REGIONE DEL VENETO
ULSS7 PEDEMONTANA
Via dei Lotti, n. 40
36061 Bassano del Grappa (VI)
Codice fiscale e partita IVA 00913430245

N. 492 DEL 24/03/2023

DELIBERAZIONE
del

DIRETTORE GENERALE

Nominato con D.P.G.R. n. 26 del 26/02/2021

Coadiuvato dai sigg.:

DIRETTORE AMMINISTRATIVO dott.ssa MICHELA CONTE

DIRETTORE SANITARIO dr. ANTONIO DI CAPRIO

DIRETTORE DEI SERVIZI SOCIO – SANITARI dott. EDDI FREZZA

OGGETTO: AUTORIZZAZIONE ALLA CONDUZIONE DELLO STUDIO CLINICO FOR-PROFIT: REACTION UTILIZZO DI RAVULIZUMAB SECONDO PRATICA CLINICA IN PAZIENTI ITALIANI AFFETTI DA EMOGLOBINURIA PAROSSISTICA NOTTURNA: UNO STUDIO DI COORTE MULTICENTRICO, OSSERVAZIONALE, RETROSPETTIVO E PROSPETTICO E APPROVAZIONE CONTRATTO

IL DIRETTORE GENERALE
DELL'AZIENDA ULSS 7 PEDEMONTANA
dott. Carlo Bramezza

Proponente: UOC AFFARI GENERALI
Anno Proposta: 2023 Numero Proposta: 517/23

Il Dirigente, Direttore dell'UOC Affari Generali, nonché Responsabile del procedimento, attesta che la presente proposta di deliberazione è stata regolarmente istruita nel rispetto della vigente normativa nazionale, regionale e regolamentare: f.to Cristiano Galizian

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Il Direttore dell'U.O.C. Affari Generali relaziona quanto segue.

Premesso che:

- con deliberazione n. 316 del 31.03.2017 si è provveduto ad istituire, ai sensi della deliberazione della Giunta Regionale del Veneto n. 2174 del 23.12.2016, recante "*Disposizioni in materia sanitaria connesse alla riforma del sistema sanitario regionale approvata con L.R. 25 ottobre 2016 n. 19*", il Nucleo per la Ricerca Clinica (N.R.C.) dell'Azienda ULSS7 Pedemontana;
- la citata DGRV n.. 2174/2016, Allegato L, richiama l'applicazione della disciplina regionale in materia di sperimentazione clinica (DGR n. 1066/2013 e DGR n. 925/2016), che prevede l'istituzione di un N.R.C. per ciascuna Azienda ULSS della Regione;
- la DGR n. 1066/2013 (Allegato B) prevede che il N.R.C. sia istituito preferibilmente " *presso il Servizio di Farmacia Ospedaliera ovvero Servizio Farmaceutico territoriale ovvero Servizio di Farmacologia delle istituzioni sanitarie, fermo restando i criteri di indipendenza e di assenza di conflitti di interesse"* e sia composto *" da professionalità multidisciplinari appartenenti all'ambito sanitario, epidemiologico-statistico, etico-giuridico e organizzativo-gestionale*";
- con deliberazione n. 1477 del 05/08/2022 è stato approvato, in aggiornamento della disciplina aziendale regolata con la deliberazione n. 453 del 28/05/2014, il Regolamento aziendale sulla gestione delle sperimentazioni cliniche profit e no-profit, comprensivo anche della regolamentazione dei fondi per la gestione della ricerca con determinazione delle quote dei fondi stessi e fissazione dei criteri per l'attribuzione dei compensi;
- con deliberazione n. 1684 del 09/09/2022 sono stati aggiornati i componenti del Nucleo per la Ricerca Clinica Aziendale (N.R.C.) ai sensi della DGRV n. 2174 del 23/12/2016.

Considerato che :

- in data 03/02/2022, ns. prot. 10760 del 08/02/2022, la società Medineos S.U.R.L. (CRO) che agisce in nome proprio e per conto del Promotore Alexion Pharma Italy S.r.l., ha chiesto la pertinente autorizzazione all'effettuazione dello studio promosso da Alexion Pharma S.r.l. e così identificato

SCHEDA STUDIO CLINICO

Titolo	REACTION "*Utilizzo di Ravulizumab secondo pratica clinica in pazienti italiani affetti da emoglobinuria parossistica notturna: uno studio di coorte multicentrico, osservazionale, retrospettivo e prospettico" e approvazione contratto*
Codice protocollo	HEMRAV601IT_REACTION
Strutture interessate	U.O.C Oncoematologia P.O. Bassano
Sperimentatore Principale	dr. Eros Di Bona - Direttore U.O.C. Oncoematologia del P.O. Bassano
Co sperimentatori	dr.ssa Anna Artuso – dirigente medico U.O.C. Oncoematologia del P.O. Bassano

Promotore	Alexion Pharma Italy S.r.l. – Via Melchiorre Gioia, 8 – 20124 Milano
CRO	Medineos S.U.R.L. – Viale Virgilio, 54/U - 41123 Modena

- è stato individuato, quale Responsabile dello studio presso questa Azienda, il dr. Eros Di Bona – Direttore dell'U.O.C. Oncoematologia del P.O. Bassano;
- in data 07/02/2022 il dr. Eros di Bona ha chiesto la valutazione e l'autorizzazione allo svolgimento dello studio sopra citato.

Tenuto conto che:

- il N.R.C. Aziendale, nella sua composizione prevista dalla deliberazione n. 1684 del 09/09/2022, in data 31/01/2023 ha attestato – considerata la regolarità della documentazione presentata dallo sperimentatore – la fattibilità locale della ricerca sopra citata;
- il Comitato Etico per le sperimentazioni Cliniche della Provincia di Vicenza (CESC) in occasione della seduta del 14/02/2023, ns. prot. 19867 del 06/03/2023, ha espresso parere favorevole all'unanimità allo svolgimento dello studio;
- trattasi di uno studio for-profit, osservazionale, non interventistico, di coorte multicentrico italiano, retrospettivo e prospettico, con l'obiettivo di raccogliere dati sull'efficacia secondo pratica clinica in una coorte di pazienti italiani affetti da emoglobinuria parossistica notturna (EPN) già trattati con eculizumab per almeno 26 settimane e che iniziano il trattamento con ravulizumab secondo la normale pratica clinica, per un periodo di follow-up di 52 settimane;
- saranno arruolati nello studio tutti i pazienti che forniscono il consenso informato scritto e che soddisfano i criteri di eleggibilità dello studio. Una popolazione di circa 120 pazienti sarà arruolata presso circa 30 centri italiani dello studio e sarà osservata in modo prospettico per 52 settimane. Il periodo di arruolamento avrà una durata di 9 mesi, nel nostro Centro saranno arruolati circa 4 pazienti;
- il Contratto, per la gestione degli aspetti economici inerenti la sperimentazione clinica, è redatto secondo la normativa vigente in materia;
- l'introito totale per paziente eleggibile, valutabile e completato secondo il Protocollo e per il quale sia stata compilata validamente la relativa CRF/eCRF, corrisponde ad € 1.000,00 (mille/00)+IVA per paziente (complessivi € 4.000,00+IVA - se dovuta - (quattromila/00) per n. 4 pazienti) per ulteriori dettagli si rinvia al contratto allegato alla presente proposta;
- trattandosi di studio osservazionale senza procedure diagnostiche e/o terapeutiche divergenti dalla normale pratica clinica non è necessario stipulare specifica polizza assicurativa per la responsabilità civile verso i pazienti;
- l'attività inerente lo studio in argomento sarà svolta, ai sensi dell'art.15 del Regolamento per lo svolgimento delle sperimentazioni (deliberazione del Direttore Generale n. 1477/2022), dal dr. Eros Di Bona (P.I.) e dal Co sperimentatore dr.ssa Artuso Anna in orario aggiuntivo oltre a quello istituzionalmente dovuto. La stessa verrà remunerata con i proventi derivanti dalla sperimentazione secondo le indicazioni contenute nella deliberazione sopra citata che regolamenta anche la gestione dei fondi per l'attribuzione dei compensi.

Per quanto sopra, il Direttore dell'U.O.C. Affari Generali, propone di autorizzare lo studio clinico for-profit REACTION "*Utilizzo di Ravulizumab secondo pratica clinica in pazienti italiani affetti da emoglobinuria parossistica notturna: uno studio di coorte multicentrico, osservazionale, retrospettivo e prospettico"* il cui sperimentatore Responsabile è il dr. Eros Di Bona, Direttore della U.O.C. Oncoematologia del P.O. Bassano e di approvare il contratto con la Società Medineos S.U.R.L., CRO dello studio in questione

IL DIRETTORE GENERALE

Vista la relazione e la proposta del Responsabile del procedimento;

Dato atto che il responsabile del Servizio competente ha attestato l'avvenuta regolare istruttoria della pratica, in ordine alla compatibilità con la vigente legislazione statale, regionale e regolamentare;

Visti:

- il decreto ministeriale 15/07/1997;
- la circolare del Ministero della Salute 02/09/2002 n. 6;
- il D.lgs 24/06/2003, n. 211;
- il decreto ministeriale 17/12/2004;
- la DGRV 28/12/2006, n. 4430;
- il decreto ministeriale 12/05/2006;
- il D.lgs 6/11/2007, n. 200;
- il decreto ministeriale 21/12/2007;
- la determinazione AIFA 20/03/2008;
- la DRGV 07/10/2008, n. 2855;
- la Legge 08/11/2012, n. 189 – Decreto Balduzzi;
- il decreto del Ministero della Salute 08/02/2013;
- la DRGV 28/06/2013 n. 1066;
- il D.M. 30/11/2021

Acquisito il parere favorevole del Direttore Amministrativo, Sanitario e dei Servizi Socio-Sanitari, per quanto di rispettiva competenza

DELIBERA

1. di prendere atto che il Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza (CESC) in occasione della seduta del 14/02/2023 ha espresso parere favorevole in ordine alla conduzione dello studio clinico for- profit REACTION "*Utilizzo di Ravulizumab secondo pratica clinica in pazienti italiani affetti da emoglobinuria parossistica notturna: uno studio di coorte multicentrico, osservazionale, retrospettivo e prospettico"* la cui documentazione è conservata agli atti della Segreteria del NRC;
2. di autorizzare, per quanto in premessa illustrato, lo svolgimento del predetto studio for-profit presso questa Azienda, sotto la diretta Responsabilità del dr. Eros Di Bona, dirigente medico a rapporto esclusivo, Direttore dell'U.O.C. Oncoematologia del P.O. Bassano, in collaborazione con la dr.ssa Anna Artuso – dirigente medico a rapporto esclusivo presso la medesima sruttura;
3. di dare atto che l'attività inerente lo studio in argomento sarà svolta, ai sensi dell'art.15 del Regolamento per lo svolgimento delle sperimentazioni (deliberazione del Direttore Generale n. 1477/2022), dal dr. Eros Di Bona (P.I.) e dal Co sperimentatore dr.ssa Artuso Anna in orario aggiuntivo oltre a quello istituzionalmente dovuto, e remunerata con i proventi derivanti dalla sperimentazione secondo la disciplina della gestione dei fondi per l'attribuzione dei compensi agli sperimentatori (art. 12 Regolamento su citato);
4. di dare atto che lo studio clinico dovrà essere eseguito secondo quanto previsto dal protocollo di studio, dalla normativa vigente in ambito di sperimentazioni e dalle norme di buona pratica clinica GCP, che allegato alla presente deliberazione ne costituisce parte integrante e sostanziale;
5. di approvare il testo del contratto allegato al presente provvedimento quale parte integrante e

sostanziale dello stesso, all'uopo predisposto per disciplinare gli aspetti normativi ed economici dei rapporti tra l'Azienda ULSS7 Pedemontana e la società Medineos S.U.R.L.;

6. di dare atto che il contratto di cui al precedente punto 4 decorrerà dalla data di sottoscrizione e fino al momento di conclusione dello studio presso questa Azienda, salvo proroga o anticipato scioglimento per mutuo consenso scritto o per recesso di una delle parti, fermo restando quanto previsto dall'art. 6 del contratto;
7. di dare atto che il Promotore si impegna a fornire gratuitamente all'Azienda come indicato nell'articolo 4 del Contratto, per tutta la durata dello studio, ogni materiale necessario all'esecuzione dello Studio;
8. di stabilire che l'introito totale per paziente arruolato, completato e valutabile è pari ad € 1.000,00 +IVA (se dovuta) ovvero 4.000,00 € per un totale di circa 4 pazienti;
9. di dare atto che ai sensi dell'art.8 del Regolamento aziendale sulla gestione delle sperimentazioni cliniche (deliberazione n. 1477 2022):
   a) il Responsabile della sperimentazione durante il corso dello studio è tenuto a comunicare al CESC, per il tramite del NRC, le informazioni necessarie a consentire il, periodico aggiornamento sull'andamento della ricerca, ogni evento o reazione avversa, l'interruzione anticipata di uno studio, con l'indicazione dettagliata dei motivi e degli eventuali risultati parziali ottenuti;
   b) lo sperimentatore si impegna a fornire annualmente al CESC un rapporto scritto sullo stato avanzamento dello studio –monitoraggio periodico – e una relazione analitica alla conclusione dello studio e pubblicazione se prevista;
10. di dare atto che dall'esecuzione del predetto studio non deriverà nessun onere aggiuntivo di spesa in capo all'Azienda ULSS7 Pedemontana;
11. di dare atto che nessun costo riferito allo studio in argomento sarà a carico del Servizio Sanitario Nazionale (SSN) né dei soggetti arruolati nello studio;
12. di dare atto che il presente provvedimento è soggetto a pubblicazione ai sensi dell'art. 23, lettera d) del D.L.vo 14 marzo 2013 n. 33;
13. di dare atto che la presente deliberazione viene pubblicata all'albo del sito istituzionale dell'Azienda per 10 gg. continuativi, inviata contestualmente al Collegio Sindacale e diventa esecutiva il giorno stesso della sua pubblicazione come da norma regolamentare approvata con deliberazione n. 1386 del 22/07/2022.

OBSERVATIONAL STUDY PROTOCOL

REACTION:

Real Life Use of **R**avulizumab in Italian Pati**E**nts with P**A**roxysmal No**C**turnal Hemoglobinuria a Mul**T**icenter Observat**ION**al Retrospective and Prospective Cohort Study.

Version 1.7, 09/11/2021

Short Title: Real Life Use of Ravulizumab in Italian Patients with Paroxysmal Nocturnal Hemoglobinuria

Sponsor Name:

Alexion Pharma Italy, srl via Melchiorre Gioia 8 20124 Milano

Protocol Number: HEMRAV601IT

Signature page

This study protocol has been carefully reviewed and agreed upon by:

Study coordinator

_____

Date, signature

Medical Supervisor

_____

Date, signature

For Contract Research Organization

Associate Director, Clinical Operations — Alessandra Ori

_____

Date, signature

Head of Real World Unit of CDM, Biostatistics & Epidemiology — Lucia Simoni

_____

Date, signature

Scientific Director — Giovanni Fiori

_____

Date, signature

INVESTIGATOR'S AGREEMENT

I have read and understood all clinical and administrative sections of the protocol. I agree to participate and conduct the observational study as outlined in the protocol 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 Investigator

_____

Signature of Investigator

_____

Date

_____ _____

signature date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Not Applicable

MILESTONES

Milestone	Planned date
Start of data collection	01/2022
End of data collection	09/2023
Interim report 1	10/2022
Interim report 2	06/2023
Final report of study results	01/2024

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1. PROTOCOL SUMMARY

1.1. Title

REACTION:

Real Life Use of **R**avulizumab in Italian Pati**E**nts with P**A**roxysmal No**C**turnal Hemoglobinuria a MulTicenter Observat**ION**al Retrospective and Prospective Cohort Study.

1.2. Synopsis

Rationale

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, clonal, hematopoietic stem cell disorder that manifests with a hemolytic anemia from uncontrolled complement activation, bone marrow failure, and a propensity for thrombosis [1].

Ravulizumab is a new recombinant humanized monoclonal antibody targeting the complement protein C5. It produces immediate, complete and sustained inhibition of C5 with an extended, 8-week dosing interval. The non-inferiority of ravulizumab compared with eculizumab was shown in both adult patients with PNH naïve to complement inhibitors and in adult patients with PNH who had previously been treated with a C5 inhibitor [2]. The safety profiles of eculizumab and ravulizumab turned out to be similar, with overlapping frequency of headache (up to one-third in the first period) and a small but clinically significant risk of meningococcal infection [2]. Based on these results, ravulizumab was approved by the US FDA on 21 December 2018, by PMDA on 18 June 2019 and by EMA on 2 July 2019. Although effective and well known, its predecessor eculizumab requires a frequent dosing schedule that can be burdensome for some patients and increases the risk of breakthrough intravascular hemolysis. Ravulizumab better manages this aspect producing immediate, complete, and sustained inhibition of C5 with an extended, 8-week dosing interval. This led to a renewed administration scheme, characterized by a dosing frequency of every 8 weeks, less burdensome for patients with PNH, and a weight-based dosing regimen. It has a longer half-life, and it is characterized by the same benefits as eculizumab but with a more convenient and effective dosing schedule. It allows the patients to receive 6 or 7 infusions per year (following loading dose), as opposed to the 26 required by eculizumab: switching from a 2 weeks to a 8 weeks dosing schedule results in substantial savings to the patient's productivity [6]. Indeed the lower frequency of dosing for ravulizumab (e.g. due to the time spent by patients in the hospital as well as going to and from the hospital) translates into a reduction of lost productivity for patients in clinic by 64% [7]. Relative to clinical settings, home treatment reduces lost productivity by 38% and by 79% in the USA for eculizumab and ravulizumab, respectively [7].

The REACTION study, an Italian multi-center observational (non-interventional) retrospective and prospective cohort study aims to collect data of effectiveness in a cohort of Italian patients (excluded by the PNH registry - ClinicalTrials.gov Identifier: NCT01374360) affected by PNH, already treated with Eculizumab for at least 26 weeks and started the treatment with ravulizumab as per clinical practice, over 52-week follow-up period. Quality of Life, preference to treatment, safety profile, resource consumption and costs will be investigated in real-world setting within standard clinical practice in Italy.

Indeed, ravulizumab showed to guarantee non-inferior efficacy and safety profiles, providing a much better management of the disease due to the more convenient and effective dosing schedule, allowing the patients to receive 6 or 7 infusions per year (following loading dose), as opposed to the 26 required by eculizumab. This is supposed to lead to higher QoL and cost savings.

Objectives and endpoints

Objective	Endpoints
Primary	
To describe the 52-week control of hemolysis with ravulizumab in a routine clinical practice.	1. The percentage change in lactate dehydrogenase (LDH) from baseline to end of observation.
Secondary	
To describe the 52-week effectiveness of ravulizumab with respect to eculizumab, both administered as per routine clinical practice.	1. The percentage change in lactate dehydrogenase (LDH) from baseline to end of observation on patients treated with ravulizumab with respect to the observed treatment period with eculizumab.
	2. The proportion of patients who needed transfusions and descriptive statistics on the total number of packed red blood cell units transfused during the treatment period with ravulizumab with respect to the observed treatment period with eculizumab.
	3. The proportion of patients undergoing ravulizumab without a ≥ 2-g/dL decrease in hemoglobin level in the absence of transfusion, with respect to the observed treatment period with eculizumab.
	4. Descriptive statistics of breakthrough hemolysis (defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE] including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal (ULN) after prior LDH reduction to <1.5xULN while on therapy) during the treatment period with ravulizumab with respect to the observed treatment period with eculizumab.

