

PHYSICIAN'S AGREEMENT

I have read and understand all clinical and administrative sections of the protocol. I agree to participate and conduct the study as outlined in the protocol entitled: "PNH Registry" and in accordance with the guidelines and all applicable government regulations. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Physician

_____

Signature of Physician

_____

Date

PNH REGISTRY CONTACTS

Table 1: Contact Information

Alexion Pharmaceuticals, Inc.	121 Seaport Boulevard Boston, MA 02210
Email	Clinicaltrials@alexion.com

Country-specific contact information will be distributed to each participating site.

2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Alexion Pharmaceuticals, Inc.</td></tr>
<tr><td colspan="2">Title of Study: PNH Registry</td></tr>
<tr><td colspan="2">Study center(s): No limit</td></tr>
<tr><td>Studied period (years): 5 years from enrollment of the first patient treated with Ultomiris®
Date first patient treated with Soliris® enrolled:
Aug 2008</td><td>Phase of development:
Postmarketing</td></tr>
<tr><td colspan="2">Objectives:
Primary:
• The PNH Registry will collect and evaluate safety data specific to the use of Soliris or Ultomiris in patients with PNH
• The PNH Registry will collect data to characterize the progression of PNH as well as clinical outcomes, mortality and morbidity in all enrolled patients
Secondary:
• Increase PNH knowledge in the medical community and patient/potential patient population</td></tr>
<tr><td colspan="2">Analysis:
The primary analyses will assess safety endpoints, including occurrence and time to first event of the following clinical outcome measures/events for patients treated with Soliris or Ultomiris:
- Neisserial infections;
- Malignancies (solid as well as hematologic malignancies);
- Thrombotic events;
- Pregnancies (both maternal and fetal events);
- Infusion reactions;
- Bone marrow transplant, and
- Mortality.
- All serious adverse events, including serious infections, regardless of causality.

The primary analysis will also evaluate the rates of Soliris or Ultomiris discontinuation and the reasons associated with it, and any Soliris or Ultomiris dose adjustments.

The progression of PNH and clinical outcomes will be assessed in all enrolled patients.</td></tr>
<tr><td colspan="2">Number of patients (planned): No limit</td></tr>
<tr><td colspan="2">Diagnosis and main criteria for inclusion:
Any patient with PNH with a detected proportion of PNH cells (PNH clone) of at least 1%, as defined in Section 6.</td></tr>
</table>

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study protocol.

Table 2: Abbreviations and Special Terms

Abbreviation or specialist term	Explanation
AE	Adverse event
CRF	Case report form
EC	Ethics Committee
EDC	Electronic data capture
EIU	Exposure *i*n utero
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire Core 30 Scale
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food & Drug Administration
GDS	Global Drug Safety
HCP	Health Care Providers
HIPAA	Health Insurance Portability and Accountability Act of 1996
IRB	Institutional Review Board
MAVE	Major adverse vascular events
PNH	Paroxysmal nocturnal hemoglobinuria
SAE	Serious adverse event

4. INTRODUCTION

4.1. Overview of Paroxysmal Nocturnal Hemoglobinuria (PNH) Disease

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare and life-threatening acquired hemolytic disorder caused by uncontrolled activation of the terminal complement pathway (Brodsky, 2014; Brodsky, 2015). Chronic, uncontrolled complement C5 cleavage and formation of C5a and C5b-9 lead to inflammation, platelet activation, and red blood cell hemolysis. 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 manifesting as abdominal pain, shortness of breath, dysphagia, and erectile dysfunction; platelet activation; and a proinflammatory and prothrombotic state (Hill, 2013; Brodsky, 2014).

A substantial proportion of patients with PNH experience renal dysfunction and pulmonary hypertension (Hillmen, 2010; Hill, 2012; Hill, 2013; Brodsky, 2014). Patients also experience venous or arterial thrombosis in diverse sites, including the abdomen or central nervous system (Brodsky, 2014). 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.

