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

N. 627 DEL 11/04/2023

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 ALL'EMENDAMENTO SOSTANZIALE N. 1 ALLO STUDIO CLINICO PROFIT DAL TITOLO "STUDIO DI ESTENSIONE A LUNGO TERMINE (LTE) PER CARATTERIZZARE LA SICUREZZA E L'EFFICACIA DI DANICOPAM COME TERAPIA AGGIUNTIVA A UN INIBITORE DEL COMPONENTE 5 DEL COMPLEMENTO (C5I) IN PAZIENTI AFFETTI DA EMOGLUBINURIA PAROSSISTICA NOTTURNA (EPN) PRECEDENTEMENTE TRATTATATI CON DANICOPAN IN UNO STUDIO CLINICO SPONSORIZZATO DA ALEXION. ALXN 2040 –PNH –303", CONDOTTO PRESSO L'U.O.C. DI ONCOEMATOLOGIA DEL P.O. BASSANO.

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

Documento informatico firmato digitalmente ai sensi del D. Lgs n. 82/2005, del T.U. n. 445/2000 e norme collegate, il quale sostituisce il documento cartaceo e la firma autografa; il documento informatico è conservato digitalmente negli archivi informatici dell'Azienda.

Proponente: UOC AFFARI GENERALI
Anno Proposta: 2023 Numero Proposta: 627/23

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

---

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.

Rilevato che:

- con deliberazione in data odierna è stato autorizzato lo studio clinico profit dal titolo "Studio di estensione a lungo termine (LTE) per caratterizzare la sicurezza e l'efficacia di Danicopan come terapia aggiuntiva a un inibitore del componente 5 del complemento (C5i) in pazienti affetti da emoglobinuria parossistica notturna (EPN) precedentemente trattati con Danicopan in uno studio clinico sponsorizzato da Alexion*"* e approvato il relativo contratto con la Società IQVIA RDS Italy srl, d'ora in poi chiamato "Contratto base"
- lo studio di cui sopra, con promotore commerciale, si svolge presso l'U.O.C. Oncoematologia del P.O. di Bassano, vede come Sperimentatore Responsabile il dr. Eros Di Bona, Direttore della struttura citata, e viene svolto, come previsto da deliberazione di autorizzazione dello studio stesso, secondo quanto indicato da regolamento aziendale (vd deliberazione n. 1477/2022), al di fuori del normale orario istituzionale, e remunerato con i proventi derivanti dalla sperimentazione;
- con nota, pervenuta al ns. prot. 105984 del 2/12/2022, la Società IQVIA RDS Italy srl ha presentato al Comitato Etico per le sperimentazioni Cliniche della Provincia di Vicenza (CESC), richiesta di approvazione dell'Emendamento "SA01-PA1 dated 24 june 2022*"* alla sperimentazione citata, allegando la relativa documentazione, agli atti:

SCHEDA STUDIO CLINICO – EMENDAMENTO N 1

Titolo	Emendamento sostanziale n 1 a "Studio di estensione a lungo termine (LTE) per caratterizzare la sicurezza e l'efficacia di Danicopan come terapia aggiuntiva a un inibitore del componente 5 del complemento (C5i) in pazienti affetti da emoglobinuria parossistica notturna (EPN) precedentemente trattati con Danicopan in uno studio clinico sponsorizzato da Alexion
Struttura Centro dello Studio	U.O.C. Oncoematologia del P.O. Bassano
Sperimentatore principale	Dr. Eros Di Bona- Direttore dell'U.O.C. di Oncoematologia P.O. Bassano
Codice Protocollo	ALXN2040-PNH-303
Codice Emendamento	SA01-PA1
Fase	III
Numero EudraCT	2021- 004253 -22
Promotore	Alexion Pharmaceuticals, Inc., 121 Seaport Boulevard, Boston, MA 02210, Stati Uniti d'America
Richiedente/CRO	IQVIA RDS ITALY srl via Fabio Filzi Milano
Centro Coordinatore	Dott.ssa Wilma Barcellini –Fondazione IRCSS CA' Granda Ospedale Maggiore Policlinico