Objective	Endpoints
To describe Quality of Life during ravulizumab treatment in the routine clinical practice.	1. The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, Version 4.0: mean change from baseline (where available) to each timepoint of assessment (where available). 2. The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, Version 3.0: mean change from baseline (where available) to each timepoint of assessment (where available).
To describe patients' preference to ravulizumab treatment in the routine clinical practice.	PNH-specific Patient Preference Questionnaire (PNH-PPQ) at the end of observation (where available).
To describe the safety profile of ravulizumab in the routine clinical practice.	• adverse events serious adverse events
To describe the resource consumption and estimate costs of ravulizumab treatment with respect to eculizumab, both administered as per routine clinical practice.	• Costs sustained by NHS: - specialist visits - pharmacological and non-pharmacological treatments - emergency department admissions - hospitalizations - exams • Costs sustained by the patients related to the infusion visits: - transportations - overall time required

Baseline = start of ravulizumab

Study Design

The REACTION study is an Italian multi-centre, observational (non-interventional), cohort study composed of both retrospective and prospective observation periods on the same PNH patients. The observational study is designed to collect effectiveness data on patients who were already treated with eculizumab for at least 26 weeks and who started ravulizumab treatment as specific therapeutic strategy as per ordinary clinical practice (the decision to start ravulizumab must have been taken by the clinician before the enrolment, independently from the study). All patients who provide the written informed consent and privacy form and meet the study entry criteria will be consecutively enrolled into the study by each participant centre. A target sample of about 120 patients will be enrolled for 9 months after the First Patient In from about 30 Italian study centres, and they will be observed for 52 weeks after the start of ravulizumab (baseline, i.e. time 0). The enrolment will take place after the signature of informed consent and privacy form.

The study combines:

- a prospective observation window (enrolment ; + 52 weeks) relative to the prospective period of treatment with ravulizumab (see Figure 1.b);
- a retrospective observation window relative to the retrospective period of treatment with ravulizumab (if enrolment takes place after the baseline) and the retrospective period of treatment with eculizumab (0; - 52 weeks), which should have started at least 26 weeks before baseline date (see Figure 1.b).

The study will involve both primary and secondary data collection:

- primary data collection will be performed during the prospective observation period, or until patient's early withdrawal (if applicable).
- secondary data collection will be performed during the retrospective observation period, from enrolment backward to eculizumab initiation date (52 weeks as maximum). The data will be retrieved from medical charts in hospitals.

Study Population

Inclusion Criteria

The patients are eligible to be included in the study only if all of the following criteria apply:

1. Male or female, aged ≥ 18;
2. Documented diagnoses of PNH confirmed by high-sensitivity flow cytometry evaluation of red blood cells and white blood cells with granulocyte or monocyte clone size of ≥ 5%;
3. Treated with Eculizumab for at least 26 weeks (including patients treated with a higher dose of eculizumab, both in terms of dose administration and frequency of administration, than the one indicated in the SmPC);
4. Patient already assigned to ravulizumab treatment as specific therapeutic strategy within current routine clinical practice (this decision has to be made independently and before the enrolment of the patient in the study);
5. Vaccinated against Neisseria meningitidis (according to SmPC) < 3 years before dosing or at the time of study drug initiation to reduce the risk of meningococcal infections;
6. Signed written informed and privacy consent prior to study participation.

Exclusion Criteria

1. History of hematopoietic stem cell transplantation (evaluated at baseline);
2. Known pregnant or breastfeeding patient (evaluated at baseline);
3. Patient unable to read and write in Italian language and to autonomously fill in questionnaires and scales (evaluated at enrolment);
4. Patients enrolled in any clinical trial receiving experimental treatments for PNH (evaluated at baseline).

Exit Criteria

A patient will be withdrawn from data collection within the study for any of the following reasons:

1. Loss to follow-up;
2. Informed and privacy Consent withdrawal;
3. Death;
4. Interruption of ravulizumab treatment, defined as skipping treatment for two consecutive infusions;
5. Hematopoietic stem cell transplantation;
6. Enrolment in any clinical trial on experimental treatments for PNH;
7. Pregnancy or breastfeeding during the observation period.

Variables

- Demographics
- Physical examination
- PNH Anamnesis
- Medical history and comorbidities
- PNH related medication history
- PNH non related medication history
- PNH related concomitant medications
- PNH non related concomitant medications
- SARS-Cov2 positivity, vaccination, antibody response, where available
- Eculizumab – Ravulizumab treatments
- LDH values
- Number of transfusions (number of packed red blood cell units transfused) and number of transfusion sessions (number of days), hemoglobin assessment before transfusion
- Hemoglobin levels
- Breakthrough hemolysis (BTH) assessment
- PNH symptomatology
- Laboratory parameters (Reticulocytes, Indirect Bilirubin, Creatinine, Haptoglobin)
- Patient-Reported Outcomes:FACIT-Fatigue scale, Version 4.0, European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), PNH-specific Patient Preference Questionnaire (PNH-PPQ)
- Resource consumption: costs related to PNH sustained by NHS (specialist visits, pharmacological and non-pharmacological treatments, hospital and emergency rooms (ER) admissions, exams (by exam type)), costs sustained by the patients related to infusion visits (average cost to reach the structure and overall time required for the infusion, retirement status of the patient, lost of working day, need of caregiver)
- Adverse Events (AEs), Serious Adverse Events (SAEs)
- Major Adverse Vascular Events (MAVE)
- Off label use of Eculizumab
- Pregnancies/breastfeeding

Detailed description of collected variables can be found at the section 6.1.

Sample Size Determination

Sample size was not based on statistical considerations. Rather it was defined according to feasibility considerations, namely the extremely rare characterization of the PNH, with 1–1.5 cases per million

individuals worldwide [4], and the number of potentially eligible patients in selected sites (clinical judgement). A target sample of about 120 patients already treated with Eculizumab for at least 26 weeks and who started ravulizumab treatment as per ordinary clinical practice, will be enrolled from 30 Italian study centres. It is also reasonable to expect 20% drop-out, therefore we expect that 96 patients could be available for the evaluation.

Statistical Analyses

Analysis of Primary Endpoint

The primary endpoint is the percentage change in lactate dehydrogenase (LDH) from baseline to the end of observation during ravulizumab treatment in standard clinical practice in Italy. In order to compute the LDH percentage change, the LDH levels measured at baseline and end of observation will be employed as follows:

$$\Delta\%(\mathrm{LDH})_{\mathrm{ravulizumab}} = \frac{\mathrm{LDH}_{52\ \mathrm{weeks}} - \mathrm{LDH}_{\mathrm{baseline}}}{\mathrm{LDH}_{\mathrm{baseline}}} * 100$$

The descriptive statistics (e.g. mean, standard deviation, median, IQR [first quartile subtracted from the third quartile]) will be reported and represented with a box-plot. The analysis will be performed on the Full Analysis Set, including the patients having the LDH evaluation at both the baseline and at the end of observation (52 week) .

Detailed description of Secondary Endpoints Analyses can be found at the section 7.3.2

Milestones

Milestone	Planned date
Start of data collection	01/2022
End of data collection	09/2023
Interim report 1	10/2022
Interim report 2	06/2023
Final report of study results	01/2024

Amendments and Updates

None

Schedule of Activities (SoA)

Activities	**Baseline (start of ravulizumab)**	**10 weeks (+/- 2 weeks) after baseline**	**18 weeks (+/- 2 weeks) after baseline**	**34 weeks (+/- 2 weeks) after baseline**	**52 weeks (+/-4 weeks) after baseline**	**Enrolment** (Informed and privacy consent signature date)	**End of observation**
Screening/Patient information							
Informed consent						X	
Inclusion and exclusion criteria						X	
Patient disposition		X	X	X	X		
Exit criteria							X
Patient Demographic and Clinical Characteristics							
Demographics (a)						X	
Physical examination (b)	X						
Medical history and comorbidities (c)	***X						
PNH anamnesis (d)	X						
PNH related medication history (e)	***X						
PNH non related medication history (e)	***X						
PNH related concomitant medications (e)	*Recorded as continuum (updates will be recorded, if any)						
PNH non related concomitant medications (e)	*Recorded as continuum (updates will be recorded, if any)						
SARS-Cov2 positivity, vaccination, antobody response, where available	X		X	X	X	X	X
Eculizumab - Ravulizumab treatments							
Ravulizumab Dates of injection, dose, frequency of administration and changes. Temporary and permanent discontinuation dates and reasons	*Recorded as continuum (updates will be recorded, if any)						
Eculizumab Start date, dose, frequency of administration and changes. Temporary and permanent discontinuation dates and reasons	***X						
Control of hemolysis							
LDH values	*&Recorded as continuum (updates will be recorded, if any)						
Effectiveness/clinical response							
Number of transfusions (number of packed red blood cell units transfused) and number of transfusion sessions (number of days), hemoglobin assessment before transfusion	*Recorded as continuum (updates will be recorded, if any)						
Hemoglobin levels	*&Recorded as continuum (updates will be recorded, if any)						
Breakthrough hemolysis (BTH) assessment - medical condition (trigger) correlated to BTH, degree of correlation, associated LDH assessment	*Recorded as continuum (updates will be recorded, if any)						
PNH symptomatology (f)	*Recorded as continuum (updates will be recorded, if any)						
Laboratory parameters (other than LDH and Hemoglobin levels)							
Reticulocytes, Indirect Bilirubin, Creatinine, Haptoglobin: unit and measurement	§ X		X	X	X	X§	
Patient-reported Outcomes							
FACIT-Fatigue scale v. 4.0	X	X	X	X	X		
EORTC QLQ-C30 v. 3.0	X	X	X	X	X		
PNH-PPQ					X		X#
Resource consumption							

Costs related to PNH sustained by NHS (Drug consumption (d), specialist visits, number of transfusions, hospital stays, emergency rooms (ER) accesses, medical exams), Costs sustained by the patients related to infusion visits (average cost to reach the structure, overall time required for the infusion, retirement status of the patient, loss of working days, need of caregiver)	X		X	X	X	X	
Safety data							
AE, SAE	*Recorded as continuum (updates will be recorded, if any)						
MAVE (g)	*Recorded as continuum (updates will be recorded, if any)						
Off label use of eculizumab						X	
Pregnancy/breastfeeding (h)	*Recorded as continuum (updates will be recorded, if any)						
Study completion							X

*Data will be prospectively collected up to 52 weeks after the baseline during ravulizumab treatment. Also the retrospective period, relative to the treatment with ravulizumab and back to 52 weeks (0; -52) from baseline during eculizumab, if available from hospital medical charts or from other documents.

§ The retrospective data referred to -26 weeks (+/- 10 days) and -52 weeks (+/- 10 days) will be collected at enrolment.

& LDH values and Hemoglobin levels will be collected at least at the following timepoints, if available: -52 weeks, -26 weeks, baseline, 18 weeks, 34 weeks, 52 weeks.

In case the patient leaves the study prior to 52 weeks.

*** Retrospectively collected at enrolment, from baseline up to 52 weeks backward during eculizumab treatment period, if available from hospital medical charts or from other documents.

(a) Demographics: age, gender, ethnicity
(b) Physical examination: height, weight, BMI
(c) Medical history and comorbidities: histories of acute, chronic, or infectious disease and any reported conditions affecting major body systems. Concomitant conditions/disorders will be collected as well.
(d) PNH anamnesis: date of diagnosis, history of hemoglobinuria, history of any MAVEs, bone marrow disorder, shortness of breath, fatigue, pulmonary hypertension.
(e) Medication history/ concomitant medications (e.g. prescription or over-the-counter, vitamins, meningococcal vaccination,). Pharmacological treatments (e.g., drug type, drug compound, date of treatment initiation, dose, date of and reason for discontinuation, if any) and non-pharmacological treatments (e.g., treatment type, number of sessions, date of treatment initiation, date of and reason for discontinuation, if any).
(f) PNH symptomatology: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, erectile dysfunction, Thrombosis, Anemia (hemoglobin levels).
(g) MAVE: pulmonary embolus, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis, acute peripheral vascular occlusion, mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, epatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, renal arterial thrombosis, gangrene (nontraumatic; nondiabetic), amputation (nontraumatic; nondiabetic), dermal thrombosis.Thrombophlebitis/deep vein thrombosis
(h) Pregnancy/breastfeeding: these events are exit criteria and are managed as described in section 8.2

Patient Reported Outcomes FACIT-Fatigue scale v. 4.0 and EORTC QLQ-C30 v. 3.0 will be collected, if available, at baseline, 10 weeks (+/- 2 weeks), 18 weeks (+/- 2 weeks), 34 weeks (+/- 2 weeks), and at 52-week follow-up visit or until patient's early withdrawal (if applicable). PNH-PPQ will be collected, if available, at 52-week follow-up visit or until patient's early withdrawal (if applicable).

2. INTRODUCTION

2.1. Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, clonal, hematopoietic stem cell disorder that manifests with a hemolytic anemia from uncontrolled complement activation, bone marrow failure, and a propensity for thrombosis [1]. PNH arises when a somatic mutation in the phosphatidylinositol glycan class A (*PIGA*) gene develops in a self-renewing, hematopoietic stem cell. The *PIGA* gene is found on the X chromosome and is responsible for producing one of the seven proteins involved in the first step of glycosylphosphatidylinositol (GPI) anchor biosynthesis. While a number of different somatic mutations on *PIGA* have been described in patients with PNH, most mutations are small insertions or deletions arising on exon 2 that result in a severe deficiency or absence of GPI. While the GPI moiety is responsible for anchoring more than 150 different proteins to the cell surface, the deficiency of complement-inhibitor proteins CD55 and CD59 leads to the primary clinical manifestations of PNH. CD55 and CD59 are specifically responsible for protecting red blood cells from complement mediated lysis. In the alternative pathway of complement activation, C3 spontaneously hydrolyzes leading to the creation of C3 convertase (C3 convertase can also be formed through the lectin and classical pathways of complement). C3 convertase then cleaves C3 to C3a and C3b. Once formed, C3b joins with C5b and additional terminal complement proteins to form the membrane attack complex (MAC). Under normal circumstances, this process is regulated by CD55 and CD59. CD55 accelerates the rate of destruction of membrane-bound C3 convertase while CD59 blocks the formation of the MAC. In patients with PNH, the absence of CD55 and CD59 results in increased C3 convertase activity, uncontrolled MAC formation, and continual complement-mediated intravascular hemolysis. In the setting of infection, inflammation, or surgery, all of which increase complement activation, the rate of hemolysis further rises [2]. The clinical features of this disease arise as a result of complement-mediated hemolysis in unprotected red cells, leukocytes, and platelets as well as the release of free hemoglobin that occurs with erythrocyte destruction. Free hemoglobin is toxic, and it has two primary consequences. The first is progressive renal damage resulting from the buildup of hemoglobin deposits in the kidney, which can culminate in renal failure. Second, free hemoglobin causes depletion of nitric oxide, a compound important for maintaining smooth muscle relaxation and normal endothelial function. This depletion triggers multiple effects, including impaired regulation of smooth muscle tone, platelet hyper-reactivity, and local vasoconstriction. Among the clinical effects of nitric oxide depletion are smooth muscle spasms and ischemia resulting in dysphagia, chest pain, and abdominal pain; dyspnea; pulmonary hypertension; increased risk of thromboses; and erectile dysfunction. In addition to the loss of red blood cells, PNH also increases leukocyte and platelet activation and aggregation [3]. PNH incidence is estimated at 1–1.5 cases per million individuals worldwide, but might be higher in certain regions. The median survival of patients with PNH was approximately 10 years in the 1990s, but increased to >20 years in the early 2000s. Since the introduction of eculizumab therapy, patients with PNH can live a relatively normal lifespan, and patients with haemolytic PNH receiving eculizumab have a more-favourable prognosis than patients with a more profound bone

marrow failure component, such as aplastic anaemia. The reason for this difference is that eculizumab does not treat the underlying production deficit in the bone marrow. For the 122 patients who have died since enrolment into the International PNH Registry, the most frequent cause of death (11.7%) was bone marrow failure in patients who met the diagnostic criteria for PNH and aplastic anaemia. Estimations using data from the registry indicate that approximately 75% of patients with PNH are treated with eculizumab [4].

2.2. Study Rationale

Eculizumab, a humanized monoclonal antibody that inhibits terminal complement C5 activation, was the first approved treatment for patients with PNH and has changed the paradigm of PNH management. Intravenous infusion of eculizumab every 2 weeks reduces hemolysis and increases hemoglobin stabilization, improving the rate of transfusion independence, and enhancing patient quality of life (QoL). Despite established efficacy, up to 27% of patients continue to experience breakthrough intravascular hemolysis while receiving approved dosages of eculizumab that may require dosing intervals to be shortened to <14 days or individual dosages to be increased. Breakthrough hemolysis (BTH) in patients with PNH typically occurs around the time of low serum concentrations of eculizumab or in the setting of infection, operative stress, or pregnancy, but residual intravascular hemolysis may occur even when serum levels of eculizumab are adequate. The infusions every two weeks and the risk of BTH represent a burden to patients. Thus, to further enhance the treatment for patients with PNH, providing complete C5 inhibition (by maintaining free C5 levels below a threshold of <0.5 μg/mL) may help to minimize the occurrence of BTH and benefit patients with PNH [5].

Ravulizumab is a new recombinant humanized monoclonal antibody targeting the complement protein C5. It produces immediate, complete and sustained inhibition of C5 with a schedule maintenance infusion every 8 weeks. The non-inferiority of ravulizumab compared with eculizumab was shown in both adult patients with PNH naïve to complement inhibitors and in adult patients with PNH who had previously been treated with a C5 inhibitor [2]. The safety profiles of eculizumab and ravulizumab turned out to be similar, with overlapping frequency of headache (up to one-third in the first period) and a small but clinically significant risk of meningococcal infection [2]. Based on these results, ravulizumab was approved by the USA FDA on 21 December 2018, by PMDA on 18 June 2019 and by EMA on 2 July 2019.

In an open label study (ClinicalTrials.gov Identifier: NCT02946463) adults with PNH took eculizumab or ravulizumab for 26 weeks. Then they either continued taking ravulizumab or switched from eculizumab to ravulizumab. Ravulizumab continued to be effective and well-tolerated through 52 weeks of treatment. In the primary evaluation period of this phase III randomized controlled trial, ravulizumab was well tolerated and demonstrated durable efficacy comparable with that of eculizumab in adult patients with PNH naïve to complement inhibitor therapy. Results from the first 26 weeks of the open-label extension showed that improvements in LDH normalization, transfusion avoidance, BTH, hemoglobin stabilization, and patient-reported QoL seen with ravulizumab treatment during the 26-week primary evaluation period were generally maintained with up to 52 weeks of treatment. In addition, complete suppression of free C5 was accompanied by a decreased incidence of BTH, with no events of BTH associated with incomplete terminal complement inhibition. Results strengthen the evidence that patients on a prior

fixed dose of eculizumab therapy can safely switch to weight-based dosing of ravulizumab without interruption of treatment while ensuring terminal complement inhibition is sustained, which is the primary goal for patient management [5]. Ravulizumab better manages this aspect producing immediate, complete, and sustained inhibition of C5 with an extended, 8-week dosing interval. This led to a renewed administration scheme, characterized by a dosing frequency of every 8 weeks, less burdensome for patients with PNH, and a weight-based dosing regimen. It has a longer half-life, and it is characterized by the same benefits as eculizumab but with a more convenient and effective dosing schedule. It allows the patients to receive 6 or 7 infusions per year (following loading dose), as opposed to the 26 required by eculizumab: switching from a 2 weeks to a 8 weeks dosing schedule results in substantial savings to the patient's productivity [6].

Indeed the lower frequency of dosing for ravulizumab (e.g. due to the time spent by patients in the hospital as well as going to and from the hospital) translates into a reduction of lost productivity for patients in clinic by 64% [7]. Relative to clinical settings, home treatment reduces lost productivity by 38% and by 79% in the USA for eculizumab and ravulizumab, respectively [7].