The incidence of PNH is estimated at 1 to 1.5 cases per million individuals worldwide (Hill, 2017). A study in England found the prevalence of patients with a PNH clone in this population to be 15.9 per million with an annual incidence of approximately 1.3 per million (Hill, 2006), while a study from Spain suggested an annual incidence of 2.5 per million persons (Morado, 2017).

4.2. Rationale and Background

Alexion Pharmaceuticals, Inc. has been the Sponsor of a global PNH Registry since August 2004 and has been enrolling patients with PNH worldwide, including patients treated with Soliris® since its first approval (2007). The primary aim of this Registry has been to record the natural progression of PNH in a multinational database. Data from the PNH Registry were intended for Health Care Providers (HCP) to optimize clinical decision making through enhanced understanding of the variability, progression and natural history of PNH with the ultimate goal of better guiding and assessing therapeutic interventions. Methods of PNH diagnosis and monitoring the patient's clinical course, PNH treatment, including assessing the long term safety and clinical outcomes of available treatment strategies were also collected. An additional objective was to encourage collaboration and the sharing of expertise through a global community of PNH clinical investigators and physicians as well as patients with PNH.

With the approval of Soliris® (eculizumab; first approval, 2007) and Ultomiris® (ravulizumab; first approval, 2018), which are both indicated for the treatment of patients with PNH, the PNH Registry has 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. The PNH Registry will also continue to collect information to characterize the

progression of PNH, as well as clinical outcomes, mortality, and morbidity in all patients for a period of 5 years from the date that the first patient treated with Ultomiris is enrolled. Periodic reporting will be performed.

4.2.1. Rationale for Expanding the PNH Registry

The PNH Registry will be expanded to include patients with PNH treated with Ultomiris (including those who have completed participation in Sponsored clinical studies of Ultomiris) in order to expand the overall safety and efficacy profile of Ultomiris.

The consolidation of safety information into the existing PNH Registry has several advantages. Physicians and patients already familiar with the existing Registry can continue to participate with minimal adaptation from their current process. Existing PNH Registry data collection provides much needed information on patient demographics, diagnostic methods and disease characteristics that enhances the additional safety information collected. A single PNH Registry is the preferred method to capture disease, safety and efficacy data in a rare disease population and maximizes physician and patient participation.

Research and therapeutic development for patients with PNH is ongoing. The PNH Registry is a disease-based registry with no inclusion or exclusion criteria either linked to treatments that patients may receive, or the ability to participate in a clinical study. As clinical studies are conducted for new investigational therapies for patients with PNH, rules for handling of patients enrolled in the PNH Registry who are entering into clinical studies have been developed, see Section 7.1 for details.

5. PNH REGISTRY OBJECTIVES AND PURPOSE

The objectives of the PNH Registry are as follows:

5.1. Primary Objective

- The PNH Registry will collect and evaluate safety data specific to the use of Soliris or Ultomiris in patients with PNH
- The PNH Registry will collect data to characterize the progression of PNH, as well as clinical outcomes, mortality and morbidity, in all enrolled patients

5.2. Secondary Objectives

- Increase PNH knowledge in the medical community and patient/potential patient population

6. PNH REGISTRY DESIGN

The PNH Registry is a multi-center, multi-national, observational, non-interventional study with enrollment of patients with PNH, whether treated or not with Soliris or Ultomiris. Patients with PNH meeting the criteria outlined in Section 8.1 will be enrolled. The PNH Registry will capture post-marketing long term safety data on patients treated with Soliris or Ultomiris as well as clinical outcome data on all enrolled patients. Additionally, it will collect information on the progression of disease in the PNH population, including those patients who discontinue Soliris or Ultomiris. Patients and physicians in countries where Soliris or Ultomiris are not licensed may participate in the PNH Registry.