- il CESC di Vicenza in occasione della seduta del 14/03/2023, nota ns. prot n.24753 del 21/03/2023, ha esaminato la documentazione presentata ed ha espresso parere favorevole all'unanimità in ordine all'emendamento di cui sopra, approvando pertanto il Protocollo Emendato e allegato alla presente proposta di deliberazione di cui è parte integrante e sostanziale;
- si prevede in particolare la fornitura centralizzata da parte del Promotore di Ravulizumab ed Eculizumab, come meglio illustrato nell'Emendamento 1 del Contratto, la cui ultima versione è pervenuta via pec il 3/04/2023 ns prot. 29213, anch'esso allegato alla presente proposta di cui è parte integrante e sostanziale;

Dato atto che:

- per gli aspetti di cui sopra, è necessario aggiornare il Protocollo alla versione 1.0 datata 24/06/2022, che va a sostituire il precedente, e aggiornare anche il contratto, che viene solo integrato con l'Emendamento n l suindicato, al ns prot.29213 del 3/04/2023;
- restano fermi e invariati tutti i termini e le condizioni del Contratto base, già approvato con precedente deliberazione odierna, e non espressamente emendati, in particolare il totale previsto a paziente arruolato rimane invariato.

Tutto ciò premesso, il Direttore dell'U.O.C. Affari Generali, propone di approvare il Protocollo aggiornato v 1.0 datato 24/06/2022 e di autorizzare l'emendamento n.1 al Contratto con la Società IQVIA RDS Italy, relativo allo studio profit dal titolo: "Studio di estensione a lungo termine (LTE)

per caratterizzare la sicurezza e l'efficacia di Danicopan come terapia aggiuntiva a un inibitore del componente 5 del complemento (C5i) in pazienti affetti da emoglobinuria parossistica notturna (EPN) precedentemente trattati con Danicopan in uno studio clinico sponsorizzato da Alexion" che si svolge presso l'U.O.C. Oncoematologia del P.O. Bassano, sotto la Responsabilità del dr. Eros Di Bona, entrambi allegati alla presente proposta di deliberazione per farne parte integrante e sostanziale;

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 del parere favorevole espresso dal Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza (CESC), in occasione della seduta del 14/03/2023, ns prot. 24753 del 21/03/2023, in ordine all'emendamento n. 1, di cui in premessa, relativo allo studio clinico profit "Studio di estensione a lungo termine (LTE) per caratterizzare la sicurezza e l'efficacia di Danicopan come terapia aggiuntiva a un inibitore del componente 5 del complemento (C5i) in pazienti affetti da emoglobinuria parossistica notturna (EPN) precedentemente trattati con Danicopan in uno studio clinico sponsorizzato da Alexion";
2. di autorizzare pertanto l'emendamento sostanziale, codice SA01-PA 1 datato 24/06/2022, relativo allo Studio di estensione a lungo termine (LTE) per caratterizzare la sicurezza e l'efficacia di Danicopan come terapia aggiuntiva a un inibitore del componente 5 del complemento (C5i) in pazienti affetti da emoglobinuria parossistica notturna (EPN) precedentemente trattati con Danicopan in uno studio clinico sponsorizzato da Alexion";
3. di approvare pertanto il Protocollo di studio aggiornato "v.1.0 del 24/06/2022", allegato al presente atto per farne parte integrante e sostanziale;

4. di approvare l'Emendamento n. 1 al Contratto, allegato al presente atto per farne parte integrante e sostanziale, relativo alla sperimentazione clinica profit di cui sopra, sotto la Responsabilità del dr. Eros Di Bona – Direttore dell'U.O.C. Oncoematologia del P.O. di Bassano, che va ad integrare il contratto base già approvato;