Always in the USA, a cost-utility analysis showed that in adult patients with PNH ravulizumab is a dominant strategy compared to eculizumab, being associated with cost-savings and higher quality of life [8]. The patient preferences of patients treated with both ravulizumab and eculizumab have been investigated also in the sub-study of the 302 clinical trial ALXN1210-PNH-302. The study reported that overall, 93% of pts (n = 88) preferred ravulizumab vs 7% (n = 7; $P < 0.001$) who had no preference (n = 6) or preferred eculizumab (n = 1). With regard to specific aspects of treatment, ravulizumab was widely preferred on frequency of infusions (98%), ability to plan activities (98%), overall quality of life (88%), convenience of receiving treatment (85%), and effectiveness of medication until the next infusion (78%) [9]. While considerable research has been performed and published with regard to the pathophysiology and treatment PNH, much less is known regarding both diseases' psychosocial issues and their impact on quality of life (QoL). At the time of this study protocol writing, literature numbers six publications/studies reporting QoL and/or treatment outcomes in PNH patients and the most reliable data on QoL stem from the pivotal eculizumab trials called TRIUMPH and SHEPHERD [10]. In particular, severe fatigue and transfusion requirements, have a substantial negative impact on patients' quality of life, restricting their ability to perform normal daily activities [11], but limited data from real-world settings exist about it [12].

The REACTION study, an Italian multi-center observational (non-interventional) retrospective and prospective cohort study, aims to collect data of effectiveness in a cohort of Italian patients (excluded by the PNH registry - ClinicalTrials.gov Identifier: NCT01374360) affected by PNH, already treated with Eculizumab for at least 26 weeks and started the treatment with ravulizumab as per clinical practice, over 52-week follow-up period. Quality of Life, preference to treatment, safety profile, resource consumption and costs will be investigated in real-world setting within standard clinical practice in Italy.

Indeed, ravulizumab showed to guarantee non-inferior efficacy and safety profiles, providing a much better management of the disease due to the more convenient and effective dosing schedule, allowing the patients to receive 6 or 7 infusions per year (following loading dose), as opposed to the 26 required by eculizumab. This is supposed to lead to higher QoL and cost savings.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoints
Primary	
To describe the 52-week control of hemolysis with ravulizumab in a routine clinical practice.	1. The percentage change in lactate dehydrogenase (LDH) from baseline to end of observation.
Secondary	
To describe the 52-week effectiveness of ravulizumab with respect to eculizumab, both administered as per routine clinical practice.	1. The percentage change in lactate dehydrogenase (LDH) from baseline to end of observation on patients treated with ravulizumab with respect to the observed treatment period with eculizumab.
	2. The proportion of patients who needed transfusions and descriptive statistics on the total number of packed red blood cell units transfused during the treatment period with ravulizumab with respect to the observed treatment period with eculizumab.
	3. The proportion of patients undergoing ravulizumab without a ≥ 2-g/dL decrease in hemoglobin level in the absence of transfusion, with respect to the observed treatment period with eculizumab.

Objective	Endpoints
	4. Descriptive statistics of breakthrough hemolysis (defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE] including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal (ULN) after prior LDH reduction to <1.5xULN while on therapy) during the treatment period with ravulizumab with respect to the observed treatment period with eculizumab.
To describe Quality of Life during ravulizumab treatment in the routine clinical practice.	1. The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, Version 4.0: mean change from baseline (where available) to each timepoint of assessment (where available). 2. The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, Version 3.0: mean change from baseline (where available) to each timepoint of assessment (where available).
To describe patients' preference to ravulizumab treatment in the routine clinical practice.	PNH-specific Patient Preference Questionnaire (PNH-PPQ) at the end of observation (where available).
To describe the safety profile of ravulizumab in the routine clinical practice.	• adverse events • serious adverse events

Objective	Endpoints
To describe the resource consumption and estimate costs of ravulizumab treatment with respect to eculizumab, both administered as per routine clinical practice.	• Costs sustained by NHS: - specialist visits - pharmacological and non-pharmacological treatments - emergency department admissions - hospitalizations - exams • Costs sustained by the patients related to the infusion visits: - transportations - overall time required

Baseline = start of ravulizumab

4. STUDY DESIGN

4.1. Overall Design

The REACTION study is an Italian multi-centre, observational (non-interventional), cohort study composed of both retrospective and prospective observation periods on the same PNH patients.

The observational study is designed to collect effectiveness data on patients who were already treated with eculizumab for at least 26 weeks and who started ravulizumab treatment as specific therapeutic strategy as per ordinary clinical practice (the decision to start ravulizumab must have been taken by the clinician before the enrolment, independently from the study). All patients who provide the written informed consent and privacy form and meet the study entry criteria will be consecutively enrolled into the study by each participant centre.

A target sample of about 120 patients will be consecutively enrolled for 9 months after the First Patient In from about 30 Italian study centres , and they will be observed for 52 weeks after the start of ravulizumab (baseline, i.e. time 0) (see Figure 1.a). The enrolment will take place after the signature of informed consent and privacy form.

The study combines:

- a prospective observation window (enrolment ; + 52 weeks) relative to the prospective period of treatment with ravulizumab (see Figure 1.b);
- a retrospective observation window relative to the retrospective period of treatment with ravulizumab (if enrolment takes place after the baseline) and the retrospective period of treatment with eculizumab (0; -52 weeks), which should have started at least 26 weeks before baseline date (see Figure 1.b).

The study will involve both primary and secondary data collection:

- primary data collection will be performed during the prospective observation period, or until patient's early withdrawal (if applicable).
- secondary data collection will be performed during the retrospective observation period, from enrolment backward to eculizumab initiation date (52 weeks as maximum). The data will be retrieved from medical charts in hospitals.

Figure 1: Study Design Schematic

Figure 1.a

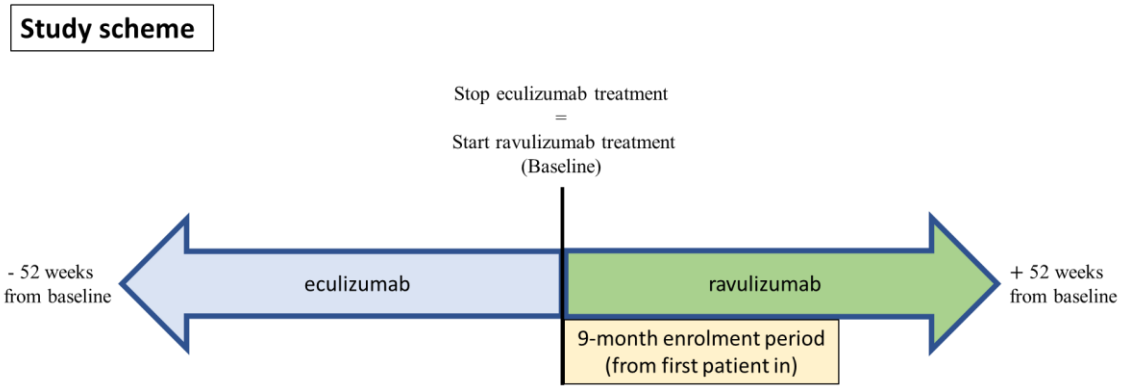
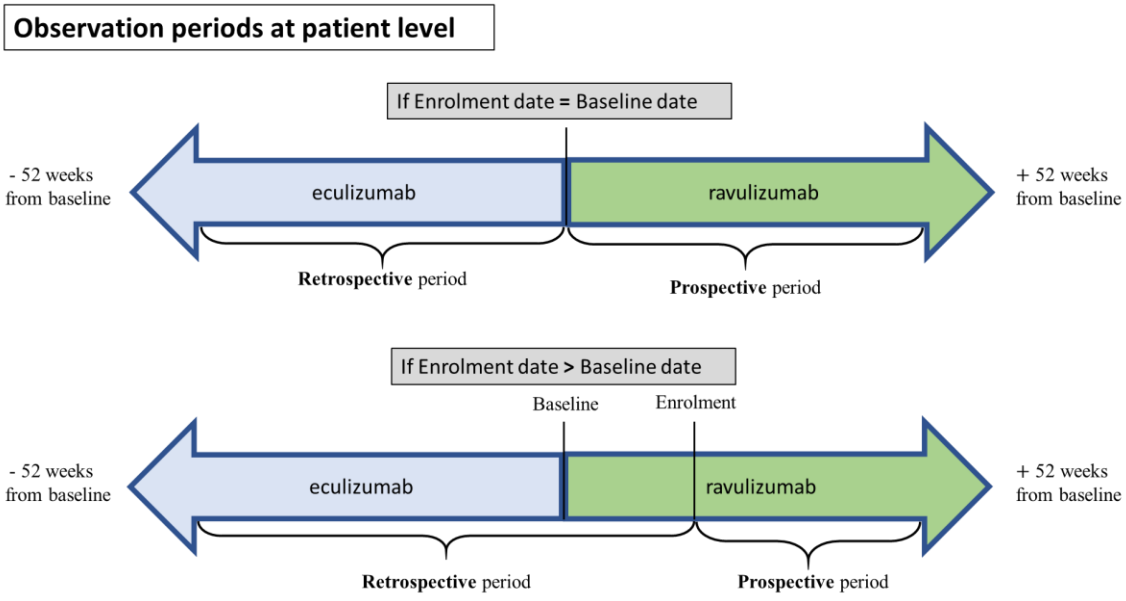


Figure 1.b



After patient's signature of study informed consent and privacy form, patient clinical data will be collected from the hospital medical charts of participant sites according to their ordinary clinical practice. Retrospective clinical data will be retrieved from hospital medical charts or from other documents. The Investigator at each site will be responsible for ensuring that the required both retrospective and prospective data from the patient medical charts are collected and all required data for each enrolled patient are entered into the eCRF.

Only data recorded in patient medical records during clinical practice will be collected within this studyin accordance with Italian regulations.

Information regarding treatment with eculizumab will be collected at enrolment visit (at Informed consent and privacy signature date) for all patients.

The expected frequency and timing of data collection in this non-interventional study are summarized in the Schedule of Activities provided in Section 1.1 (Table 1).

4.2. Scientific Rationale for Study Design

This is a non-interventional study in which physicians and patients will follow Italian clinical practice.

The study is classified as 'non-interventional' per Directive 2001/20/EC and will follow the *Guidelines for Good Pharmacoepidemiology Practices* (GPP) (Epstein, 2016).
According to Regulatory aspects in Observational Research in Italy, this study will be conducted as stated by:

- Ministry of Health's Circular No. 6 of 02 September 2002 ('Attività dei Comitati Etici' issued within Gazzetta Ufficiale No. 214 of 12 September 2002), according to 2nd clause indications.
- AIFA Determination of 20 March 2008 (issued within Gazzetta Ufficiale No. 76 of 31 March 2008), art.10 ('Procedure generali per l'avvio degli studi osservazionali').
- Supervisor Italian Authority Guideline of 24 July 2008.
- European Regulation (EU) No. 679/2016 (GDPR) effective since 25 May 2018.
- Authorization No. 9/2016 of the Supervisor Italian Authority as extended with provision n. 497 of 13 December 2018 and D.Lgs. 196/2003 updated by D.Lgs. 101/2018, in force since 19 September 2018.
- Regulation (EU) No. 1235/2010 (EU Pharmacovigilance Regulation).

This means that:

- Treatments are prescribed in the usual manner in accordance with the terms of the Summary of Product Characteristics (SmPC) and the marketing authorization.
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.
- During the study the patient will be treated at the Investigator or other referring physician discretion, according to current clinical practice.
- No additional diagnostic or monitoring procedures are applied to the patients. Questionnaires, other assessments and patient follow-up may be performed as part of normal clinical practice.

Observational Design

The study will include subjects affected by PNH, already treated with eculizumab for at least 26 weeks and starting or having started ravulizumab treatment as specific therapeutic strategy as per ordinary clinical practice. Participating sites will enroll the subjects in a consecutive manner when subjects come for their regular visit, in order to minimize the risk of selection bias. Prior to data collection, all participating subjects must sign the informed consent and privacy form. The decision of subjects to participate in this study must not, in any way, impact upon the standard of care that they are receiving or any benefits to which they are otherwise entitled. Any treatment decision must have been taken prior to and independently of the subject's inclusion in the study. The prescription of treatments during the study period is at the discretion of the Investigator and independent from the inclusion in the study.

Duration of Patient Observation

Individual patients will participate in this study for a maximum of 52 weeks ± 4 weeks after the baseline date (Figure 1, section 4.1). This period will be sufficient to adequately document the percentage change in LDH from baseline to end of observation during treatment with ravulizumab in a setting of routine clinical practice; this duration also allows for a sufficient period of time to observe the secondary objectives of this NIS.

Enrolment of Patients

Approximately 120 subjects will be consecutively enrolled in indicatively 30 sites across Italy, corresponding to approximately 4 subjects/site. This target sample size is expected to be reached during an enrolment period of about 9 months from First Patient In (first signed informed consent and privacy form by the first enrolled subject in the study), and as determined by the management capabilities of the participant centers after study feasibility results. Participating sites will be given the possibility of including a higher number of subjects until the total target sample size is reached without specific limitation for each center unless otherwise communicated by Alexion, since competitive enrolment strategy will be adopted since the beginning. Alexion will evaluate the opportunity to

prolong the recruitment beyond the conclusion of the 9-month enrolment in order to reach the target sample size. Any enrolment plan amendments will only affect administrative aspects of the study and will not require formal Protocol amendments or IEC approval, but the IECs will be informed of such administrative changes. Communications about any changes in the enrolment plan will be provided in writing to investigational sites by Alexion through MediNeos.

4.3. Schedule of Activities (SoA)

The chart below summarizes the data expected to be collected at each time point as applicable for this study.

Table 1: Schedule of Activities

Activities	**Baseline (start of ravulizumab)**	**10 weeks (+/- 2 weeks) after baseline**	**18 weeks (+/- 2 weeks) after baseline**	**34 weeks (+/- 2 weeks) after baseline**	**52 weeks (+/-4 weeks) after baseline**	**Enrolment** (Informed and privacy consent signature date)	**End of observation**
Screening/Patient information							
Informed consent						X	
Inclusion and exclusion criteria						X	
Patient disposition		X	X	X	X		
Exit criteria							X
Patient Demographic and Clinical Characteristics							
Demographics (a)						X	
Physical examination (b)	X						
Medical history and comorbidities (c)	***X						
PNH anamnesis (d)	X						
PNH related medication history (e)	***X						
PNH non related medication history (e)	***X						
PNH related concomitant medications (e)	*Recorded as continuum (updates will be recorded, if any)						
PNH non related concomitant medications (e)	*Recorded as continuum (updates will be recorded, if any)						
SARS-Cov2 positivity, vaccination, antobody response, where available	X		X	X	X	X	X
Eculizumab - Ravulizumab treatments							
Ravulizumab Dates of injection, dose, frequency of administration and changes. Temporary and permanent discontinuation dates and reasons	*Recorded as continuum (updates will be recorded, if any)						
Eculizumab Start date, dose, frequency of administration and changes. Temporary and permanent discontinuation dates and reasons	***X						
Control of hemolysis							
LDH values	*&Recorded as continuum (updates will be recorded, if any)						
Effectiveness/clinical response							
Number of transfusions (number of packed red blood cell units transfused) and number of transfusion sessions (number of days), hemoglobin assessment before transfusion	*Recorded as continuum (updates will be recorded, if any)						
Hemoglobin levels	*&Recorded as continuum (updates will be recorded, if any)						
Breakthrough hemolysis (BTH) assessment - medical condition (trigger) correlated to BTH, degree of correlation, associated LDH assessment	*Recorded as continuum (updates will be recorded, if any)						
PNH symptomatology (f)	*Recorded as continuum (updates will be recorded, if any)						
Laboratory parameters (other than LDH and Hemoglobin levels)							
Reticulocytes, Indirect Bilirubin, Creatinine, Haptoglobin: unit and measurement	§ X		X	X	X	X§	
Patient-reported Outcomes							
FACIT-Fatigue scale v. 4.0	X	X	X	X	X		
EORTC QLQ-C30 v. 3.0	X	X	X	X	X		
PNH-PPQ					X		X#
Resource consumption							

Costs related to PNH sustained by NHS (Drug consumption (d), specialist visits, number of transfusions, hospital stays, emergency rooms (ER) accesses, medical exams), Costs sustained by the patients related to infusion visits (average cost to reach the structure, overall time required for the infusion, retirement status of the patient, loss of working days, need of caregiver)	X		X	X	X	X	
Safety data							
AE, SAE	*Recorded as continuum (updates will be recorded, if any)						
MAVE (g)	*Recorded as continuum (updates will be recorded, if any)						
Off label use of eculizumab						X	
Pregnancy/breastfeeding (h)	*Recorded as continuum (updates will be recorded, if any)						
Study completion							X

*Data will be prospectively collected up to 52 weeks after the baseline during ravulizumab treatment. Also the retrospective period, relative to the treatment with ravulizumab and back to 52 weeks (0; -52) from baseline during eculizumab, if available from hospital medical charts or from other documents.

§ The retrospective data referred to -26 weeks (+/- 10 days) and -52 weeks (+/- 10 days) will be collected at enrolment.

& LDH values and Hemoglobin levels will be collected at least at the following timepoints, if available: -52 weeks, -26 weeks, baseline, 18 weeks, 34 weeks, 52 weeks.

In case the patient leaves the study prior to 52 weeks.

*** Retrospectively collected at enrolment, from baseline up to 52 weeks backward during eculizumab treatment period, if available from hospital medical charts or from other documents.(a) Demographics: age, gender, ethnicity
(b) Physical examination: height, weight, BMI
(c) Medical history and comorbidities: histories of acute, chronic, or infectious disease and any reported conditions affecting major body systems. Concomitant conditions/disorders will be collected as well.
(d) PNH anamnesis: date of diagnosis, history of hemoglobinuria, history of any MAVEs, bone marrow disorder, shortness of breath, fatigue, pulmonary hypertension.
(e) Medication history/ concomitant medications (e.g. prescription or over-the-counter, vitamins, meningococcal vaccination,). Pharmacological treatments (e.g., drug type, drug compound, date of treatment initiation, dose, date of and reason for discontinuation, if any) and non-pharmacological treatments (e.g., treatment type, number of sessions, date of treatment initiation, date of and reason for discontinuation, if any).
(f) PNH symptomatology: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, erectile dysfunction, Thrombosis, Anemia (hemoglobin levels).
(g) MAVE: pulmonary embolus, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis, acute peripheral vascular occlusion, mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, epatic/portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, renal arterial thrombosis, gangrene (nontraumatic; nondiabetic), amputation (nontraumatic; nondiabetic), dermal thrombosis.Thrombophlebitis/deep vein thrombosis
(h) Pregnancy/breastfeeding: these events are exit criteria and are managed as described in section 8.2

Patient Reported Outcomes FACIT-Fatigue scale v. 4.0 and EORTC QLQ-C30 v. 3.0 will be collected, if available, at baseline, 10 weeks (+/- 2 weeks), 18 weeks (+/- 2 weeks), 34 weeks (+/- 2 weeks), and at 52-week follow-up visit or until patient's early withdrawal (if applicable). PNH-PPQ will be collected, if available, at 52-week follow-up visit or until patient's early withdrawal (if applicable).

Study assessments and their timing are summarized in the SoA (section 6.1).

4.4. End of observation

The end of observation is defined as the achievement of 52 weeks (± 4 weeks) follow-up during treatment with ravulizumab or patient withdrawal from the study, whichever comes first.