Prescribing physicians and other HCPs will be informed by the Sponsor or Sponsor's designee that a PNH Registry has been established and that patients of any age, with PNH with a detected PNH clone, whether treated or not, will be eligible for enrollment subsequent to providing informed consent. PNH diagnosis is left to physician discretion (ie, all diagnostic methods are accepted). The detected proportion of PNH cells (PNH clone) is defined by the identification of glycosylphosphatidylinositol-deficient granulocytes, glycosylphosphatidylinositol-deficient erythrocytes or both. Glycosylphosphatidylinositol deficiency can be classified as partial (Type II) or complete (Type III). Patients with any combination of Type II or Type III clones/cells are eligible for enrollment into the registry. A minimum proportion of PNH cells (PNH clone) at a level of 1% is required.

Physicians will be encouraged to enter all available data for all enrolled patients into the PNH Registry at specified data entry time points, as well as to follow patients who discontinue Soliris or Ultomiris. To preserve the integrity of data collected for any interventional therapy for PNH in clinical studies, as well as to mitigate duplicate safety reporting, patients should be discontinued from the PNH Registry when they enroll in an interventional clinical study for a PNH therapy.

After a patient completes participation in an interventional clinical study, they may be re-consented to enroll again in the PNH Registry. Every effort will be made to capture information identifying them as a patient who was previously enrolled in the PNH Registry.

6.1. Data Collection

6.1.1. Data Variables

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

- Patient demographics
- Medical history and concomitant medication (eg, anticoagulants, erythropoiesis stimulating agents, steroids, other immunosuppressive therapies and analgesics) and other treatments
- 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
  - Major Adverse Vascular Events (MAVE), including thrombosis
  - Morbidity including myeloproliferative disease and other malignancies (solid as well as hematologic malignancies)
  - Infections, with a particular focus on neisserial infections
  - Impaired renal function
  - Impaired hepatic function
  - Hemolysis
  - Bone marrow transplant
  - Mortality
- Quality of life data using the validated Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 instruments, as well as pre-specified PNH symptoms by patient reported outcomes, and physician assessment of health burden
- Pregnancy status

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

- Pregnancy (both maternal and fetal events), lactation, and follow-up of neonates for 3 months after delivery, especially when the neonate has experienced Soliris or 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 Soliris or Ultomiris during breastfeeding also will be collected, as well as any adverse events (AEs) an infant may experience following breastfeeding. Follow-up information on neonates for 3 months after delivery, especially when the neonate has experienced Soliris or Ultomiris EIU, will be collected.
- All serious adverse events (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
- Outcomes associated with the discontinuation of Soliris or 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 12-16 days dosing interval for Soliris and 8 weeks ± 7 days for Ultomiris
- Special events regarding the use of Soliris or Ultomiris including any events of misuse, overdose, medication errors, occupational exposure or falsified product, and lack of therapeutic efficacy will also be reported:

6.1.2. Data Collection Frequency

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

Table 3: PNH Registry Data Entry Time Points

Visit Type	All Registry Patients	Soliris or Ultomiris Treated Registry Patients
Enrollment	X	X
Month 6	X	X
Every 6 months	X	X
Soliris or Ultomiris discontinuation follow-up (8 weeks and 16 weeks post-discontinuation of Soliris or Ultomiris, respectively)		X
PNH Registry discontinuation	X	X

Data will be collected on an ongoing basis for all actively enrolled patients in the PNH Registry as outlined in Section 6.1, as well as during the 8- or 16-week follow-up period should a patient discontinue Soliris or Ultomiris, respectively. Patients who discontinue Soliris or Ultomiris are encouraged to remain in the PNH Registry.

7. SELECTION AND WITHDRAWAL OF PHYSICIANS

7.1. Physician Participation

7.1.1. Responsibilities

To be eligible for PNH Registry participation, physicians should meet the following qualifications:

- Agree to comply with PNH Registry processes.
- Complete a quality of life questionnaire at Baseline and every 6 months thereafter, and enter the data into the PNH Registry case report form (CRF).
- Agree to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations or General Data Protection Regulation, as applicable, and/or institution/country-specific subject privacy requirements, as applicable (see also Section 12.2.1).