5. di dare atto che:

   – le modifiche al Contratto base già approvato riguardano in particolar modo la fornitura centralizzata da parte del Promotore dei farmaci Ravulizumab ed Eculizumab;

   – restano fermi e invariati tutti i termini e le condizioni del Contratto base, non espressamente emendati con il presente Emendamento n 1 al Contratto, già approvato con precedente deliberazione in data odierna;

6. di dare atto altresì 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 di avanzamento dello studio (monitoraggio periodico) e una relazione analitica alla conclusione dello studio e pubblicazione se prevista;

7. 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;

8. 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

TITLE PAGE

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

Protocol Number: ALXN2040-PNH-303

Amendment Number: 1

Compound: Danicopan (ALXN2040)

Study Phase: Phase 3

Short Title: A Long-term Safety and Efficacy Study of Danicopan as an Add-on Therapy to C5i in Patients with PNH.

Sponsor Name: Alexion Pharmaceuticals, Inc.**Legal Registered Address:** Alexion Pharmaceuticals, Inc., 121 Seaport Boulevard, Boston MA, 02210, USA

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND	127367
EudraCT	2021-004253-22

Release Date: 24 June 2022

Sponsor Signatory:

12-Jul-2022

Gleb Filippov, MD, PhD
Senior Medical Director,
Clinical Development and Translational Sciences

Date

Medical Monitor Name and Contact Information will be provided separately.

INVESTIGATOR'S AGREEMENT

I have read the study protocol amendment and agree to conduct the study in accordance with this protocol amendment, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice (GCP), and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol amendment.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 1: 24 June 2022

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add an additional secondary endpoint, update procedures for dose interruptions and criteria for study drug withdrawal.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints	Added "*Proportion of patients with Hgb increase of ≥ 2g/dL in the absence of transfusion over time*" to Secondary endpoints	Based on expert feedback and patient insights, Alexion added the composite key secondary endpoint of "Proportion of patients with Hgb increase greater or equal than 2 g/dL in the absence of transfusions" to provide a more robust assessment of the expected clinical benefit of danicopan. An increase of 2 g/dL is considered clinically significant.
Table 1 Schedule of Assessments	Removed "urine" from pregnancy test and updated footnote to include *"Serum pregnancy test should be conducted at Follow-up Visit."*	Updated to indicate that a serum pregnancy test is required at the Follow-up Visit.
2.3.1 Benefit Assessment	Removed *"at least 1 packed RBC or whole blood transfusion within 6 months prior to the start of the study"* from the definition of clinically evident EVH.	This change has been implemented based on the expert advice and feasibility data. Alexion considers that danicopan can provide clinical benefit to patients with PNH who continue to experience anemia and reticulocytosis despite receiving adequate C5 inhibitor treatment, regardless of their requirement for transfusion support (Socie, 1996; Lustberg, 2012).
6.1 Study Intervention Administered	• Removed 50 mg and 100 mg dosage levels and the term "blister packs" from Table 3 • Added nasogastric tube to route of administration	• Updated as 50 mg dose was not used in the parent studies and there were no participants on the 100 mg dose. Also, for clinical studies bottles (rather than blister packs) are provided. • To allow for administeration of danicopan to patients who are unable to swallow the study drug.
6.6.2 Dose Interruptions	Updated procedures for dose interruptions.	To provide clarity on the procedures to be followed in the case of dose interruption.
7.1 Discontinuation of Danicopan	Updated the criteria for study drug withdrawal.	To account for laboratory abnormalities commonly seen in patients with PNH as part of their underlying disease (eg, ALT increase in the context of hemolysis)
7.2 Dose Taper	• Added "dose interruption" as a criteria for dose taper • Deleted 100 mg tid from Table 4	• For clarity • Study will not have participants who are receiving 100mg tid.
9.4.2 Secondary Analyses	Added "proportion of patients with Hgb increase of ≥ 2g/dL in the absence of transfusion over time" to secondary statistical analyses	Updated as a new secondary endpoint was added.