5. STUDY POPULATION

5.1. Inclusion Criteria

The patients are eligible to be included in the study only if all of the following criteria apply:

1. Male or female, aged ≥ 18;
2. Documented diagnoses of PNH confirmed by high-sensitivity flow cytometry evaluation of red blood cells and white blood cells with granulocyte or monocyte clone size of ≥ 5%;
3. Treated with Eculizumab for at least 26 weeks (including patients treated with a higher dose of eculizumab, both in terms of dose administration and frequency of administration, than the one indicated in the SmPC);
4. Patient already assigned to ravulizumab treatment as specific therapeutic strategy within current routine clinical practice (this decision has to be made independently and before the enrolment of the patient in the study);
5. Vaccinated against Neisseria meningitidis (according to SmPC) < 3 years before dosing or at the time of study drug initiation to reduce the risk of meningococcal infections;
6. Signed written informed and privacy consent prior to study participation;

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply :

1. History of hematopoietic stem cell transplantation (evaluated at baseline);
2. Known pregnant or breastfeeding patient (evaluated at baseline);
3. Patient unable to read and write in Italian language and to autonomously fill in questionnaires and scales (evaluated at enrolment);
4. Patients enrolled in any clinical trial receiving experimental treatments for PNH (evaluated at baseline);

5.3. Exit Criteria

A patient will be withdrawn from data collection within the study for any of the following reasons:

1. Loss to follow-up;
2. Informed and privacy Consent withdrawal;
3. Death;
4. Interruption of ravulizumab treatment, defined as skipping treatment for two consecutive infusions;
5. Hematopoietic stem cell transplantation;
6. Enrolment in any clinical trial on experimental treatments for PNH;
7. Pregnancy or breastfeeding during the observation period;

In case of withdrawal, the Investigator must fill in the relevant form in the electronic Case Report Form (eCRF), reporting the main reason for withdrawal.

6. STUDY ASSESSMENTS

Study assessments and their timing are summarized in the SoA (section 1.1).

6.1. Collected variables

Demographics

Age, gender, ethnicity will be collected at enrolment visit.

Physical examination:

Height, weight, BMI will be collected at enrolment visit.

Medical history and comorbidities

The patient's medical history will be retrospectively collected at enrolment visit, from baseline up to 52 weeks backward during eculizumab treatment period, if available from hospital medical charts or from other documents including histories of acute, chronic, or infectious disease and any reported conditions affecting major body systems. Concomitant conditions/disorders will be collected as well.

PNH Anamnesis

Medical history of PNH will be collected at enrolment visit in terms of date of diagnosis, history of hemoglobinuria, history of any MAVEs, bone marrow disorder, shortness of breath, fatigue, pulmonary hypertension.

PNH related medication history – concomitant medications

Pharmacological treatments related to PNH (e.g. anticoagulants, selective immunosuppressants, erythropoiesis stimulating agents, steroids) will be collected in terms of drug type, drug name, date of treatment initiation, dose, frequency, date of and reason for discontinuation, if any. Non-pharmacological treatments related to PNH (e.g. Oxygen therapy, vitamins) will be collected in terms of treatment type, date of treatment initiation, frequency, date of and reason for discontinuation, if any.
The medication history related to PNH, relative to the 52 weeks prior to baseline, will be collected at enrolment. The concomitant medications related to PNH will be collected and updated (if updates take place) from baseline to end of observation.

PNH non related medication history – concomitant medications

Pharmacological treatments due to other chronic diseases will be collected in terms of drug type, date of treatment initiation, dose, frequency, date of discontinuation, if any. Non-pharmacological treatments due to other chronic diseases will be collected in terms of treatment type, date of treatment initiation, frequency, date of discontinuation, if any. The medication history for other chronic diseases, relative to the 52 weeks prior to baseline, will be collected at enrolment. The concomitant medications for other chronic diseases will be collected and updated (if updates take place) from enrolment to end of observation.

Sars-COV-2 positivity, vaccination, antibody response

If the subject is tested positive to SARS-Cov2 or received the relative vaccination or was tested for antibody response, this information will be recorded, where available, at enrolment, baseline, 18 weeks, 34 weeks, 52 weeks and updated (if updates take place) at the end of observation.

Ravulizumab

The assessment of ravulizumab treatment will be performed from its start to the end of observation. The following variables will be collected: Dates of injections, dose, frequency of administration, changes, temporary and permanent discontinuation dates and reasons.

Eculizumab

The data collection of eculizumab treatment history will be performed at enrolment, up to - 52 weeks backward (retrospectively) with respect to the baseline, if available. The following variables will be collected: start date, dose, frequency of administration, changes, temporary and permanent discontinuation dates and reasons.

6.1.1. Effectiveness/Clinical Response Measures

Main measurement of effectiveness is the percentage change in lactate dehydrogenase (LDH) from baseline (start of ravulizumab) to end of observation.

Lactate DeHydrogenase (LDH)

LDH values during ravulizumab treatment, will be collected from baseline to the end of observation. The retrospective LDH values relative to eculizumab treatment will be collected at enrolment and will cover the period from the baseline backward to 52 weeks , if available. LDH values will be collected at least at the following timepoints, if available: -52 weeks, -26 weeks, baseline, 18 weeks, 34 weeks, 52 weeks.

Number of transfusions and number of transfusion sessions

The number of transfusions (number of packed red blood cell units transfused) and the number of transfusion sessions (number of days) during ravulizumab treatment, will be collected from baseline to the end of observation. The retrospective data relative to eculizumab treatment will be collected at enrolment and will cover the period from the baseline backwardto 52 weeks , if available.

Hemoglobin levels

Hemoglobin levels during ravulizumab treatment, will be collected from baseline to the end of observation. The retrospective hemoglobin levels relative to eculizumab treatment will be collected at enrolment and will cover the period from the baseline backwardto 52 weeks , if available. Hemoglobin levels will be collected at least at the following timepoints, if available: -52 weeks, -26 weeks, baseline, 18 weeks, 34 weeks, 52 weeks.

Breakthrough hemolysis (BTH)

The occurrence of BTH during ravulizumab treatment, will be collected from the baseline to the end of observation. Such events relative to eculizumab treatment will be retrospectively collected at enrolment and will cover the period from the baseline backwardto 52 weeks , if available. BTH occurrence will be recognized by the Investigator, who will be asked to evaluate its correlation with PNH. BTH is defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin < 10 g/dL), major adverse vascular event (MAVE) including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal (ULN) after prior LDH reduction to <1.5xULN while on therapy. (See MAVE definition at section 8.2). Relative to the BTH event, the medical condition (trigger) correlated to BHT, the degree of correlation and the associated LDH assessment will be collected as well.

PNH symptomatology

Fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, erectile dysfunction, thrombosis and anemia (hemoglobin levels) during ravulizumab treatment, will be collected from baseline to the end of observation. These events relative to eculizumab treatment will be retrospectively collected at enrolment and will cover the period from the baseline backwardto 52 weeks , if available.

Laboratory parameters

Reticulocytes, Indirect Bilirubin, Creatinine and Haptoglobin values during ravulizumab treatment, will be collected at 18 weeks (+/-2 weeks), 34 weeks (+/-2 weeks) and 52 weeks (+/-4 weeks). Such parameters relative to eculizumab treatment will be retrospectively collected at enrolment, referred to baseline, – 26 weeks (+/- 10 days) and – 52 weeks (+/- 10 days), if available.

6.1.2. Patient-Reported Outcomes

In this study ePROs (electronic Patient-Reported Outcomes) will be used. Patients will be able to complete the questionnaires by the means of their own electronic devices (i.e. smartphone, tablet, personal computer).

Two validated QoL scales will be prospectively collected, if available, at the time points specified in the Schedule of Assessment (see section 1.1). For patients enrolled after baseline, mesurements occurred before enrolment will not be collected.

- The FACIT-Fatigue scale, Version 4.0, is a collection of QoL questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days. Patients will score each item on a 5-point scale. Total scores range from 0 to 52, with higher score indicating better QoL. The questionnaire completed by patients will be collected at the following timepoints: baseline, 10 weeks (+/- 2 weeks), 18 weeks (+/- 2 weeks), 34 weeks (+/- 2 weeks) and at 52-week follow-up visit or until patient's early withdrawal (if applicable).

- The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, is a questionnaire developed to assess the QoL of cancer patients over the preceding 7 days. The questionnaire includes the following subscales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain), and single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Thirty questions related to QoL, with the first 28 questions scored on a 4-point scale and the final 2 questions that probe the patient's overall health and QoL scored on a scale of 1 (very poor) to 7 (excellent). Each subscale has a range of 0 to 100%. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problem [16]. The QLQ-C30 version 3.0 is validated and available in Italian [17]. The questionnaire completed by patients will be collected at the following timepoints: baseline, 10 weeks (+/- 2 weeks), 18 weeks (+/- 2 weeks), 34 weeks (+/- 2 weeks) and at 52-week follow-up visit or until patient's early withdrawal (if applicable).

To evaluate the preference to treatment, 11 item PNH-specific Patient Preference Questionnaire (PNH-PPQ) [18, 19] will be collected, if available, at the time point specified in the Schedule of Assessment (see section 1.1).

- The PNH-PPQ provides a patient-centered approach for evaluating preferences for the treatment of PNH. The questionnaire contains 11 questions assessing overall treatment preference , evaluating treatment preference according to nine treatment characteristics (eg, "controlling fatigue," "frequency of infusions"), assessing the most important treatment characteristic for patient overall medication preference, and evaluating those same aspects of treatment with ravulizumab (eg, "the frequency of infusions with eculizumab disrupted my life" and "the frequency of infusions with ravulizumab disrupted my life;" Q4-11). The Italian version of this questionnaire will be available at the time of data collection. The questionnaire completed by patients will be collected at 52 weeks or at the end of observation (if applicable), whichever comes first.

6.1.3. Resource consumption

- Resource consumption relative to eculizumab treatment during the 52 weeks prior to baseline, will be retrospectively collected at enrolment, if available.
- Resource consumption relative to ravulizumab treatment will be collected from baseline up to the end of observation.

The following medical costs related to PNH sustained by NHS will be collected: specialist visits, pharmacological and non-pharmacological treatments, hospital and emergency rooms (ER) admissions, exams (by exam type).

The following costs sustained by the patients, related to the infusion visits, will be collected: average cost to reach the structure, overall time required for the infusion (time to reach the structure + time of infusion), retirement status of the patient, loss of working days, need of caregiver.

6.1.4. Safety Assessments

AEs occurred during the ravulizumab treatment will be collected, recording the following details: description of the event, start date, severity grade, seriousness (and corresponding criteria), causality with respect to ravulizumab, action taken, outcome, recovery date. In particular AE, SAE, (see definition at section 8.2) will be collected in the eCRF. Pregnancy/breastfeeding events, will be recorded and properly managed (see section 8.2), and represent exit criteria.

Planned time points for all safety assessments are provided in the SoA (see section 1.1).

6.2. Data management

All data required to address the study objectives will be collected and entered into an electronic case report form (eCRF). The Investigator at each site will be responsible for ensuring that the required retrospective data from the charts are extracted and all the prospective data for each participant patient are collected and entered into the eCRF.
The eCRF used for the study is validated according to Good Automated Manufacturing Practice, version 5 (GAMP5). The Information Technology (IT) infrastructure supporting the eCRF solution will be monitored and controlled both in terms of security (i.e., intrusion detection, antiviruses, etc.) and operational performance. Backups and operative controls will be properly managed in order to guarantee the business continuity.
Access to eCRF will be granted to the site staff only after appropriate training. The validity of data will be granted by all quality control procedures.

The Investigator at each site will be responsible for ensuring that the required data are extracted from the medical charts and entered into the eCRF. The Investigator will review the eCRF for completeness and accuracy. Furthermore, the Investigator will retain full responsibility for the accuracy and authenticity of all data entered into the eCRF. The CRO “MediNeos S.U.R.L.”, working on behalf of Alexion, will instruct the site personnel to make any required corrections or additions. The Clinical Data Manager of MediNeos working on behalf of Alexion will perform the cleaning session reviewing the warning messages raised by on-line checks and running post-entry checks by means of validation programs and data listings specific for the study. During this process, if clarifications are needed, the Clinical Data Manager will raise queries by means of data query forms through the web application. Designated investigator site staff is required to respond to the queries and make the corrections to the database on the basis of the query response.
Medical terms (e.g. AEs and relevant medical conditions) will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. Medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical (ATC) classification. The dictionary version to be use will be the most current version at the time the data collection starts.

Patients questionnaires will be collected electronically, and data will be automatically saved in eCRF. In details, the Study Investigator will open the appropriate Questionnaires section in EDC system and will provide the link to the questionnaire to the patient for electronic completion. The patient will complete the questionnaire by the means of his/her own electronic device, i.e. smartphone, tablet, personal computer (laptop and desktop). After the completion of data collection and cleaning, a review meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Once the database has been declared to be complete and accurate, the clinical database will be locked and the planned statistical analysis will be performed.

The Investigator will review the eCRF for completeness and accuracy. Furthermore, the investigator will retain full responsibility for the accuracy and authenticity of all data entered into the eCRF.

6.3. Adverse Events, Serious Adverse Events, Adverse Drug Reactions and Serious Adverse Drug Reactions

The definitions of AEs, SAEs, ADRs, SADRs can be found in Section 8.2

All AEs, SAEs, ADRs and SADRs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE,SAE, ADR, SADR and remain responsible for following up AEs that are serious, considered related to Alexion drugs.

Procedures for recording, evaluating, follow-up, and reporting AEs, SAEs, ADRs and SADRs are outlined in Section 8.2.

6.3.1. Time Period and Frequency for Collecting AE and SAE Information

For all enrolled patients, all AEs, SAEs, ADRs and SADRs will be collected in the eCRF, both for the retrospective and prospective period, from the signing of the ICF until the follow-up visit (Section 8.2).

For retrospective period, all AEs, SAEs, ADRs and SADRs will be recorded by the investigator immediately into the eCRF. All retrospective AEs, SAEs, ADRs and SADRs will be listed and sent to Alexion monthly.

For prospective period, all AEs, SAEs, ADRs and SADRs will be recorded and reported by the investigator immediately troughout the eCRF to CRO.

Note: AEs includes Special situations listed in 8.2.

When the investigator will record prospective AEs/SAEs/ADRs/SADRs as applicable, CRO will inform Alexion within24hrs of it being aware.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE/ADR/ SADR, including a death, at any time after a participant has been discharged from the study the Investigator must promptly notify Alexion using the contacts reported in section 8.2.5 of the study protocol.

6.3.2. Method of Detecting AEs, SAEs, ADRs and SADRs

The method of recording and evaluating AEs, SAEs, ADRs, SADRs and the procedures for completing and transmitting SAEs and SADRs reports are provided in Section 8.2.

Care will be taken not to introduce bias when detecting AEs, SAEs, ADRs and SADRs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about these occurrences.

6.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE/ADR/SADR report, the Investigator is required to proactively follow-up on each participant at subsequent visits/contacts. All SAEs/SADRs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is provided in Section 8.2.

6.3.4. Regulatory Reporting Requirements for SAEs/SADRs

Prompt notification of prospective AEs, SAEs, ADRs, SADRs by the Investigator to CRO so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment are met.

Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and Investigators.

An Investigator who receives an Investigator safety report describing an SAE/SADR or other specific safety information (eg, summary or listing of SAEs/SADRs) from CRO or from Alexion, will review and then file it along with the Investigator's Brochure or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

6.3.5. Adverse Events of Special Interest

Consult the appropriate medically qualified team member if unsure if this section is applicable for a particular protocol.The description should include the following: The definition of the event. Is it a measurable quantity? If yes, how will the measurement be done? If it is a clinical event, how will it be confirmed? If this section is not applicable suggest stating as such (eg, there have been no adverse events of special interests (AESIs) associated for this intervention) rather than deleting the section. If non-serious AESIs are of interest, include timing of reporting.

6.4. Pharmacodynamics

Not Applicable in the present study

6.5. Genetics

Genetic data will not be collected in this study.

6.6. Biomarkers

LDH and Hemoglobin will be collected from – 52 week prior to baseline, up to end of observation. They will be collected at least at the following timepoints, if available: -52 weeks, -26 weeks,

baseline, 18 weeks, 34 weeks, 52 weeks. Reticulocytes, Indirect Bilirubin, Creatinine and Haptoglobin relative to ravulizumab treatment, will be collected at 18 weeks (+/-2 weeks), 34 weeks (+/-2 weeks) and 52 weeks (+/-4 weeks) as investigated by routine clinical practice. Such parameters relative to eculizumab treatment will be collected at baseline, – 26 weeks (+/- 10 days) and – 52 weeks (+/- 10 days), if available.

6.7. Immunogenicity Assessments

Not Applicable in the present study

7. STATISTICAL CONSIDERATIONS

No formal statistical hypotheses were set for the study, as it has a descriptive aim.

Patients with missing data for one or more variables will not be excluded from the study and their data will not be replaced (unless, for ePROs instruments, missing answers can be pro-rated or imputed as specified by the author's indications, if any), but will not be considered for the analyses for which that variables are taken into account. Frequency of missing data will be given for all analysed variables.

7.1. Sample Size Determination

Sample size was not based on statistical considerations. Rather it was defined according to feasibility considerations, namely the extremely rare characterization of the PNH, with 1–1.5 cases per million individuals worldwide [4], and the number of potentially eligible patients in selected sites (clinical judgement). A target sample of about 120 patients already treated with Eculizumab for at least 26 weeks and who started ravulizumab treatment as per ordinary clinical practice, will be enrolled from 30 Italian study centres. It is also reasonable to expect 20% drop-out, therefore we expect that 96 patients could be available for the evaluation.

7.2. Populations for Analyses

Enrolled patients will be defined as all the subjects entered into the eCRF.

The population sets used for analysis sets will be defined as follows:

- Safety Set (SS) will be composed by enrolled patients who will have started the treatment with ravulizumab and signed the ICF.
- Full Analysis Set (FAS) will be composed by eligible patients (i.e. enrolled patients meeting all the inclusion criteria and not meeting any of the exclusion criteria). Minor deviations will be evaluated, if any.

7.3. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP). Summary statistics will be computed Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Analyses will be performed using the SAS® software Version 9.2.

7.3.1. Analyses of Primary Endpoint

The primary endpoint is the percentage change in lactate dehydrogenase (LDH) from baseline to the end of observation during ravulizumab treatment in standard clinical practice in Italy. In order

to compute the LDH percentage change, the LDH levels measured at baseline and end of observation will be employed as follows:

$$\Delta\%(\mathrm{LDH})_{\mathrm{ravulizumab}} = \frac{\mathrm{LDH}_{52\ \mathrm{weeks}} - \mathrm{LDH}_{\mathrm{baseline}}}{\mathrm{LDH}_{\mathrm{baseline}}} * 100$$

The descriptive statistics (e.g. mean, standard deviation, median, IQR [first quartile subtracted from the third quartile]) will be reported and represented with a box-plot. The analysis will be performed on the Full Analysis Set, including the patients having the LDH evaluation at both the baseline and at the end of observation.

7.3.2. Analyses of Secondary Endpoints

Secondary objectives #1, #2, #3, #5 (**#1** – to describe the 52-week effectiveness of ravulizumab with respect to eculizumab, both administered as per routine clinical practice; **#2** – to describe Quality of Life during ravulizumab treatment in the routine clinical practice; **#3** – to describe patients' preference to ravulizumab treatment in the routine clinical practice ; **#5** – to describe the resource consumption and estimate costs of ravulizumab treatment with respect to eculizumab both administered as per routine clinical practice) will be evaluated on the Full Analysis Set.