7.2. Physician Withdrawal

Should a physician leave his/her medical practice, Alexion Pharmaceuticals, Inc. should be informed in advance, and another physician should be identified to whom patients will be referred. The replacing physician will be trained on PNH Registry processes, and then will assume Registry responsibilities for patients enrolled in the PNH Registry.

Patient data entered in the PNH Registry will remain in the database.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Selection

The following criteria should be used to identify patients for the PNH Registry:

Appropriate Patients:

- Patients of any age, with PNH with a detected proportion of PNH cells (PNH clone) of at least 1%, whether treated or not with Soliris or Ultomiris, or previously treated with Soliris or Ultomiris and withdrawn from treatment.
- Ability to comprehend and sign consent or able to give assent to have data entered in the PNH Registry. Patients who are minors must have parent/legal guardian consent. Patients who are minors must be willing and able to give assent, if applicable as determined by the Ethics Committees/Institutional Review Boards (EC/IRB). Upon attaining adulthood, these patients must be re-consented.
- Patients currently enrolled in an interventional clinical study for treatment of PNH cannot be enrolled in the PNH Registry while enrolled/participating in the clinical study for PNH therapy.

8.2. Patient and/or Registry Discontinuation

Participation in the PNH Registry is voluntary. Patients 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 patients who discontinue treatment with Soliris or 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 Soliris or Ultomiris, assessed by the physician as treatment-related should be reported during the 8- and 16-week follow-up period, respectively, 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 patient may be withdrawn from the Registry by Sponsor or the participating physician if: (1) the Registry is stopped by Sponsor; (2) it is discovered that the patient did not meet the requirements for participation in the Registry; (3) the Institution and/or Registry Physician is no longer participating in the Registry; or (4) relevant Regulatory Authorities and/or IRB/IEC decide to stop the Registry.

9. REGISTRY GOVERNANCE

The PNH Registry is funded and administered by Alexion. Each participating site/physician will enter into a Registry Agreement with Alexion governing the terms and obligations of the parties in the Registry. Each individual patient's Registry data may be longitudinally represented within the Registry and accessed by participating physicians at their discretion.

The Registry is overseen by an Executive Committee, comprised of international experts involved in the research or care of patients with PNH. Details of the Executive Committee's activities are provided in Section 14.

10. ADVERSE EVENT REPORTING FOR ALL PATIENTS

All SAEs including special events (for Soliris or Ultomiris treated patients), and pregnancies (for Soliris or Ultomiris treated patients and partners of male patients receiving Soliris or Ultomiris only), will be recorded and reported as per the instructions below.

10.1. Reporting of Serious Adverse Events and Special Events

SAEs and Special Events must be reported for all patients receiving Soliris or Ultomiris. The physician/site must submit the SAE/special event into the Electronic Data Capture (EDC) system using the SAE electronic CRF.

In the event that the EDC system/Safety Gateway is unavailable at the site(s) and the SAE/special event needs to be reported, please refer to the contingency plan for reporting the SAE on a paper CRF (Safety Reporting Plan).

If additional supporting information is available (ie, hospital discharge summary, relevant laboratory reports and/or diagnostic data, medical records, death certificate), the physician should complete, sign, and date the SAE cover page, verify the accuracy of the information recorded on the SAE/special event cover page, and send the SAE/special events cover page along with the associated (redacted) source documents to Alexion Global Drug Safety (GDS) via:

Email: ClinicalSAE@alexion.com

*Fax: + 1-203-439-9347

*Please note - Email is the preferred route of transmission. However, the Fax# is provided as a back-up/contingency plan for the Investigational site to report the SAE/special event in the event that the site is unable to email the report.