Section # and Name	Description of Change	Brief Rationale
10.2 Clinical Laboratory Tests Table 5	Removed '*only required if positive urine test*' from serum human chorionic gonadotropin pregnancy test	Updated for clarity as a serum pregnancy test is required following a positive urine test and also is required at the Follow-up Visit.
10.4. Contraceptive Guidance and Collection of Pregnancy Information	Added the term "acceptable" to highly effective contraception methods. Also added acceptable contraceptive methods for both male and female participants.	Updated for clarity
10.11 Protocol Amendment History	Added new section	To align with the common protocol template
Throughout	Replaced AP hemolysis with AP activity and CH50 with CP activity	The terms "AP hemolysis" and "CH50" refer to specific assays. The AP activity and CP activity are more appropriate terms as outcome measures.
Throughout	Updated document date and version	Administrative changes
Throughout	Minor editorial and document formatting revisions	For clarity

Abbreviations: ALT = alanine aminotransferase; AP = alternative pathway; C5 = complement component 5; C5i = C5 inhibitor; CP = classical pathway; CH50 = 50% hemolytic complement activity; EVH = extravascular hemolysis; Hgb = hemoglobin; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; tid = three times daily

TABLE OF CONTENTS

TITLE PAGE 1
INVESTIGATOR'S AGREEMENT 2
PROTOCOL AMENDMENT SUMMARY OF CHANGES 3
TABLE OF CONTENTS 5
LIST OF TABLES 9
LIST OF FIGURES 10
1. PROTOCOL SUMMARY 11
1.1. Synopsis 11
1.2. Schema 13
1.3. Schedule of Assessments 14
2. INTRODUCTION 17
2.1. Study Rationale 17
2.2. Background 17
2.2.1. Disease Background 17
2.2.2. Treatments and Unmet Medical Need 18
2.2.3. Danicopan (ALXN2040) 19
2.3. Benefit/Risk Assessment 19
2.3.1. Benefit Assessment 19
2.3.2. Risk Assessment 19
2.3.2.1. Coronavirus Disease 2019 20
2.3.3. Overall Benefit: Risk Conclusion 20
3. OBJECTIVES AND ENDPOINTS 21
4. STUDY DESIGN 22
4.1. Overall Design 22
4.2. Scientific Rationale for Study Design 23
4.3. Justification for Dose 23
4.4. End of Study Definition 23
5. STUDY POPULATION 24
5.1. Inclusion Criteria 24
5.2. Exclusion Criteria 24
5.3. Lifestyle Considerations 24

5.4. Screen Failures....24
6. STUDY INTERVENTION....25
6.1. Study Intervention Administered....25
6.1.1. Danicopan Packaging and Labeling....25
6.2. Preparation/Handling/Storage/Accountability....25
6.3. Measures to Minimize Bias: Randomization and Blinding....26
6.4. Danicopan Compliance....26
6.5. Concomitant Therapy....27
6.5.1. Background C5 Inhibitor Therapy....27
6.5.2. Vaccines....27
6.5.3. Transfusion Guidelines During the Study....28
6.6. Dose Modification & Interruption....28
6.6.1. Missed Doses....29
6.6.2. Dose Interruptions....29
6.6.3. Permanent Dose Discontinuation....29
6.7. Intervention After the End of the Study....29
7. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL....30
7.1. Discontinuation of Danicopan....30
7.2. Dose Taper....31
7.2.1. Follow-up Period....32
7.3. Patient Discontinuation/Withdrawal from the Study....32
7.4. Lost to Follow-up....32
8. STUDY ASSESSMENTS AND PROCEDURES....34
8.1. Efficacy Assessments....34
8.1.1. Disease-Related Laboratory Parameters....34
8.1.2. Transfusion Avoidance....34
8.1.3. Patient-Reported Outcome Measures....34
8.2. Safety Assessments....35
8.2.1. Physical Examinations....35
8.2.2. Vital Signs....35
8.2.3. Clinical Safety Laboratory Assessments....36
8.2.4. Pregnancy....36