Secondary objective **#1 (**to describe the 52-week effectiveness of ravulizumab with respect to eculizumab, both administered as per routine clinical practice):

1. The difference of percentage change in lactate dehydrogenase (LDH) from baseline to end of observation will be calculated on patients treated with ravulizumab (over the 52 weeks after baseline) and on the same patients treated with eculizumab (during up to 52 weeks before baseline). Moreover, as explorative analysis a repeated measure regression model will be performed with LDH values as dependent variable and gender, age, treatment (eculizumab / rabulizumab), time on treatment (i.e. adjusting for the effective exposure), as fixed effects.
2. The proportion of patients who needed transfusions, with relative frequency and percentage, and descriptive statistics (e.g. mean, standard deviation, median, IQR) on the total number of transfusions (number of packed red blood cell units transfused) and number of transfusion sessions (number of days) will be calculated for both the treatment period with ravulizumab and the treatment period with eculizumab.
3. The proportion of patients without a ≥ 2-g/dL decrease in hemoglobin level in the absence of transfusion will be calculated for both the treatment period with ravulizumab and the treatment period with eculizumab.
4. The descriptive statistics (e.g. mean, standard deviation, median, IQR) will be reported to describe the events of breakthrough hemolysis (defined as at least one new or worsening

symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE] including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal (ULN) after prior LDH reduction to <1.5xULN while on therapy) will be calculated for both the treatment period with ravulizumab and the treatment period with eculizumab.

Secondary objective #**2 (**to describe Quality of Life during ravulizumab treatment in the routine clinical practice):

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, Version 4.0 (see section 6.1.2), will be collected, if available, at baseline, 10 weeks (+/- 2 weeks), 18 weeks (+/- 2 weeks), 34 weeks (+/- 2 weeks) visit and at 52-week follow-up visit or until patient's early withdrawal (if applicable). The mean change from baseline to each timepoint of assessment will be calculated. Only the patients in FAS with filled in questionnaire at the baseline date and with filled in questionnaire at the specific timepoint of assessment will be considered for this analysis. Descriptive statistics (e.g. mean, standard deviation, median, IQR) will be reported for the questionnaire domain scores. Questionnaire scores will be calculated according to indications received from the authors, where possible.

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, Version 3.0 (see section 6.1.2), will be collected, if available, at baseline, 10 weeks (+/- 2 weeks), 18 weeks (+/- 2 weeks), 34 weeks (+/- 2 weeks) visit and at 52-week follow-up visit or until patient's early withdrawal (if applicable). The mean change from baseline to each timepoint of assessment will be calculated. Only the patients in FAS with filled in questionnaire at the baseline date and with filled in questionnaire at the specific timepoint of assessment will be considered for this analysis. Descriptive statistics (e.g. mean, standard deviation, median, IQR) will be reported for the questionnaire domain scores at both times. Questionnaire scores will be calculated according to indications received from the authors, where possible.

Secondary objective #**3** (to describe patients' preference to ravulizumab treatment in the routine clinical practice).

The 11 item PNH-specific Patient Preference Questionnaire (PNH-PPQ) will be collected, if available, at the end of observation to the patients who will have received at least two doses of ravulizumab. The questionnaire scores will be calculated according to indications received from the authors/ copyright holders, where possible.

Secondary objective #5: To describe the resource consumption and estimate costs of ravulizumab treatment with respect to eculizumab, both administered as per routine clinical practice.

The resource consumption will be estimated for both the treatment period with ravulizumab and the treatment period with eculizumab.

The medical costs related to drug consumption (overall dose, n. of units), number of specialist visits, number of transfusions, hospital stays, emergency rooms (ER) accesses, medical exams will be reported through descriptive statistics (e.g. mean, standard deviation, median, IQR). Total direct medical costs related to PNH borne by the NHS (C_i) per patient (i) will be appraised considering quantity (q_m) of resource consumption by medical resource (m) and its unit costs (c_m):

$$C_i = \sum_m^M q_{mi} * c_m$$

Unit costs will be estimated based on national tariffs, national legislation, and available published literature, if needed.

The national tariffs will be retrieved by:

Ministero della Salute. Tariffe delle prestazioni di assistenza specialistica ambulatoriale. GU Serie Generale n.23 del 28-01-2013 – Supplemento ordinario n. 8, allegato 3.

Ministero della Salute. Tariffe delle prestazioni di assistenza ospedaliera per acuti, per tipo di ricovero (euro). GU Serie Generale n.23 del 28-01-2013 – Supplemento ordinario n. 8, allegato 1.

The total cost related to infusion visits sustained by the patients, will be calculated in terms of total cost of transports and overall time required for infusion, respectively calculated as:

$$Total\ cost\ of\ transports = \overline{C_{1tr}} * N_{inf}$$

where:

$\overline{C_{1tr}}$ = average cost of one travel to reach the structure for one infusion visit (back and forth)

N_{inf} = number of infusion visits

$$Overall\ time\ required\ for\ infusion = (T_{inf} + I_{\text{inf}}) * N_{inf}$$

where:

T_{inf} = minutes spent to reach the structure for one infusion visit (back and forth)

I_{inf} = minutes spent for the infusion

N_{inf} = number of infusion visits

The Statistical Analysis Plan will describe the analyses of section 7.3 in greater detail.

7.3.3. Safety Analyse(s)

All safety analyses will be made on the Safety Set. Secondary objective **#4** is aimed at describing the safety profile of ravulizumab. The safety profile of ravulizumab will be described through descriptive statistics, reporting number and proportion of patients with adverse events (AE), and serious adverse events (SAE) together with the total number of such events. All collected Aes, regardless of seriousness, severity, or causality, will be summarized in the statistical report. Moreover, frequency distribution will be provided for type and severity of any event. See section 8.2 for safety event definitions.

7.3.4. Other Analyses

Although it is not anticipated that patients on ravulizumab will switch back to eculizumab, if it might happen, the patients switching back on eculizumab will not be followed further while back on eculizumab, as the study is focusing on ravulizumab. The number of patients switching back to eculizumab will be captured and reported. And the reason for stopping ravulizumab will be reported with descriptive statistics too.

7.4. Interim Analyses

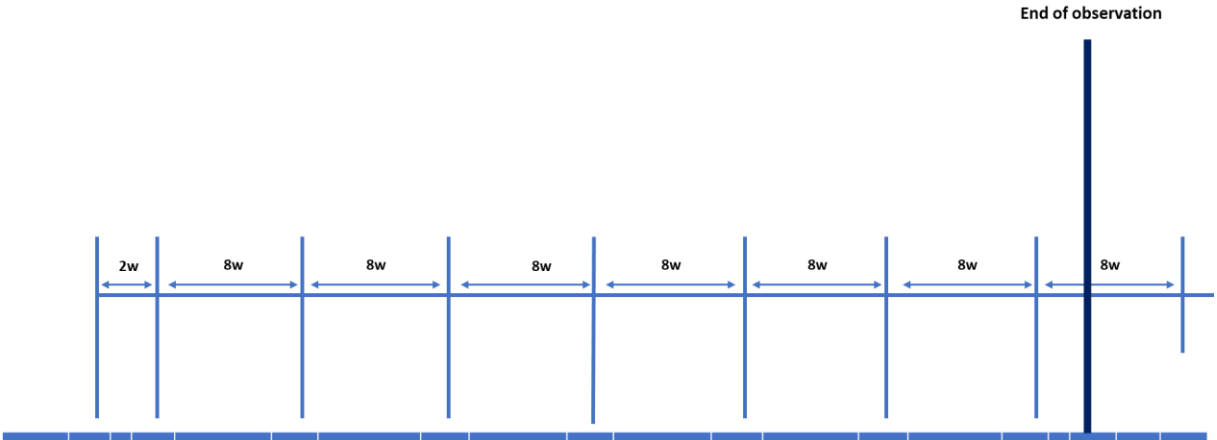
It is planned to perform two interim analyses.

The first one is planned to be performed when about 60 patients are enrolled and treated with ravulizumab for 18 weeks.

The second one is planned to be performed approximately at half of the observation period.

The Statistical Analysis Plan will describe the planned interim analyses in greater detail. See figure 2 below for a greater detail about dosing schedule and follow-up.

Figure 2: Dosing Schedule and follow-up



Week	w0		w2		w10		w18		w26		w34		w42		w50		w52		w58
N.dose	I-1 (L)		I-2 (M)		I-3 (M)		I-4 (M)		I-5 (M)		I-6 (M)		I-7 (M)		I-8 (M)				I-9 (M)
F-UP visit	F1						F2				F3				F4	-	F4		

I = Infusion
L = Loading
M = Maintenance

7.5. Limitations of the research methods

This is an observational (non-interventional) study with a retrospective and a prospective data collection Information, selection and recall bias have to be taken into account, as in all observational studies.

Information and recall bias might affect the quality of collected retrospective data: however, most of the variables assessed at enrolment are expected to be available in the patient's medical chart, in particular: LDH levels, number of transfusions, hemoglobin levels, symptoms or signs of intravascular hemolysis, events of breakthrough hemolysis. In fact, such information should be monitored during the eculizumab treatment, as per current clinical practice. In addition, the retrospective period of eculizumab treatment is limited to maximum 52 weeks prior to the baseline.

By design, patients treated with eculizumab for less than 26 weeks before starting ravulizumab will not be included in the study. The systematic exclusion of these patients introduces a selection of the target population, potentially affecting external validity. However, it is of interest in the study to have a period of observation long enough (26 weeks is considered acceptable) to describe the clinical outcomes, quality of life, treatment preference and resource consumption. Individual retrospective observation duration during eculizumab could be different from patient to patient (depending on the date of eculizumab treatment start), ranging from 26 weeks (as per inclusion criterion # 3) to longer period. During data elaboration, depending on the patients' distribution according to duration of eculizumab treatment, it might be evaluated the opportunity to perform

stratified analyses with respect to treatment duration in order to evaluate clinical outcomes in more homogeneous patients subgroups, according to the number of patients within subgroups.

Information bias could occur if missing or incorrect information exposure or outcomes is collected in the study.

- Bias due to use of ePROs instruments: inclusion of the subjects in the study may alter their perception of their medical care or clinical condition, but this is not likely to depend on the administered medical treatment. Moreover, subjects' answers may be influenced by the Investigators or by the subjects themselves to meet the Investigator expectations. However, the influence should not be more than the potential influence faced during standard practice. Thus, applicable questionnaires will be completed by subjects without involvement or with minimal support of the Investigator. This will be explained during the training of Investigators. In addition, according to the exclusion criteria defined in the Protocol section 5.2, patients who are unable to read and write in Italian language and to autonomously fill in questionnaires and scales will be excluded from the study. This is necessary in order to properly address key study objectives. This limitation shall be taken into account when interpreting the study results, but it is expected that the number of PNH patients meeting this exclusion criterion would be negligible (therefore, the impact is deemed to be not relevant).

- Since LDH evaluation is one of the key parameters in monitoring patients affected by PNH and a feasibility about the collection of this biomarker confirmed its measurement in current clinical practice, , the risk of missing LDH data is deemed to be residual. However, with regards to the secondary objective aiming at describing the QoL, this will be possible only for patients having undergone the baseline assessment and the specific timepoints of assessment described in section 6.1.2. Therefore, ePROs evaluations will be performed on a subgroup of the cohort with available information (which could not be representative of the whole enrolled sample), and will not be possible for patients who do not perform a standard clinical visit within the expected time frame. However, according to treatment schedule patients are expected to be visited regularly at their respective clinical site, in line with the assessment schedule planned in the current study.

- In order to limit information bias, direct medical costs sustained by patients will not be collected and are not objectives of the study. However, information bias could also affect data collection regarding cost of transportation, especially referred to the eculizumab treatment, which is retrospective. As a mitigation action, investigators will engage patients in order to explain the aim of the research. Results will have to be interpreted by taking this limitation into account.

Another possible source of bias, is selection bias. Since study sites will not be randomly sampled from the whole pool of Italian clinics but sites will be selected according to their experience in PNH patients management, conclusions on the study results will be referred to PNH patients treated with ravulizumab in the study sites. Selection criteria for the target population were written with the aim to limit any selection bias and to make this sample representative of clinical practice as much as possible.

Since sites were not randomly selected, but chosen according to their experience in clinical research, results will have to be interpreted by keeping this into account.

Despite the above listed limitations, the study will allow to have a wide real-world description of the Italian current clinical practice of treatment with ravulizumab in PNH patients enrolled in the specific sites.

8. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

8.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

8.1.1. Regulatory and Ethical Considerations

Regulatory considerations

This observational study is planned to enroll subjects treated as per current clinical practice. Overall, data provided in sections 2.1 and 2.2 support the conduct of the proposed study.
The REACTION study will be conducted in compliance to the study protocol, with the Declaration of Helsinki (1964 and amendments) [13], Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) [14], Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and with local regulation for observational studies conduct. This study is not in the scope of Good Clinical Practice (GCP) studies but for several applicable aspects it will be managed according to the current International Council on Harmonization (ICH) E6 GCP [15].

The study proposal will be submitted to the IRB/IEC in accordance with the local requirements of each participant site.

The Investigator will perform the REACTION observational study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the Observational Study and in accordance with currently standard clinical practice.

The final Protocol of the Observational Study, including the final version of the subject informed consent form and privacy, must be approved or given a favourable opinion in writing by the IRB/ IEC - clearly identifying the study number, study title and subject informed consent form and privacy form version.

Ethical considerations

Compliance with Alexion and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.
This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).
The Investigator will perform the study in accordance with the regulations and guidelines governing medical practice and ethics in Italy and in accordance with currently acceptable techniques and know-how.
The final protocol of the study, including the final version of the informed consent form, must be approved or given a favourable opinion in writing by the Ethics Committee.
Patients enrolment will not start before the approval of the Ethics Committee. This study does not include treatments or diagnostic examinations other than those prescribed in the ordinary clinical practice, therefore no insurance agreements are applicable.
The Ethics Committee must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

8.1.2. Informed Consent Process

It is the responsibility of the physicians to obtain written informed and privacy consent from each patient prior to the collection of any data from the patient's records. The patient will be given sufficient time to read the participation agreement/ICF and will be given the opportunity to ask questions. Before enrolment in the study, the participating physician or an authorized member of the participating site personnel must explain to potential participating patients their involvement in the study and data protection. Patients will be informed that their participation in the study is voluntary and that they may withdraw consent for data collection at any time. They will be informed that choosing not to participate in this study will not affect the standard of care the patient will receive. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's personally dated signature. After having obtained the consent, a copy of the ICF must be provided to the patient. The ICF that is used must be reviewed and approved in accordance with local regulations, applicable regulatory requirements and Alexion policy, and must be in a language that the patient can read and understand. Moreover, the Investigator must sign and date the informed consent form too. Each patient's signed informed and privacy consent must be kept on file by the Investigator. One copy must be given to the patient.

8.1.3. Data Protection

The Investigator must assure that the patient's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the patient's study numbers, names and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Alexion.
All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Only the patient number

will be recorded on the eCRF. Study findings stored on a computer will be stored in accordance with local data protection laws.
The Investigators will maintain a list to enable patients' records to be identified. However, if the results of the study are published, the patient's identity will remain confidential.
Personal data - including sensitive data - collected during the execution of the activities will be processed in accordance with the local laws on data protection.

8.1.4. Dissemination of Clinical Study Data

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Alexion standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

In agreement to applicable laws and regulations the final study report and/or progress reports, including interim reports of study results, if applicable and when required, will be provided to all ECs/IRBs, to the Competent Authority and to Investigators.

Alexion is entitled to publish and/or present any results of this study at scientific meetings; Alexion furthermore reserves the right to use such data for industrial purposes.

Investigators will inform Alexion before using the results of the study for publication or presentation, and agree to provide Alexion with a copy of the proposed presentation. Data from individual study sites shall not be published separately without the previous consent of Alexion.

Operative management of Medical Writing Aspects
The results of this study may be published or presented at scientific meetings. If this is the case, the Investigator agrees to submit all manuscripts or abstracts to Alexion prior to submission. This allows Alexion, respectfully of the rights relating to the ownership of the data collected, to provide comments based on information from other studies that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, Alexion will generally support publication of multi-centre studies only in their entirety and not as individual centre data. In this case, a coordinating investigator will be designated.

The Investigator has to provide Alexion all data derived by the Investigator from the study. During the study, only Alexion may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials, is the sole responsibility of Alexion.

Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared

in accordance with this section and the Study Site Agreement, which has to be written consequently.

Alexion also adheres to any additional standards concerning authorship required by a specific journal or congress to which the publication is submitted. The responsible individuals at Alexion apply, at a minimum, the following criteria to determine who is named as an author on a publication:

- Substantial contributions to the concept and design, acquisition of data, or analysis and interpretation of data
- Drafting of the publication or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authorship criteria and obligations apply equally to Alexion employees and non-employees. Each listed author must have participated in the work enough to take public responsibility for appropriate portions of the content.

Individuals contributing to the publication but not meeting authorship criteria may be appropriately acknowledged in the publication.

Ghost-writing and Guest/Ghost Authorship

Ghostwriting, guest authorship, and ghost authorship are strictly prohibited. The contribution of a writer, which, when performed under the direction of the author(s), is considered a form of specialized, technical assistance, is acknowledged in the earliest draft in which the writer is involved.

Determining Order of Authorship

Author order is determined by mutual agreement at the earliest possible time, with due consideration to overall contributions to the study, to the publication, or to scientific knowledge of the subject matter.

8.1.5. Data Quality Assurance

The designated CRO, MediNeos will assure database quality processes are followed including review of the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan

Study Monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.
The designated CRO, MediNeos will assure compliance monitoring.
Monitoring activity will include reviews of the progress of the study and compliance with protocol, SOPs, applicable regulation, Good Pharmacoepidemiology Practices (GPP), ENCePP Guide on Methodological Standards in Pharmacoepidemiology.
On site and remote study monitoring will be performed by MediNeos.
It is understood that the CRA(s)/Clinical Monitor(s) will contact and/or visit the Investigator/centre regularly throughout the study, and that they will be permitted to inspect the various study records: eCRFs, filled questionnaires (ePROs), Investigator study file and all available source data (source data, as first observation recorded elsewhere to the eCRFs), provided that patient confidentiality is respected.
The purposes of these visits/phone contacts are:

- to assess the progress of the study;
- to evaluate the compliance with the study protocol;
- to discuss any emerging issue;
- to check the eCRFs for accuracy and completeness.

In addition, during on-site visits, for a set of variables prior defined by Alexion, the monitor will validate the contents of the eCRFs against the source documents (where they are available as for clinical practice).
Prior to each on site monitoring visit, the Investigator or staff will record all data generated since the last visit on the eCRFs. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.
During each remote monitoring contact, the Investigator or staff will be expected to be available for the phone call to answer questions and to provide any missing information.

Guidelines for Epidemiological Studies

The guidelines for Good Pharmacoepidemiology Practices (GPP) in non-interventional studies as well as recommendations for non-interventional study and principles of epidemiology studies will be respected. This study is not in the scope of Good Clinical Practice (GCP) studies, but for several applicable aspects it will be managed according to it.

Investigator’s Files / Retention of Documents

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient’s file.

The physician must give Alexion (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries. No information in source documents about the identity of the patients will be disclosed.
The Investigator must maintain adequate and accurate records to enable the conduct of the study data to be subsequently verified. These documents should be classified into two different separate categories: Investigator's Study File and patient clinical source documents.
The Investigator's Study File will contain the observational protocol study/amendments, IEC/IRB and governmental approval with correspondence, sample informed and privacy form consent, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.
Patient clinical source documents would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, pathology and special assessment reports, signed informed consent forms, consultant letters and patient screening and enrolment logs. The Investigator must keep these two categories of documents on file according to local regulations after completion or discontinuation of the study. After that period, the documents may be destroyed accordingly to local regulations.
Should the Investigator wish to assign the study records to another party or move them to another location, Alexion must be notified in advance.

Audits and Inspections

This protocol has been audited by Alexion QA.

A quality assurance audit/inspection of this study may be conducted by Alexion or Alexion’s designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator’s study-related files and correspondence, and the informed consent documentation of this study at any time according to Alexion’s Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with GPP.
The Investigators and Institution must permit study-related monitoring, audits, IRBs/IECs review or regulatory inspection, providing direct access to source data/documents.

Completion of study

The IRB/IEC/competent authority will be notified about the end of the study (date of termination of observational study, last patient out date, number of patients observed) or early termination of the observation accordingly.