10.2. Reporting Exposure during Pregnancy, Lactation, and Follow-up of Neonates

All pregnancies in female patients receiving Soliris or Ultomiris, and in partners of male patients receiving Soliris or Ultomiris, must be reported to GDS following the site's initial awareness. Although pregnancies are not considered SAEs, the physician is required to initially report all pregnancies by completing the "Pregnancy Reporting and Outcome Form and Breastfeeding form" and SAE email/fax coversheet. Investigational sites should collect all information upon initial pregnancy awareness, each trimester, upon outcome of the pregnancy and at 3 months post-partum making sure to include any post-natal sequelae in the infant. This information should be sent to:

Email: ClinicalSAE@alexion.com

Fax: + 1-203-439-9347

Exposure of an infant to Soliris or Ultomiris during breastfeeding will also be reported on the "Pregnancy Reporting and Outcome Form and Breastfeeding Form", and any AEs an infant may experience following breastfeeding will be reported to Alexion GDS.

Alexion will supply the physician with a copy of a "Pregnancy Reporting and Outcome Form and Breastfeeding Form". The patient will be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) and the neonate will be followed for 3 months after birth, even if the patient discontinued Soliris or Ultomiris, or discontinues from the study. When the outcome of the pregnancy becomes known and 3-month neonate follow-up becomes known, the form will be completed and returned to Alexion GDS.

Complications of pregnancy and abnormal outcomes of pregnancy are considered AEs and may meet the criteria of an SAE. Complications of pregnancy and abnormal outcomes of pregnancy (such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death or congenital anomaly) would meet criteria of an SAE and therefore, must be reported as an SAE to Alexion GDS. Elective abortions without complications should not be handled as AEs.

11. DATA ANALYSIS

Alexion will maintain the PNH Registry for a period of 5 years from enrollment of the first patient treated with Ultomiris. Periodic analyses of the data to look for trends and signals will be performed and reported as well as analyses at the end of the study. Following termination of the PNH Registry, a final report will be written.

Primary analyses will assess safety endpoints, including occurrence and time to first event for patients treated with Soliris or Ultomiris for the following events: neisserial infections, malignancy (solid as well as hematologic malignancies), thrombotic events, hemolysis, pregnancies (including follow-up with Alexion GDS for at least 3 months on infants with Soliris or Ultomiris EIU), infusion reactions, bone marrow transplant, and mortality.

In addition, all SAEs, regardless of causality, will be collected for patients treated with Soliris or Ultomiris to characterize the long-term safety profile.

The primary analysis will also evaluate and describe Soliris or Ultomiris discontinuation, reasons for Soliris or Ultomiris discontinuation, and Soliris or Ultomiris dose adjustments. The progression of PNH and clinical outcomes will also be assessed in all patients.

Secondary analyses will include descriptions of the patient population (sociodemographic and clinical characteristics, comorbid conditions), PNH-specific treatments, and pre-specified concomitant medications. Secondary analyses will also include an assessment of health-related quality of life. Analyses will be detailed in a Statistical Analysis Plan.

Sub-populations of interest may include patients who are newly versus previously diagnosed, those with different PNH disease characteristics, and pediatric patients. Analyses may be stratified based on these criteria and will be detailed in a Statistical Analysis Plan.

Patients may change from non-Soliris or non-Ultomiris treatment to Soliris or Ultomiris treatment and/or may discontinue Soliris or Ultomiris treatment but remain in the PNH Registry. In general, the time that patients are on Soliris or Ultomiris will be included in person-years denominator when estimating rates of safety outcomes for Soliris and Ultomiris, while the time they are not on Soliris or Ultomiris will contribute to person-years of non-Soliris or non-Ultomiris treatment.

12. REGULATORY, ETHICAL, AND REGISTRY OVERSIGHT CONSIDERATIONS

12.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable laws and regulations

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

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The physician will be responsible for the following:

- 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
- Providing oversight of the conduct of the study at the site

12.2. Informed Consent Process

The physician or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the patient's legally authorized representative.

12.2.1. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.2.2. Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The physician is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The physician must maintain accurate documentation (source data) that supports the information entered in the CRF.