8.2.5. Patient Safety Card 37
8.3. Adverse Events and Serious Adverse Events 37
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 37
8.3.2. Method of Detecting AEs and SAEs 37
8.3.3. Follow-up of AEs and SAEs 38
8.3.4. Regulatory Reporting Requirements for SAEs 38
8.4. Treatment of Overdose 38
8.5. Pharmacokinetics 39
8.6. Pharmacodynamics 39
8.7. Genetics 39
8.8. Biomarkers 39
8.9. Immunogenicity Assessments 39
8.10. Health Economics Data and/or Medical Resource Utilization 39
8.11. Other Assessments and Procedures 39
8.12. Remote Visit Options in Times of Emergency 40
9. STATISTICAL CONSIDERATIONS 41
9.1. Statistical Hypotheses 41
9.1.1. Primary Hypothesis 41
9.2. Sample Size Determination 41
9.3. Populations for Analyses 41
9.4. Statistical Analyses 41
9.4.1. Primary Analysis 41
9.4.2. Secondary Analyses 41
9.4.3. Pharmacokinetic/Pharmacodynamic/Biomarker Analysis 41
9.4.4. Efficacy Analyses 42
9.4.5. Safety Analyses 42
9.5. Interim Analyses 42
9.6. Data Monitoring Committee 42
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 43
10.1. Regulatory, Ethical, and Study Oversight Considerations 43
10.1.1. Regulatory and Ethical Considerations 43
10.1.2. Financial Disclosure 43

10.1.3. Informed Consent Process 44
10.1.4. Data Protection 44
10.1.5. Dissemination of Clinical Study Data 45
10.1.6. Data Quality Assurance 45
10.1.7. Source Documents 46
10.1.8. Study and Site Start and Closure 46
10.1.9. Publication Policy 47
10.1.10. Good Clinical Practice Compliance 48
10.2. Clinical Laboratory Tests 49
10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 51
10.3.1. Definition of AE 51
10.3.2. Definition of SAE 52
10.3.3. Recording and Follow-Up of AE and/or SAE 53
10.3.4. Reporting of SAEs 54
10.4. Contraceptive Guidance and Collection of Pregnancy Information 55
10.4.1. Definitions 55
10.4.2. Contraception Guidance 55
10.4.2.1. Guidance for Female Patients 56
10.4.2.2. Guidance for Male Patients 57
10.4.3. Collection of Pregnancy Information 58
10.4.3.1. Male Patients with Partners Who Become Pregnant 58
10.4.3.2. Female Patients Who Become Pregnant 58
10.5. Biomarkers 60
10.6. Patient-Reported Outcome Instruments 61
10.6.1. FACIT-Fatigue Subscale Version 4 61
10.6.2. EORTC Quality-of-Life Questionnaire (EORTC-QLQ-C30) 62
10.7. COVID-19 Risk Assessment 64
10.8. COVID-19 Vaccine Risk Assessment 66
10.9. Abbreviations 67
10.10. Protocol Amendment History 69
11. REFERENCES 70

LIST OF TABLES

Table 1: Schedule of Assessments 14
Table 2: Objectives and Endpoints 21
Table 3: Danicopan 25
Table 4: Danicopan Taper Schedule 31
Table 5: Laboratory Assessments 49
Table 6: Potential Risks and Mitigation Measures due to COVID-19 64
Table 7: Potential Risks and Mitigation Measures due to COVID-19 Vaccine 66
Table 8: Abbreviations and Specialist Terms 67

LIST OF FIGURES

Figure 1: Study Design Schematic 13
Figure 2: Complement Pathways in PNH (EVH and IVH) 18

1. PROTOCOL SUMMARY

1.1. Synopsis

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

Short Title: A Long-term Safety and Efficacy Study of Danicopan as an Add-on Therapy to C5i in Patients with PNH.