8.1.6. Source Documents

Investigator will complete the electronic Case Report Form (eCRF) with assessments and information according to the protocol. The study will involve both a primary data collection and secondary use of data. After patient's signature of study informed consent and privacy form, patient clinical data will be collected from the hospital medical charts of participant sites according to their ordinary clinical practice. In addition, participating patients will be asked to provide data through ePRO tools, according to routine clinical practice.

Data sources will be both medical records and eCRF (for ePRO data) according to ordinary site clinical practice that will be defined at site level and registered in first site monitoring visit on-site.

Some information useful for Pharmacoeconomics analyses (costs sustained by the patients related to the infusion visits) might not be reported in medical chart. These data can be directly recorded into the eCRF, according to standard clinical practice, meaning that the eCRF will be the relative data source.

Data sources that will be used are deemed to be appropriate for the purposes of the study.

8.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

8.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the studytreatment. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study treatment are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.] • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Special Situations (to be reported as such, irrespective of being associated to an AE or ADR)

Abuse of a medicinal product	Persistent or sporadic intentional excessive use of medicinal product which is accompanied by harmful physical or psychological effects.
Lack of efficacy / Lack of therapeutic efficacy	Lack of desired therapeutic effect after product administration
Medication Error	An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.
Misuse of a medicinal product	Situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorization.
Occupational exposure to a medicinal product	For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation.
Off-label use	Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization.
Overdose	Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information.
Pregnancy	Product use during pregnancy, where embryo or fetus may have been exposed to medicinal product (either through maternal exposure and/or if the suspected medicinal product was taken by the father).
Suspected transmission of an infectious agent	Suspected transmission of an infectious agent via the medicinal product
Breastfeeding	Exposure to medicinal product from breast milk

Definition of ADR

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

8.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" 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, which hypothetically might have caused death, if it was more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in

An SAE is defined as any untoward medical occurrence that, at any dose:
the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.2.3. Definition of SADR, NSAE, Other Relevant Safety Information, PC

A serious response to a medicinal product which is noxious and unintended. Serious response in this context means that a causal relationship between a medicinal product and and serious adverse event is at least a reasonable possibility. Serious Adverse Reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Non-Serious Adverse Event or "NSAE" means an AE that is not an SAE.

Other Relevant Safety Information means any report of a woman who is pregnant or breastfeeding while taking a medicinal product, even if there is no specific AE, any report of a lack of efficacy, overdose, abuse or misuse of a medicinal product, medication errors, or occupational exposure to a medicinal product, or any other information that may be relevant to the benefit-risk evaluation of a medicinal product.

Product Complaint or "PC" means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a finished product or its packaging after it is released for distribution. This does not include adverse drug reaction (e.g. reported as AEs), shipping errors or billing concerns.

8.2.4. Recording and Follow-Up of AE and/or SAE

Recording of AE and/or SAE
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF according to the protocol. • It is not acceptable for the Investigator to send photocopies of the participant's medical records to CRO in lieu of completion of the AE/SAE eCRF page.

Recording of AE and/or SAE

- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Other measures to evaluate AEs and SAEs may be utilized (eg, National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study treatment and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF according to the study protocol and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study treatment caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study treatment.
  - Related (ADR, SADR): There is a reasonable possibility the study treatment caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study treatment.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

Assessment of Causality
• There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to CRO. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to CRO. • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to CRO. • CRO shall forward to Sponsor via Alexion ADR form any information, including initial and follow up reports, that becomes known to CRO from any source in any form relating to a PV event for a Sponsor product as soon as it becomes available.

8.2.5. Reporting of prospective AEs, SAEs, ADRs, SADRs and special situations

AE Reporting to CRO via an Electronic Data Collection Tool
• The primary mechanism for reporting an AE to CRO will be the electronic data collection tool. • If the electronic system is unavailable at the time that the Investigator or site becomes aware of an AE, the site will use the paper Contingency Form for AE reporting via fax or email. Facsimile transmission or email may be used in the event of electronic submission failure. • all reports of AEs, SAEs, NSAEs or Other Relevant Safety Information to the Email: adverseeventreporting@alexion.com. The site will enter the AE data into the EDC system as soon as it becomes available. • CRO shall send all reports of PCs to the Email: productcomplaints@alexion.com • When further information becomes available, the EDC should be updated within 24 hours with the new information and an updated SAE report should be submitted to CRO. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new AE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the CRO, Clinical Research Associete, Medical Monitor/SAE Coordinator by telephone.

Major Adverse Vascular Events (MAVE).

A MAVE is defined as follows:

- Thrombophlebitis/deep vein thrombosis
- Pulmonary embolus
- Myocardial infarction
- Transient ischemic attack
- Unstable angina
- Renal vein thrombosis

- Acute peripheral vascular occlusion
- Mesenteric/visceral vein thrombosis or infarction
- Mesenteric/visceral arterial thrombosis or infarction
- Hepatic/portal vein thrombosis (Budd-Chiari syndrome)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Renal arterial thrombosis
- Gangrene (nontraumatic; nondiabetic)
- Amputation (nontraumatic; nondiabetic)
- Dermal thrombosis

8.3. Appendix 3: Collection of Pregnancy Information

8.3.1. Collection of Pregnancy Information

As a special situation, information on Pregnancy, breastfeeding, partner exposure have to be reported regardless of association to an AE or ADR.

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study treatment via semen following paternal exposure. If a female participant becomes pregnant during the observation period, the Investigator will first data enter it into the eCRF and then CRO will send ADR Form to Alexion.

Alexion will send to the investigator the "Pregnancy Reporting and Outcome/Breastfeeding" form as a Follow-up, consequently Investigator will fill it and send back to Alexion.

Any female participant who becomes pregnant while participating in the study will be discontinued from study.

8.3.2. Female Participants who become pregnant

The Investigator will collect pregnancy information on any female participant who becomes pregnant during the observation period. The initial Information will be recorded on eCRF and alert sent to CRO, who will transmit ADR Form onto Alexion.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study. Alexion will follow-up with the Investigator.

Reconciliation of Safety Information

CRO shall keep a written record of all AE, SAE, ADRs, SADRs, PC and Other Relevant Safety Information that it transmits to Alexion under the terms of this Section. CRO shall ensure that its written records are reconciled with Alexion no less than once per calendar month. Any discrepancies shall be dealt with immediately.

Training of Service Provider Staff

CRO shall be responsible for training the staff on identification, collection and reporting of SAEs, NSAEs, PCs and Other Relevant Safety Information to Alexion. CRO shall access the online training on AEs and PCs reporting provided by Alexion at:

Link: https://alexion.myabsorb.com/

Enrolment Key: Alexion Pharmaceuticals

ADR Form and Instructions will be provided to Service Provider by Alexion before the study starts.

8.4. Appendix 4: abbreviations

ADR: Adverse Drug Reaction
AE: Adverse Event
BMI: Body Mass Index
BTH: Breakthrough hemolysis
CIOMS: Council for International Organizations of Medical Sciences
CRF: Case Report Form
CRA: Clinical Research Associate
CRO: Contract Research Organization
eCRF: Electronic Case Report Form
ePRO: Electronic Patient Reported Outcome
EC: Ethic Committee
EMA: European Medicines Agency
ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EORTC: European Organization for Research and Treatment of Cancer
ER: Emergency Room
FACIT: Functional Assessment of Chronic Illness Therapy
FAS: Full Analysis Set
FDA: Food and Drug Authority
GCP: Good Clinical Practice
GPI: Glycosylphosphatidylinositol
GPP: Good Pharmacoepidemiology Practices
EORTC: European Organisation for Research and Treatment of Cancer
ICF: Informed Consent Form
ICH: International Council on Harmonization
ICMJE: International Committee of Medical Journal Editors
IEC: Independent Ethics Committee
IQR: Inter Quartile Range
IRB: Internal Review Board
LDH: lactate dehydrogenase
MAC: Membrane Attack Complex
MAVE: Major Adverse Vascular Event
NHS: National Health System
NIS: Non Interventional Study
NSAE: Non Serious Adverse Event
PIGA: PhosphatIdylinositol Glycan class A
PMDA: Pharmaceuticals and Medical Devices Agency
PNH: Paroxysmal nocturnal hemoglobinuria
PPQ: Patient Preference Questionnaire
QA: Quality Assurance
QoL: Quality of Life
SADR: Serious Adverse Drug Reactions
SAE: Serious Adverse Event
SAP: Statistical Analysis Plan

SmPC: Summary of Product Characteristics
SoA: Schedule of Activities
SOP: Standard Operating Procedure
SS: Safety Set
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology Statement
ULN: Upper Limit Normal
US: United States

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CONTRATTO PER LA CONDUZIONE DI STUDIO OSSERVAZIONALE
"REACTION - Utilizzo di Ravulizumab secondo pratica clinica in pazienti italiani affetti da emoglobinuria parossistica notturna: uno studio di coorte multicentrico, osservazionale, retrospettivo e prospettico"

TRA

L'Azienda Sanitaria ULSS 7 Pedemontana (d'ora innanzi denominata "Azienda"), con sede legale in Via dei Lotti, 40 - 36061 Bassano del Grappa (VI) - C.F. e P. IVA n. 00913430245, in persona del Legale Rappresentante, dott. Carlo Bramezza, in qualità di Direttore Generale munito di idonei poteri di firma del presente atto

E

La Società **Medineos S.U.R.L**., società soggetta a direzione e coordinamento di IQVIA Ltd, con sede legale in Viale Virgilio 54/U – 41123 Modena, C.F. e P. IVA n. 02041030350, in persona di suoi Procuratori speciali Dr.ssa Alessandra Ori e Dr. Giovanni Borrelli (d'ora innanzi denominata "CRO") che agisce in nome proprio e per conto di Alexion Pharma Italy S.r.l. (d'ora innanzi denominato/a "Promotore"), in forza di idonea delega conferita in data 17/11/2021

di seguito per brevità denominati/e singolarmente/collettivamente "la Parte/le Parti"

Premesso che:

- è interesse del Promotore effettuare lo studio osservazionale dal titolo: "Real Life Use of Ravulizumab in Italian PatiEnts with PAroxysmal NoCturnal Hemoglobinuria a MulTicenter ObservatIONal Retrospective and Prospective Cohort Study", titolo in italiano "Utilizzo di Ravulizumab secondo pratica clinica in pazienti italiani affetti da emoglobinuria parossistica notturna: uno studio di coorte multicentrico, osservazionale, retrospettivo e prospettico" (di seguito "Studio"), avente ad oggetto il Protocollo versione n. 1.7 del 09/11/2021 (di seguito "Protocollo"), presso l'Azienda ULSS 7 Pedemontana, sotto la responsabilità del dott. Eros Di Bona, Direttore della U.O. C. di Oncoematologia, in qualità di Responsabile scientifico dello Studio oggetto del presente Contratto (di seguito "Sperimentatore principale"), presso l'U.OC. di Oncoematologia del P.O. Bassano (di seguito "Centro di Studio");
- la CRO individua quale proprio referente scientifico per la parte di propria competenza la dott.ssa Alessandra Ori, Associate Director Clinical Operations & Office Manager. La CRO può modificare il referente scientifico per la parte di propria competenza con notifica scritta all'Azienda;
- il Centro di Studio possiede le competenze tecniche e scientifiche per lo Studio ed è struttura adeguata alla conduzione dello Studio nel rispetto della normativa vigente;
- lo Sperimentatore e i collaboratori che svolgono qualsiasi parte dello Studio sotto la supervisione dello Sperimentatore (di seguito "Co-sperimentatori") sono idonei alla conduzione dello Studio in conformità alla normativa applicabile, conoscono il Protocollo e le norme di buona pratica clinica e possiedono i requisiti normativi e regolamentari necessari, nel rispetto della normativa vigente;
- salvo quanto eventualmente, successivamente, diversamente concordato per iscritto dalle Parti, l'Azienda dovrà condurre lo Studio esclusivamente presso le proprie strutture;
- l'Azienda è dotata di apparecchiature idonee, necessarie all'esecuzione dello Studio secondo quanto indicato nel Protocollo;

- la CRO ha presentato al Comitato Etico competente di Vicenza in virtù della Determina AIFA 20.03.2008 la pratica autorizzativa utile per lo svolgimento dello Studio e ha ottenuto il Parere favorevole in data 14/02/2023;
- in data 23/02/2022, il Comitato Etico competente dell'Università La Sapienza di Roma e coordinatore in Italia per lo studio ha espresso Parere Unico favorevole all'effettuazione dello Studio presso l'Azienda.

Tutto ciò premesso, tra le Parti si conviene e si stipula quanto segue:

1. Premesse

1.1. Le premesse, il Protocollo, anche se non materialmente accluso, e tutti gli allegati, incluso il budget (Allegato A) e il glossario relativo alla protezione dati personali (Allegato B), fanno parte integrante e sostanziale del presente Contratto.

2. Oggetto

2.1 La CRO per conto del Promotore affida all'Azienda l'esecuzione dello Studio alle condizioni indicate nel presente Contratto, in accordo col Protocollo, con gli eventuali successivi emendamenti, nonché con le modifiche al presente Contratto/budget da questi derivanti e formalizzate mediante i necessari atti di modifica tempestivamente sottoscritti.

2.2 Lo Studio deve essere condotto nel più scrupoloso rispetto del Protocollo, nella versione vigente, accettata dallo Sperimentatore principale e approvata dal Comitato Etico e dall'Autorità Competente, in conformità alla vigente normativa in materia di sperimentazioni cliniche di medicinali e ai principi etici e deontologici che ispirano l'attività medica dei professionisti a vario titolo coinvolti.

2.3 Lo Studio deve essere altresì condotto in conformità ai principi contenuti nella Convenzione sui Diritti dell'Uomo e la Biomedicina, nella Dichiarazione di Helsinki nella versione aggiornata, nelle vigenti regole della Buona Pratica Clinica, e in conformità delle leggi applicabili in tema di trasparenza e prevenzione della corruzione, nonché di protezione dei dati personali secondo la normativa vigente.

2.4 Con la sottoscrizione del presente Contratto, le Parti dichiarano di conoscere e accettare il contenuto di quanto sopra richiamato.

2.5 Poiché lo Studio prevede l'arruolamento competitivo dei pazienti, è prevista da parte dell'Azienda l'inclusione di circa 4 soggetti, con il limite del numero massimo di 120 pazienti candidabili allo Studio a livello nazionale e nei termini previsti dal Promotore. Il periodo previsto di inclusione è suscettibile di modifiche in funzione del suo andamento anche a livello nazionale. Al raggiungimento del numero totale dei pazienti previsti per l'intero Studio, l'inclusione di ulteriori pazienti verrà automaticamente chiusa, indipendentemente dal numero di pazienti inclusi presso l'Azienda, a eccezione dei pazienti che hanno già fornito il loro consenso a partecipare allo Studio, a meno che essi stessi non ritirino il consenso. Il Promotore tramite la CRO provvederà a inviare all'Azienda adeguata e tempestiva comunicazione.

2.6 Le Parti prendono atto che un eventuale aumento del numero di pazienti da arruolare oltre il numero di pazienti attesi presso il centro di ricerca dell'Azienda, dovrà essere preventivamente concordato tra lo Sperimentatore principale e la CRO. Resta inteso che l'aumento della casistica, effettuato alle suddette condizioni, non richiede la stipula di un atto integrativo alla presente Convenzione.

2.7 L'Azienda e il Promotore conserveranno la documentazione inerente lo Studio (fascicolo permanente "*trial master file"*) per il periodo di tempo secondo le specifiche indicate dalla vigente legislazione. L'Azienda si impegna, alla data del presente provvedimento, a conservare la documentazione per un periodo di sette anni (o per un periodo più lungo, qualora ciò sia richiesto da altre norme applicabili o da un accordo economico tra Azienda e Promotore).

2.8 Indipendentemente dal fatto che l'archiviazione della documentazione inerente lo Studio riguardi o meno dati personali (di natura particolare o meno), secondo la definizione del Regolamento (UE) n. 679/2016, l'Azienda e il Promotore dovranno adottare tutte le misure fisiche e tecniche di cui all'art. 32 del citato Regolamento (UE) n. 679/2016 ed effettuare gli eventuali controlli di sicurezza previsti dalla ISO 27011 e sue successive modificazioni, a protezione di dati, informazioni e documenti (sia cartacei che elettronici). Il sistema di archiviazione adottato dovrà garantire non solo l'integrità dei dati, delle informazioni e dei documenti cartacei ed elettronici, ma altresì la loro futura leggibilità per tutto il periodo previsto dall'obbligo di conservazione. Per l'espletamento di tale obbligazione, sia il Promotore che l'Azienda potranno avvalersi di soggetti esterni che gestiscano tale obbligo di archiviazione.

2.9 Il Promotore, l'Azienda e lo Sperimentatore principale devono rispettare le direttive, le indicazioni, le istruzioni e le raccomandazioni impartite dal Comitato Etico e dall'Autorità competente.

3. Sperimentatore principale e Co-sperimentatori

3.1 Lo Sperimentatore principale sarà coadiuvato nell'esecuzione dello Studio dal personale, sanitario e non sanitario, nonché da eventuali collaboratori incaricati dall'Azienda stessa, designati dallo stesso e operanti sotto la sua responsabilità per gli aspetti relativi al presente Studio, che sia qualificato per la conduzione dello Studio, che abbia ricevuto preventivamente adeguata formazione prevista dalla normativa vigente dalla CRO e che abbia manifestato la propria disponibilità a partecipare allo Studio (di seguito "Co-sperimentatori"). Fermo quanto precede, non rientra nella definizione di "Sperimentatori" il personale medico e non medico che nell'ambito dello Studio svolga attività istituzionale propria (ad es. farmacisti ospedalieri che allestiscono i medicinali sperimentali).

3.2 Le Parti prendono atto che lo Sperimentatore principale è tenuto a ogni responsabilità e obbligo imposti a tale figura dalla normativa vigente in materia di sperimentazioni cliniche di medicinali.

3.3 Il presente rapporto intercorre tra la CRO e l'Azienda. La CRO è estranea a rapporti esistenti tra l'Azienda, lo Sperimentatore principale e Co-sperimentatori, restando quindi sollevata da qualsiasi pretesa che il personale dell'Azienda coinvolto nello studio dovesse avanzare in relazione allo Studio.

3.4 In relazione allo Studio oggetto del presente Contratto, è fatto divieto allo Sperimentatore principale e ai Co-sperimentatori di ricevere, direttamente o indirettamente, compensi dal Promotore/CRO, così come di avere contatti o di intrattenere con il Promotore/CRO rapporti di qualsiasi natura, che non siano di carattere tecnico scientifico.

3.5 Qualora il rapporto tra lo Sperimentatore principale e l'Azienda dovesse per qualsiasi ragione concludersi, l'Azienda deve informarne tempestivamente per iscritto la CRO, indicando il nominativo di un sostituto. L'indicazione del sostituto deve essere oggetto di approvazione da parte del Promotore e del Comitato Etico competente. L'Azienda garantisce che il nuovo Sperimentatore principale abbia i requisiti idonei a proseguirlo, accetti i termini e le condizioni del presente Contratto e assuma l'impegno di rispettare il Protocollo nell'esecuzione dello Studio. Nelle more

dell'approvazione dell'emendamento sostanziale di cambio dello Sperimentatore principale, lo sperimentatore indicato dal Promotore garantisce la necessaria attività sperimentale.
Nel caso in cui il Promotore non intenda accettare il nominativo del sostituto proposto dall'Azienda oppure questi non proponga un sostituto, la CRO potrà recedere dal presente Contratto in accordo a quanto previsto dall'art. 6.