The physician must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing remote data review and confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, and all applicable local regulations.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the physician for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13. DATA COLLECTION AND DATA MANAGEMENT

13.1. Physician-Reported Data

The PNH Registry database will be programmed and maintained by Alexion or its designee specializing in the development of web-based electronic data collection systems. PNH Registry sites will enter data into an EDC system; data will be stored at a secure and confidential location. Registry data will be reviewed and analyzed on a regular basis. Paper case report forms will be made available when required and entered into the database on behalf of the site by Alexion or its designee.

During each assessment period, physicians will note changes in patient's clinical status since the last assessment period. All necessary information will be gathered from the patient's medical records. If no change in clinical status has occurred, or if the physician has not seen the patient since the last data entry, this will be appropriately noted (by the treating HCP or designee).

Registry site personnel (eg, physicians and/or Study Coordinators) will be able to access the PNH Registry EDC system at any time for the following purposes:

- Entering and editing data
- Reporting SAEs via the Rave Safety Gateway
- Responding to queries

Should a site's Internet access become either temporarily or permanently disconnected, the country specific number provided should be contacted so that alternative data management processes can be arranged.

13.2. Communications

Registry sites will receive regular updates on key findings related to the PNH Registry by Sponsor or Alexion GDS for SAE follow-up requests. These may include quarterly newsletters, site-specific reports or site versus aggregate data reports.

13.3. Access to the PNH Registry

All patients will be assigned a number upon enrollment in the PNH Registry. Patient details will be de-identified. Registry sites will then enter data as periodic updates as required. The Sponsor's designee will remind the physician to update information in the PNH Registry. Physicians will have access to the secure EDC system of the PNH Registry for entering patient data as well as accessing patient data already entered. Paper copies of the CRF will also be available to the physician, if required.

13.4. REGISTRY TRAINING AND SUPPORT

13.4.1. Site Training

Each site will participate in a training session conducted via web-conference or on-line/CD-ROM training modules. Sites may contact the Sponsor or designee, with any questions by telephone or email.

13.4.2. Ongoing Site Support

Sites will have access to continuous technical support throughout the PNH Registry, including PNH Registry protocol questions, assistance with EDC website operations, and the PNH Registry program. Sites will be provided a contact list containing a country specific phone number, country specific fax number, and email address

Sponsor staff or its designee may contact Registry sites to clarify entered data or to request additional data. All involved parties are expected to provide the clarifying information in a timely manner, so that the PNH Registry data are kept up-to-date and accurate.

14. DATA ACCESS AND PUBLICATION RULES

The Registry will be overseen by an Executive Committee, comprised of international experts involved in the research or care of patients with PNH. The Executive Committee's activities will include, but not be limited to, facilitating analysis and dissemination of Registry data via medical conferences of relevant international and national professional societies and through peer-reviewed publications. Publication of Registry data will be subject to initial review and approval from the Executive Committee. The Executive Committee, in conjunction with Alexion, will define a plan for regular publications based on analysis of global Registry data, including the contents of such publications. For each publication, the Executive Committee and Alexion will collaborate in guiding data analyses, interpretation of data analyses, and publication writing. The Executive Committee will be responsible for reviewing publication proposals, analysis requests, and identifying journals, venues, and audiences of interest.

Any participating Registry physician may publish data analysis based on his/her own patient and any physician, may submit for review an analysis request to support a publication. The Executive Committee will evaluate the scientific merit of the analysis request and the alignment with the Registry publication strategy. Prioritization of publication will be based on academic/scientific importance of the questions and the source of the request (eg, participating Registry physician, non-participating physician).

Participating physicians and patients will retain control of the patient data that they submit to the Registry and may use those data accordingly. Aggregate analyses will be the property of Alexion, and will be disseminated according to this governance structure. Alexion retains the right to use Registry data for any regulatory or reimbursement requirements without obtaining prior approval from the Committee.

Access to the PNH Registry Database is based on the permissions and responsibilities outlined in the Executive Committee Charter.

15. REFERENCES

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