3.6 Lo Sperimentatore principale prima di iniziare lo Studio, deve acquisire il consenso informato del paziente o del suo rappresentante legale, secondo quanto previsto dalla vigente normativa in materia di sperimentazioni cliniche e di studi osservazionali, oltre che ai sensi e per gli effetti del Regolamento (UE) 2016/679 e relativa normativa italiana di adeguamento (D.Lgs. n.196 del 30 Giugno 2003, così come modificato dal D.Lgs. n. 101 del 10 Agosto 2018).
Deve essere prestato anche il consenso al trattamento dei dati personali ai sensi e per gli effetti della vigente normativa nazionale e comunitaria in materia di protezione dei dati personali e sue successive modificazioni, come successivamente declinato all'art. 10, fatte salve ipotesi in cui siano applicabili prescrizioni specifiche dettate dall'Autorità sulla protezione dei dati personali che permettano il trattamento dei dati personali anche in assenza di consenso.

3.7 Lo Sperimentatore principale deve fornire informazioni alla CRO e al Comitato Etico in merito all'andamento dello Studio e comunicare tempestivamente alla CRO l'eventuale verificarsi di eventi avversi seri, fatti salvi gli eventuali obblighi di segnalazione al Comitato Etico previsti dalla vigente normativa, e oltre ogni altra informazione clinica di rilievo per la conduzione dello studio indicato nel Protocollo (ad esempio gravidanza) direttamente o indirettamente correlabili all'esecuzione dello Studio, secondo quanto previsto dal Protocollo dello Studio, dalle norme di Buona Pratica Clinica e dalla normativa applicabile in materia di farmacovigilanza e sperimentazioni cliniche di medicinali.

3.8 L'Azienda garantirà che lo Sperimentatore principale si impegni altresì a garantire lo svolgimento dello Studio secondo i più elevati standard di diligenza.

3.8.1 Lo Sperimentatore principale deve compilare tutte le Schede Raccolta Dati (Case Report Forms-CRF) correttamente, secondo termini e modalità previsti dal Protocollo dello Studio e dalla normativa applicabile, in formato cartaceo o elettronico, e comunque con tempestività come da GCP, entro i termini previsti dal Protocollo dello Studio.

3.8.2 Lo Sperimentatore principale si impegna altresì a risolvere le richieste di chiarimento (*queries*) generate dalla CRO entro i termini previsti dal Protocollo.

3.8.3 Per verificare la corrispondenza tra i dati registrati nelle Schede Raccolta Dati e quelli contenuti nei documenti originali (per es. cartella clinica), l'Azienda e lo Sperimentatore principale consentono l'accesso diretto ai dati originali durante le visite di monitoraggio e nel corso di eventuali *audit* promossi da Promotore/CRO e ispezioni da parte delle Autorità Competenti, incluse le modalità da remoto, purché non vengano violate le norme in materia di riservatezza e di protezione dei dati personali dei pazienti.

3.8.4 L'Azienda e lo Sperimentatore principale, informati con congruo preavviso, devono consentire il corretto svolgimento dell'attività di monitoraggio e di auditing presso il Centro di Studio da parte del personale del Promotore/CRO e da parte dell'Autorità Competente, attività effettuate per garantire la regolare esecuzione dello Studio.

3.9 Per quanto in ambito infrastrutture di rete e sistemi informatici, la CRO garantisce inoltre che l'utilizzo della e-CRF nell'ambito dello studio non comporta per l'Azienda oneri di assistenza, modifica o aggiornamento della rete informatica in tutte le sue componenti hardware/software e quindi che non determina per l'Azienda l'inadempimento degli obblighi contrattuali verso i fornitori diretti dell'Azienda.

3.10 L'Azienda avviserà tempestivamente il Promotore qualora un'Autorità Competente comunichi all'Azienda un avviso di ispezione/*audit* relativo allo Studio e, se non negato espressamente dall'Autorità Competente, l'Azienda autorizzerà il Promotore a parteciparvi, inviando nel contempo al Promotore ogni comunicazione scritta ricevuta e/o trasmessa ai fini o in risultanza dell'ispezione/*audit*.

3.11 Tali attività non devono però pregiudicare in alcun modo lo svolgimento dell'ordinaria attività istituzionale dell' Azienda.

4. Materiali per la conduzione dello Studio

4.1 Il Promotore si impegna a fornire gratuitamente all' Azienda , per tutta la durata dello Studio e nelle quantità necessarie e sufficienti all'esecuzione dello Studio, ogni materiale necessario all'esecuzione dello Studio (di seguito "Materiali").

5. Aspetti Economici e Corrispettivo

La CRO ha provveduto a versare alle Aziende la somma di 4.000,00 euro di cui il 70% (2.800,00 euro+ 2,00 euro di bollo) all'Azienda Ulss 8 Berica di Vicenza sede del CESC per la valutazione della ricerca e il 30% (1.200,00 euro +2,00 euro di bollo) al NRC Azienda Ulss7 Pedemontana sede dello Studio.

La CRO si impegna a versare la quota per il monitoraggio clinico dello studio prevista dalla vigente normativa della Regione Veneto (Deliberazione della Giunta Regionale Veneta n. 1066 del 28.06.2013 – Allegato B) pari ad 1.500,00 euro +IVA, come corrispettivo per la verifica dell'andamento dello studio, da versare entro 30 giorni dalla firma del Contratto secondo le modalità concordate con l'Azienda.

5.1 Il corrispettivo pattuito per paziente eleggibile, valutabile e completato secondo il Protocollo e per il quale è stata compilata validamente la relativa CRF/eCRF (ivi inclusi i questionari cartacei previsti), comprensivo di tutte le spese sostenute dall'Azienda per l'esecuzione del presente Studio e dei costi a compensazione di tutte le attività ad essa collegate, è pari ad € 1.000,00 (mille/00)+ IVA per paziente (e complessivi € 4.000,00 + IVA per n. 4 pazienti), come meglio dettagliato nel Budget qui allegato (Allegato A parte 1).

5.2 La CRO si impegna a corrispondere, a seguito dell'anticipazione da parte del Promotore delle relative somme, quanto dovuto ai sensi del presente articolo sulla base di quanto risulta da adeguato prospetto/rendiconto giustificativo, concordato tra le Parti.
Il pagamento del compenso di cui sopra verrà effettuato con la cadenza indicata nel Budget (Allegato A) sulla base del numero dei pazienti coinvolti nel relativo periodo, delle visite di follow-up effettuate secondo Protocollo e in presenza delle relative CRF/eCRF (ivi inclusi i questionari cartacei previsti) debitamente compilate e ritenute valide da CRO in base alle attività svolte.

5.3 L'Azienda non riceverà alcun compenso per pazienti non valutabili a causa di inosservanza del Protocollo, di violazione delle norme di Buona Pratica Clinica o di mancato rispetto della normativa vigente in materia di sperimentazioni cliniche di medicinali. L'Azienda non avrà diritto ad alcun compenso anche per pazienti coinvolti successivamente alla comunicazione di interruzione e/o conclusione dello Studio da parte del Promotore/CRO od oltre il numero massimo di soggetti da includere ai sensi del presente Contratto, ove non concordati con il Promotore.

5.4 Se nel corso dello svolgimento dello Studio si rendesse necessario aumentare il supporto economico a favore dell'Azienda , CRO potrà integrare, con un addendum/emendamento, il presente Contratto, prevedendo l'adeguato aumento del Budget qui allegato.

5.5 In ottemperanza alla Legge di Bilancio 2018 (comma 909) che prevede l'obbligo della fatturazione elettronica per le cessioni di beni e per la prestazione di servizi anche tra privati, l 'Azienda emetterà fatture tramite il formato XML (Extensible Markup Language) e trasmesse tramite il Sistema di Interscambio (SDI).
CRO comunica i dati necessari per l'emissione della fattura elettronica:
RAGIONE SOCIALE: Medineos S.U.R.L.
CODICE DESTINATARIO: M5UXCR1
C.F. /P.IVA 02041030350
PEC: medineos@pec.it
e richiede invio a mezzo email a: accounting@medineos.com

5.6 I pagamenti effettuati per i servizi svolti dall' Azienda (i) rappresentano il corretto valore di mercato di detti servizi, poiché adeguati rispetto al tariffario applicabile presso l'Azienda, (ii) sono stati negoziati a condizioni commerciali normali e (iii) non sono stati definiti sulla base del volume o valore di prescrizioni o comunque in riferimento a tali prescrizioni o altre attività economiche che si generino fra le Parti. A fronte delle attività svolte o delle spese sostenute includendo i Pazienti nello Studio, al cui pagamento il Promotore tramite la CRO sia tenuto, né l'Azienda né lo Sperimentatore principale chiederanno altri rimborsi o corrispettivi ad altri soggetti.

6. Durata, Recesso e Risoluzione

6.1 Il presente Contratto produrrà effetti a partire dalla data di ultima sottoscrizione ("Data di decorrenza") e rimarrà in vigore sino all'effettiva conclusione dello Studio presso l'Azienda , così come previsto nel Protocollo di studio, salvo eventuali modifiche concordate tra le Parti.
Fermo restando quanto sopra, il presente Contratto produrrà i suoi effetti a seguito del rilascio di formale autorizzazione da parte dell'Autorità Competente.

6.2 L'Azienda si riserva il diritto di recedere dal presente Contratto mediante comunicazione scritta e con preavviso di 30 giorni da inoltrare a CRO con raccomandata A.R. o PEC nei casi di:
- insolvenza della CRO, proposizione di concordati anche stragiudiziali con i creditori del Promotore o avvio di procedure esecutive nei confronti della CRO. Qualora la situazione sopra indicata riguardi la CRO, il Promotore sarà tenuto a subentrarle e proseguire l'attività, qualora non procuri l'intervento di un'altra CRO, approvata dall'Azienda, in sostituzione di quella divenuta insolvente;
- cessione di tutti o di parte dei beni della CRO ai creditori o definizione con gli stessi di un accordo per la moratoria dei debiti.

Il preavviso avrà effetto dal momento del ricevimento da parte della CRO della comunicazione di cui sopra.

6.3 La CRO, ai sensi dell'art. 1373, comma secondo, Codice Civile, si riserva il diritto di recedere dal presente Contratto in qualunque momento per giustificati motivi mediante comunicazione scritta inviata a mezzo raccomandata A.R. o PEC, con preavviso di 30 giorni. Tale preavviso avrà effetto dal momento del ricevimento da parte dell' Azienda di detta comunicazione.
In caso di recesso della CRO sono comunque fatti salvi gli obblighi assunti e le spese effettuate dall'Azienda alla data della comunicazione di recesso. In particolare, la CRO corrisponderà all'Azienda tutte le spese documentate e non revocabili che questo abbia sostenuto al fine di garantire la corretta ed efficace esecuzione dello Studio *(ove applicabile*, incluse le spese sostenute dall'Azienda nei confronti dei pazienti-partecipanti), nonché i compensi sino a quel momento maturati.

In caso di recesso anticipato, il Promotore ha diritto di ricevere, quale proprietario a titolo originario, tutti i dati e risultati, anche parziali, ottenuti dall'Azienda nel corso dello Studio e anche successivamente, se derivanti da o correlati a esso.

6.4 Le Parti prendono atto che un eventuale aumento della durata del presente contratto per il prosieguo delle attività presso il centro di ricerca dell'Azienda nell'ambito dello Studio è in relazione all'andamento dell'arruolamento complessivo dei pazienti ed al raggiungimento degli obiettivi previsti dal Protocollo. Resta inteso che la proroga del presente contratto, effettuato alle suddette condizioni, non richiede la stipula di un atto integrativo alla presente Convenzione.

6.5 Resta peraltro inteso che lo scioglimento anticipato del Contratto non comporterà alcun diritto di una Parte di avanzare nei confronti dell'altra pretese risarcitorie o richieste di pagamento ulteriori rispetto a quanto convenuto.

6.6 Gli effetti del presente Contratto cesseranno automaticamente ai sensi dell'art. 1454 del Codice Civile italiano nel caso in cui una delle Parti non abbia adempiuto a uno dei principali obblighi previsti dal presente Contratto entro 30 giorni dalla richiesta scritta di adempimento presentata dall'altra Parte.
Resta in ogni caso salva l'applicabilità dell'art. 1218 e seguenti del Codice Civile.

6.7 In caso di risoluzione del presente Contratto, non derivante da violazioni da parte dell' Azienda, questa avrà diritto al rimborso delle spese effettivamente sostenute per lo Studio prima del ricevimento della notifica di risoluzione e a un compenso per i servizi proporzionale all'attività svolta sino al momento della risoluzione. L'Azienda si impegna a restituire alla CRO eventuali importi già liquidati e relativi ad attività non svolte.

6.8 In tutti i casi di interruzione o di risoluzione del presente Contratto, sarà attuata ogni precauzione per garantire la massima tutela dei pazienti già coinvolti, in accordo con quanto previsto dal Protocollo approvato dal Comitato Etico, garantendo, laddove ritenuta clinicamente necessaria, la continuità terapeutica.

7. Copertura assicurativa

7.1 Le Parti riconoscono che, trattandosi di studio osservazionale senza procedure diagnostiche e/o terapeutiche divergenti dalla normale pratica clinica, ai sensi della Determinazione AIFA del 20/03/2008, non è necessario stipulare specifica polizza assicurativa per la responsabilità civile verso i pazienti, la cui copertura ricade nel programma di gestione del rischio nell'ambito della normale pratica clinica.

8. Relazione finale, titolarità e utilizzazione dei risultati

8.1 Il Promotore si impegna a divulgare tutti i risultati dello Studio anche qualora negativi.

8.2 Il Promotore assume la responsabilità della preparazione del rapporto clinico finale e dell'invio entro i termini previsti dalla normativa allo Sperimentatore principale e al Comitato Etico del riassunto dei risultati dello Studio stesso.

8.3 Tutti i dati derivanti dall'esecuzione dello Studio e nel perseguimento degli obiettivi dello stesso, trattati ai sensi dell'art. 10, e i risultati di questo, sono di proprietà esclusiva del Promotore.

A fronte di una procedura attivata dal Promotore per il deposito di una domanda di brevetto avente a oggetto invenzioni ricavate nel corso dello Studio, l'Azienda e lo Sperimentatore principale si impegnano a fornire tutto il supporto, anche documentale, utile a tal fine.

8.4 Le Parti riconoscono reciprocamente che resteranno titolari dei diritti di proprietà industriale e intellettuale relativi alle proprie pregresse conoscenze (*background knowledge*) e alle proprie conoscenze sviluppate o ottenute nel corso dello Studio, ma a prescindere e indipendentemente dalla sua conduzione e dai suoi obiettivi (*sideground knowledge*).

8.5 Le disposizioni del presente articolo resteranno valide ed efficaci anche dopo la risoluzione o la cessazione degli effetti del presente Contratto**.**

9. Segretezza e Diffusione dei dati

9.1 Con la sottoscrizione del presente Contratto, l'Azienda si impegna a mantenere riservate e confidenziali tutte le informazioni di natura tecnica e commerciale, contenute nella documentazione e nel materiale sperimentale messo a disposizione dal Promotore/CRO e/o sviluppato nel corso dello Studio e nel perseguimento degli obiettivi dello stesso, classificabili come "Segreti Commerciali" ai sensi degli art. 98 e 99 del Codice della Proprietà Industriale (D. Lgs. n. 30/2005, come modificato dal D. Lgs. n. 63/2018 in recepimento della Direttiva UE 2016/943), adottando ogni misura (di carattere contrattuale, tecnologico o fisico) idonea per la loro protezione, anche nei confronti di propri dipendenti, collaboratori, sub-appaltatori, danti o aventi causa.
La CRO inoltre dichiara e garantisce quanto segue:
(i) i Segreti Commerciali del Promotore sono stati acquisiti, utilizzati e rivelati lecitamente e non vi sono – per quanto al Promotore e/o CRO noto – azioni giudiziarie, contestazioni, richieste di risarcimento o di indennizzo promosse anche in via stragiudiziale, da parte di terzi rivendicanti la titolarità di tali segreti.
(ii) Pertanto, terrà indenne e manleverà l'Azienda da azioni giudiziarie, contestazioni, richieste di risarcimento o di indennizzo promosse anche in via stragiudiziale, da parte di terzi rivendicanti la titolarità di tali segreti.
A sua volta, con la sottoscrizione del presente Contratto, il Promotore e la CRO si impegnano a mantenere riservate e confidenziali tutte le informazioni di natura tecnica e commerciale, contenute nella documentazione e nel materiale sperimentale messo a disposizione dall'Azienda, classificabili come "Segreti Commerciali" ai sensi degli art. 98 e 99 del Codice della Proprietà Industriale, adottando ogni misura (di carattere contrattuale, tecnologico o fisico) idonea per la loro protezione, anche nei confronti di propri dipendenti, collaboratori, appaltatori, ulteriori sub-appaltatori, danti o aventi causa.
L'Azienda inoltre dichiara e garantisce quanto segue:
(i) i Segreti Commerciali dell'Azienda sono stati acquisiti, utilizzati e rivelati lecitamente e non vi sono - per quanto all'Azienda noto - azioni giudiziarie, contestazioni, richieste di risarcimento o di indennizzo promosse anche in via stragiudiziale, da parte di terzi rivendicanti la titolarità di tali segreti.
(ii) Pertanto, l'Azienda terrà indenne e manleverà il Promotore da azioni giudiziarie, contestazioni, richieste di risarcimento o di indennizzo promosse anche in via stragiudiziale, da parte di terzi rivendicanti la titolarità di tali segreti.

9.2 Le Parti sono obbligate all'adeguata e corretta diffusione e pubblicazione dei risultati dello Studio e all'adeguata comunicazione dei risultati dello Studio ai pazienti partecipanti e ai rappresentanti dei pazienti. Il Promotore, ai sensi della vigente normativa, è tenuto a rendere pubblici tempestivamente, non appena disponibili da parte di tutti i Centri partecipanti e comunque non oltre 12 mesi dalla conclusione dello Studio, i risultati, anche eventualmente negativi, ottenuti a conclusione dello Studio.

Ai sensi dell'art. 5, comma secondo, lett. c) del D.M. 8 febbraio 2013, lo Sperimentatore principale ha diritto di diffondere e pubblicare, senza limitazione alcuna, i risultati dello Studio ottenuti presso l'Azienda, nel rispetto delle disposizioni vigenti in materia di riservatezza dei dati sensibili, di protezione dei dati personali e di tutela della proprietà intellettuale, nonché nel rispetto dei termini e delle condizioni di cui al presente Contratto.

9.3 Per garantire la correttezza della raccolta e la veridicità dell'elaborazione dei dati, lo Sperimentatore principale dovrà trasmettere al Promotore copia del documento oggetto di presentazione o di pubblicazione almeno 60 giorni prima della sua presentazione o pubblicazione. Il Promotore avrà 60 giorni, dal ricevimento del manoscritto, per poter suggerire modifiche allo Sperimentatore principale. Nel caso in cui dovessero sorgere questioni relative all'integrità scientifica del documento e/o questioni afferenti agli aspetti regolatori, brevettuali o di tutela della proprietà intellettuale, il Promotore provvederà al riesame del documento unitamente allo Sperimentatore principale. Lo Sperimentatore principale accetterà di effettuare le modifiche suggerite dal Promotore o tenere conto dei suggerimenti del Promotore nella pubblicazione o presentazione, solo se necessarie ai fini della tutela della riservatezza delle informazioni e dei dati personali e della tutela della proprietà intellettuale, purché non in contrasto con l'attendibilità dei dati, con i diritti, la sicurezza e il benessere dei pazienti.

9.4 Il Promotore riconosce di non aver diritto di chiedere l'eliminazione delle informazioni contenute nel documento e non dovrà modificarne il contenuto, salvo quando tali richieste e modifiche siano necessarie ai fini della validità scientifica, della tutela della riservatezza dei dati, della protezione dei dati personali e della tutela della proprietà intellettuale.

9.5 Il Promotore, allo scopo di presentare una richiesta di brevetto e qualora risulti necessario, potrà chiedere allo Sperimentatore principale di differire di ulteriori 90 giorni la pubblicazione o presentazione del documento.
Lo Sperimentatore principale non potrà pubblicare i dati del proprio Centro sino a che tutti i risultati dello Studio siano stati integralmente pubblicati ovvero per almeno 12 mesi dalla conclusione dello Studio, dalla sua interruzione o chiusura anticipata.
Laddove la pubblicazione recante i risultati di uno Studio multicentrico ad opera del Promotore, o del terzo da questi designato, non venga effettuata entro 12 mesi dalla fine dello Studio multicentrico, lo Sperimentatore potrà pubblicare i risultati ottenuti presso l'Azienda, nel rispetto di quanto contenuto nel presente articolo.

10. Protezione dei dati personali

10.1 Le Parti nell'esecuzione delle attività previste dal presente Contratto si impegnano a trattare i dati personali, di cui vengano per qualsiasi motivo a conoscenza durante lo Studio, nel rispetto degli obiettivi di cui ai precedenti articoli e in conformità a quanto disposto dal Regolamento (UE) 2016/679 del Parlamento Europeo e del Consiglio del 27 aprile 2016, nonché dalle correlate disposizioni legislative e amministrative nazionali vigenti, con le loro eventuali successive modifiche e/o integrazioni (di seguito, collettivamente, "Leggi in materia di Protezione dei dati").

10.2 I termini utilizzati nel presente articolo, nel Contratto, nella documentazione di informativa e consenso e in ogni altro documento utilizzato per le finalità dello Studio devono essere intesi e utilizzati secondo il significato a essi attribuito nell'Allegato B.

10.3 L'Azienda e il Promotore si qualificano come autonomi Titolari del trattamento ai sensi dell'art. 4 paragrafo 17) del RGPD.

La CRO Medineos si qualifica come Responsabile del trattamento, ai sensi dell'art. 28 del RGPD, in riferimento alla titolarità del Promotore.

10.4 Per le finalità dello Studio saranno trattati dati personali riferiti alle seguenti categorie di interessati: soggetti partecipanti allo Studio; persone che operano per le Parti. Tali interessati sono informati sul trattamento che li riguarda a mezzo di idonea informativa. Rispetto a tali dati, la CRO è anch'essa autonomo Titolare del trattamento dati, con la finalità di comunicazioni a fini di divulgazione/ricerca scientifica. Per le finalità dello Studio saranno trattati le seguenti tipologie di dati personali: dati di cui all'art. 4 n. 1 del RGPD; dati rientranti nelle categorie "particolari" di dati personali - e in particolare dati relativi alla salute e alla vita sessuale, dati genetici - di cui all'art. 9 del RGPD. Tali dati saranno trattati nel rispetto dei principi di liceità, correttezza, trasparenza, adeguatezza, pertinenza e necessità di cui all'art.5, paragrafo 1 del RGPD.

10.5 Il Promotore potrà trasmettere i dati ad affiliate del gruppo del Promotore e a terzi operanti per suo conto, anche all'estero, in paesi al di fuori dell'Unione Europea che non offrono lo stesso livello di tutela della privacy garantito in Europa. In questo caso il Promotore si responsabilizza circa l'adozione di tutte le misure necessarie a garantire una adeguata protezione dei dati personali.

10.6 Le Parti garantiscono che le persone da esse autorizzate a trattare dati personali per le finalità dello Studio rispettino i principi posti a tutela del diritto alla protezione dei dati personali e del diritto alla riservatezza, e che le persone che hanno accesso ai dati personali siano obbligati a trattarli in conformità alle istruzioni dettate, in coerenza con il presente articolo, dal titolare di riferimento.

10.7 Lo Sperimentatore principale è individuato dall'Azienda quale persona autorizzata al trattamento ai sensi dell'art. 29 del RGPD e quale soggetto designato ai sensi dell'art. 2 quaterdecies del Codice.

10.8 Lo Sperimentatore principale, quando prescritto, deve informare in modo chiaro e completo, prima che abbia inizio lo Studio (incluse le relative fasi prodromiche e di screening) ogni paziente circa natura, finalità, risultati, conseguenze, rischi e modalità del trattamento dei dati personali; in particolare il paziente deve inoltre essere informato che Autorità nazionali e straniere, nonché il Comitato Etico, potranno accedere, nell'ambito di attività di monitoraggio, verifica e controllo sulla ricerca, alla documentazione relativa allo Studio così come anche alla documentazione sanitaria originale del paziente, e che ad esse potranno anche eccedere in visione, nell'ambito delle rispettive competenze, Monitor e Auditor.

10.9 Lo Sperimentatore principale deve acquisire dal paziente debitamente informato il documento di consenso oltre che alla partecipazione allo Studio, anche al trattamento dei dati. L'Azienda è responsabile della conservazione di tale documento.

10.10 Qualora una Parte accerti una violazione dei dati personali, si impegna a comunicarlo all'altra entro 48 ore dall'accertamento della violazione, ferma restando l'autonomia della stessa nella valutazione della sussistenza delle condizioni e nell'adempimento degli obblighi previsti dagli artt. 33 e 34 del RGPD.

11. Modifiche

11.1 Il presente Contratto e i relativi allegati/addendum, unitamente al Protocollo quale parte integrante, costituisce l'intero accordo tra le Parti.

11.2 Il Contratto può essere modificato/integrato solo con il consenso scritto di entrambe le Parti. Le eventuali modifiche saranno oggetto di addendum al presente Contratto e decorreranno dalla data della loro sottoscrizione, salvo diverso accordo tra le Parti.

12. Disciplina anti-corruzione

12.1 L'Azienda e il Promotore/CRO si impegnano a rispettare la normativa anticorruzione applicabile in Italia.

12.2 Il Promotore dichiara di aver adottato misure di vigilanza e controllo ai fini del rispetto e dell'attuazione delle previsioni del D. Lgs. 8 giugno 2001 n. 231, nonché, in quanto applicabili e non in contrasto con la normativa vigente in Italia, i principi del *Foreign Corrupt Practices Act* degli Stati Uniti, e loro successive modifiche e integrazioni. L'Azienda e le sue strutture cliniche e amministrative, si impegnano a collaborare in buona fede, nei limiti di quanto previsto dalla normativa italiana di cui sopra, con il personale e il management del Promotore al fine di facilitare la piena e corretta attuazione degli obblighi che ne derivano e l'attuazione delle procedure operative a tal fine messe a punto dal Promotore.

12.3 Ai sensi e per gli effetti della L. n. 190 del 06 novembre 2012 ("Legge Anticorruzione") e sue successive modificazioni, l'Azienda dichiara di avere adottato il Piano Triennale per la prevenzione della corruzione con deliberazione n.170 del 30/01/2023, di cui è possibile prendere visione alla pagina web istituzionale, sezione Amministrazione Trasparente dell'Azienda Ulss 7 Pedemontana, e il proprio codice di comportamento approvato con deliberazione n. 2358 del 16/12/2022 pure pubblicato sul sito web istituzionale.

Il Promotore dichiara di aver adottato il proprio Codice etico, di cui è possibile prendere visione alla pagina web www.alexion.com.

12.4 L'Azienda e il Promotore s'impegnano reciprocamente a informare immediatamente l'altra Parte circa ogni eventuale violazione del presente articolo di cui venga a conoscenza e a rendere disponibili tutti i dati informativi e la documentazione per ogni opportuna verifica.

12.5 La CRO e il Promotore possono divulgare per qualsiasi scopo legittimo, nei limiti della normativa sul trattamento dei dati, i termini del presente Contratto o di qualsiasi suo emendamento.

12.6 La violazione di quanto previsto da questo articolo costituisce grave inadempimento del presente Contratto ai sensi e per gli effetti di cui all'art. 1456 Codice Civile, risultando pregiudicato il rapporto di fiducia tra le Parti.

12.7 Le Parti e i loro dipendenti e rappresentanti: (i) non si offriranno di emettere, fare, promettere, autorizzare o accettare pagamenti o dare qualsiasi cosa di valore, incluso ma non limitato a tangenti, direttamente o indirettamente a qualsiasi funzionario pubblico, autorità o chiunque altro al fine di influenzare, indurre o premiare qualsiasi atto, omissione o decisione al fine di garantire un vantaggio improprio, o ottenere o mantenere affari; e (ii) devono rispettare tutte le Leggi applicabili anticorruzione. Le Parti, i loro dipendenti e rappresentanti non devono emettere o accettare pagamenti, fornire o accettare alcun regalo in relazione ai Servizi da fornire ai sensi del presente Accordo. Le Parti comunicheranno immediatamente al Promotore, eventuali violazioni degli obblighi delle Parti di cui alla presente sezione, non appena ne verranno a conoscenza.

12.8 L'Azienda e lo Sperimentatore principale inoltre rappresentano e garantiscono che non impiegheranno o altrimenti utilizzeranno in futuro qualsiasi persona interdetta all'assunzione di

incarichi pubblici ai sensi di qualsiasi legge applicabile nel paese in cui le attività dello Studio saranno svolte.

12.9 L'Azienda e lo Sperimentatore principale acconsentono e accettano di fornire tutte le informazioni a CRO e/o Promotore necessarie per conformarsi agli obblighi di divulgazione richiesti da qualsiasi autorità sanitaria competente (compresa, se applicabile, FDA statunitense), associazione di categoria pertinente o organismo simile (es. EFPIA), o altre leggi nazionali o locali applicabili, comprese le informazioni richieste da divulgare in relazione a qualsiasi relazione finanziaria tra il Promotore e le sue affiliate da una parte, e dall'altra parte, l'Azienda e Sperimentatore/qualsiasi co-Sperimentatore coinvolto nello studio e qualsiasi altro agente o dipendente dell'Azienda o Sperimentatore.

13. Trasferimento diritti, cessione del Contratto e sub-appalto

13.1 Il presente Contratto ha carattere fiduciario e, pertanto, le Parti non possono cedere o trasferire o subappaltare lo stesso a terzi, senza il preventivo consenso scritto dell'altra Parte.
Ogni Parte acconsente a che l'altra Parte possa cedere e/o trasferire in tutto o in parte i diritti e gli obblighi a lui pervenuti direttamente o indirettamente dalla firma del presente Contratto a un suo successore o ad una società collegata o a soggetti terzi, previa accettazione del cessionario di tutte le condizioni e i termini del presente Contratto, fatte salve ipotesi di cessioni di azienda o ramo di azienda, fusioni e comunque ipotesi di acquisizioni aziendali per le quali si considera già acquisita l'accettazione della parte ceduta. Qualsiasi trasferimento di diritti in assenza delle suddette condizioni sarà considerato nullo e mai avvenuto.

13.2 In caso di cambio di denominazione delle Parti non si renderà necessario l'emendamento alla presente convenzione. La Parte con denominazione mutata sarà comunque tenuta a notificare tempestivamente all'altra Parte tale cambio di denominazione.

14. Oneri fiscali

14.1 Il presente Contratto viene sottoscritto con firma digitale ai sensi dell'art. 24 del D. Lgs. 82/2005, giusta la previsione di cui all'art. 15, comma 2bis della Legge n. 241/1990, come aggiunto dall'art. 6, D.L. 18/10/2012, n. 179, convertito in Legge 17/12/2012 n. 22. Le imposte e tasse inerenti e conseguenti alla stipula del presente Contratto, ivi comprese l'imposta di bollo sull'originale informatico di cui all'art. 2 della Tabella Allegato A – tariffa parte I del DPR n. 642/1972 e l'imposta di registro devono essere versate, nel rispetto della normativa applicabile.
Le spese di bollo sono a carico della CRO mediante assegnazione delle marche ad uso esclusivo del presente Contratto con i seguenti codici univoci: 01200868204640 del 13/02/2023, 01200868204651 del 13/02/2023, 01200868204662 del 13/02/2023, 01200868204673 del 13/02/2023 e trattenute agli atti della CRO che assolve il tributo.

14.2 Ai sensi dell'art. 7 ter del DPR n. 633/1972 e successive modifiche, le prestazioni contrattuali sono soggette ad IVA in quanto rese a soggetto passivo stabilito in Italia.

15. Legge regolatrice e Foro competente

15.1 La normativa applicabile al presente Contratto è quella dello Stato italiano.

15.2 Per tutte le eventuali controversie che dovessero sorgere in relazione all'interpretazione, applicazione ed esecuzione del presente Contratto, sarà competente, in via esclusiva, il Foro del luogo ove si trova la sede dell'Azienda, salvo l'impegno delle Parti ad esperire un preventivo tentativo di conciliazione in sede stragiudiziale.

Le Parti si danno reciprocamente atto che il presente Contratto è stato accettato in ogni sua parte e che non trovano pertanto applicazione le disposizioni di cui all'art. 1341 Codice Civile.

Modena, li __/__/_____

Per la CRO
Il Procuratore speciale
Dott.ssa Alessandra Ori
Firmato digitalmente

Il Procuratore speciale
Dott. Giovanni Borrelli
Firmato digitalmente

Bassano del Grappa, li __/__/_____

Per l'Azienda ULSS 7 Pedemontana
Il Direttore Generale
Dott. Carlo Bramezza
Firmato digitalmente

ALLEGATO A – BUDGET ALLEGATO ALLA CONVENZIONE ECONOMICA

Si riportano di seguito indicazioni schematiche sulle informazioni da includere nel Budget allegato alla convenzione economica.

A1. Estremi di riferimento dello Studio

- Titolo Protocollo in italiano REACTION "Utilizzo di Ravulizumab secondo pratica clinica in pazienti italiani affetti da emoglobinuria parossistica notturna: uno studio di coorte multicentrico, osservazionale, retrospettivo e prospettico"
- Codice Protocollo n.d., Versione 1.7 data 09/11/2021
- Promotore Alexion Pharma Italy S.r.l., Via Melchiorre Gioia, 8 - 20124 Milano, Dr.ssa Federica Sottana email Federica.Sottana@alexion.com
- CRO Medineos S.U.R.L., Viale Virgilio 54/U, 41123 Modena, Dr.ssa Alessandra Ori, tel 059 8860134, email reaction@medineos.com
- Sperimentatore Principale dr. Eros Di Bona - Direttore U.O.C. Oncoematologia del P.O. Bassano – email eros.dibona@aulss7.veneto.it – telefono 0424/889447
- Numero di pazienti previsti a livello internazionale N.A., nazionale 120 e nel centro 4
- Arruolamento: competitivo
- Durata dello studio: 29 mesi

A2. Oneri e compensi

Parte 1 - Oneri fissi e Compenso per paziente incluso nello studio

- Oneri fissi per il CESC Ulss 8 Berica e per il NRC Aulss 7 Pedemontana: complessivi € 4.000,00 versati il 02/02/2022 (Centro satellite)
- Quota per il monitoraggio clinico dello studio: € 1.500,00 + IVA, da versare a 30 giorni dalla sottoscrizione del Contratto.
- Compenso per il Centro a paziente completato (Compenso a paziente arruolato – overhead aziendale - tutti i costi sostenuti dall'Azienda e per lo Studio[1]): € 1.000,00 + IVA.
- Fasi economiche intermedie (nel caso in cui i pazienti non completino l'iter sperimentale): Visita Compenso/paziente:
    - Prima tranche, per visita di arruolamento: € 500,00 + I.V.A.
    - Seconda tranche, per visite di follow-up: € 500,00 + I.V.A. se completate almeno due tra le tre seguenti visite di follow-up: visita a 18, 34, 52 settimane dall'arruolamento.
- Tutti i costi rimborsabili relativi allo studio, inclusi quelli coperti dal contributo per paziente coinvolto nello studio, non comporteranno aggravio di costi a carico del SSN (non vi sono prestazioni aggiuntive, gli esami strumentali e di laboratorio sono di tipo routinario per i pazienti in studio).

A3. Copertura assicurativa

- Non prevista, in quanto la natura dello studio non comporta la necessità di stipulare copertura assicurativa.

A4. Liquidazione e fatture

- Il compenso deve essere liquidato entro 60 giorni fine mese dalla ricezione della fattura.
- La Quota di Monitoraggio deve essere liquidata a 30 giorni dalla sottoscrizione del Contratto.
- La fattura deve essere emessa con cadenza prevista annuale secondo quanto maturato nel periodo di riferimento, sulla base di apposita richiesta di emissione fattura da parte della CRO.

Allegato B

GLOSSARIO RELATIVO ALLA PROTEZIONE DATI PERSONALI

- **Dato personale** - qualsiasi informazione riguardante una persona fisica identificata o identificabile ("interessato"); si considera identificabile la persona fisica che può essere identificata, direttamente o indirettamente, con particolare riferimento a un identificativo come il nome, un numero di identificazione, dati relativi all'ubicazione, un identificativo online o a uno o più elementi caratteristici della sua identità fisica, fisiologica, genetica, psichica, economica, culturale o sociale;
- **Trattamento** - qualsiasi operazione o insieme di operazioni, compiute con o senza l'ausilio di processi automatizzati e applicate a dati personali o insiemi di dati personali, come la raccolta, la registrazione, l'organizzazione, la strutturazione, la conservazione, l'adattamento o la modifica, l'estrazione, la consultazione, l'uso, la comunicazione mediante trasmissione, diffusione o qualsiasi altra forma di messa a disposizione, il raffronto o l'interconnessione, la limitazione, la cancellazione o la distruzione;
- **Pseudonimizzazione** - il trattamento dei dati personali tale che i dati non possano più essere attribuiti a un interessato specifico senza l'utilizzo di informazioni aggiuntive, a condizione che tali informazioni aggiuntive siano conservate separatamente e soggette a misure tecniche e organizzative intese a garantire che tali dati personali non siano attribuiti a una persona fisica identificata o identificabile;
- **Titolare del trattamento** - la persona fisica o giuridica, l'autorità pubblica, il servizio o altro organismo che, singolarmente o insieme ad altri, determina le finalità e i mezzi del trattamento di dati personali; quando le finalità e i mezzi di tale trattamento sono determinati dal diritto dell'Unione o degli Stati membri, il titolare del trattamento o i criteri specifici applicabili alla sua designazione possono essere stabiliti dal diritto dell'Unione o degli Stati membri;
- **Responsabile del trattamento** - la persona fisica o giuridica, l'autorità pubblica, il servizio o altro organismo che tratta dati personali per conto del titolare del trattamento;
- **Consenso dell'interessato** - qualsiasi manifestazione di volontà libera, specifica, informata e inequivocabile dell'interessato, con la quale lo stesso manifesta il proprio assenso, mediante dichiarazione o azione positiva inequivocabile, che i dati personali che lo riguardano siano oggetto di trattamento;
- **Violazione dei dati personali** - la violazione di sicurezza che comporta accidentalmente o in modo illecito la distruzione, la perdita, la modifica, la divulgazione non autorizzata o l'accesso ai dati personali trasmessi, conservati o comunque trattati;
- **Dati relativi alla salute** - i dati personali attinenti alla salute fisica o mentale di una persona fisica, compresa la prestazione di servizi di assistenza sanitaria, che rivelano informazioni relative al suo stato di salute;
- **Dati genetici** - i dati personali relativi alle caratteristiche genetiche ereditarie o acquisite di una persona fisica che forniscono informazioni univoche sulla fisiologia o sulla salute di detta persona fisica, e che risultano in particolare dall'analisi di un campione biologico della persona fisica in questione;
- **Campione biologico** - ogni campione di materiale biologico da cui possano essere estratti dati genetici caratteristici di un individuo;
- **Sponsor/Promotore** - la persona, società, istituzione oppure organismo che si assume la responsabilità di avviare, gestire e/o finanziare uno Studio Osservazionale;
- **CRO** – organizzazione di ricerca a Contratto alla quale lo sponsor può affidare una parte o tutte le proprie competenze in tema di ricerca clinica;
- **Monitor** – il responsabile del monitoraggio dello Studio individuato dallo sponsor/CRO;
- **Auditor** – il responsabile della esecuzione della verifica sulla conduzione dello Studio, come parte integrante della assicurazione di qualità, individuato dallo sponsor/CRO.