Rationale: The purpose of this LTE study is to characterize the safety and efficacy of danicopan as an add-on therapy to C5i in patients with PNH who were previously treated with danicopan in an Alexion-sponsored clinical study.

Objectives and Endpoints

Objective	Endpoints
Primary	
To characterize the long-term safety of treatment with danicopan as an add-on therapy to a complement component 5 inhibitor (C5i)	• Incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs
Secondary	
To characterize long-term efficacy of danicopan as an add-on therapy to a C5i	• Change in hemoglobin (Hgb) values over time • Proportion of patients with Hgb increase of ≥ 2g/dL in the absence of transfusion over time • Change in absolute reticulocyte count over time • Change in lactate dehydrogenase (LDH) over time • Proportion of patients with LDH ≤ 1.5 × upper limit of normal (ULN) over time • Proportion of patients with transfusion avoidance (TA), defined as patients who remain transfusion-free and do not require transfusion as per protocol-specified guidelines
To characterize the long-term effect of treatment with danicopan as an add-on therapy to a C5i on Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores and on European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 Scale (EORTC-QLQ-C30) scores	• Change in FACIT-Fatigue scores over time • Change in EORTC-QLQ-C30 scores over time
To further characterize the safety of danicopan as an add-on therapy to a C5i	• Change in safety laboratory parameters over time • TEAEs leading to discontinuation

Overall Design

This is a single arm LTE study that will enroll patients with PNH who have completed participation in Alexion-sponsored clinical studies with danicopan as an add-on therapy to a C5i. Eligible patients must complete all study assessments on the parent protocol before starting this study. All patients entering this study will receive danicopan as an add-on to a background C5i therapy. The only allowed C5i therapies are eculizumab and ravulizumab.

The total duration of the study will be up to 3 years. Patients who, in the opinion of the Investigator, are receiving benefit from danicopan will be offered the option to be enrolled directly into this study from the parent study, without dose tapering or treatment interruption. The patient will receive their last dose of danicopan from the parent study the night prior to Day 1 of this LTE study and will continue daily treatment with danicopan together with their background C5i therapy. There is no formal Screening or Eligibility Visit. For each patient, the Investigator should make the decision whether participation in this extension study would be appropriate, approximately 1 month prior to the End of Treatment Visit in the parent protocol and communicate this decision to the Medical Monitor. The End of Treatment Visit on the parent protocol will be Day 1 (Week 1) of this study. Data collected as part of the final visit for the parent protocol may be entered as the Day 1 data for this study as appropriate. Safety and efficacy monitoring will be conducted for this study.

During the first 24 weeks in this LTE study, patients will be followed up every 8 weeks. For the remainder of the study, patients will be followed up every 16 weeks. Following the last dose of danicopan in this study, all patients will complete the End of Treatment Visit assessments. Patients that discontinue danicopan and do not transition onto commercially available danicopan will have a 6-day Taper Period and a Follow-up Visit 30 (+ 7) days after the last danicopan dose. Patients that transition to commercially available danicopan will not be required to complete the dosing Taper Period Visits or the Follow-up Visit.

A patient is considered to have completed the study if he or she has completed all study visits per the Schedule of Assessments (SoA). Patients can withdraw from the study at any time. In this case, the patients are required to complete the assessments of the End of Treatment Visit, complete the 6-day danicopan Taper Period, and complete a Follow-up Visit approximately 30 (+ 7) days after receiving the last dose of danicopan. The end-of-study (EOS) is defined as the date the last patient completes the last visit as shown in the SoA. Patients who terminate the study to receive commercial danicopan, will be considered to have completed the study.

Disclosure Statement: This is a single arm LTE study.

Number of Patients: Approximately 100 patients will be enrolled in this study.

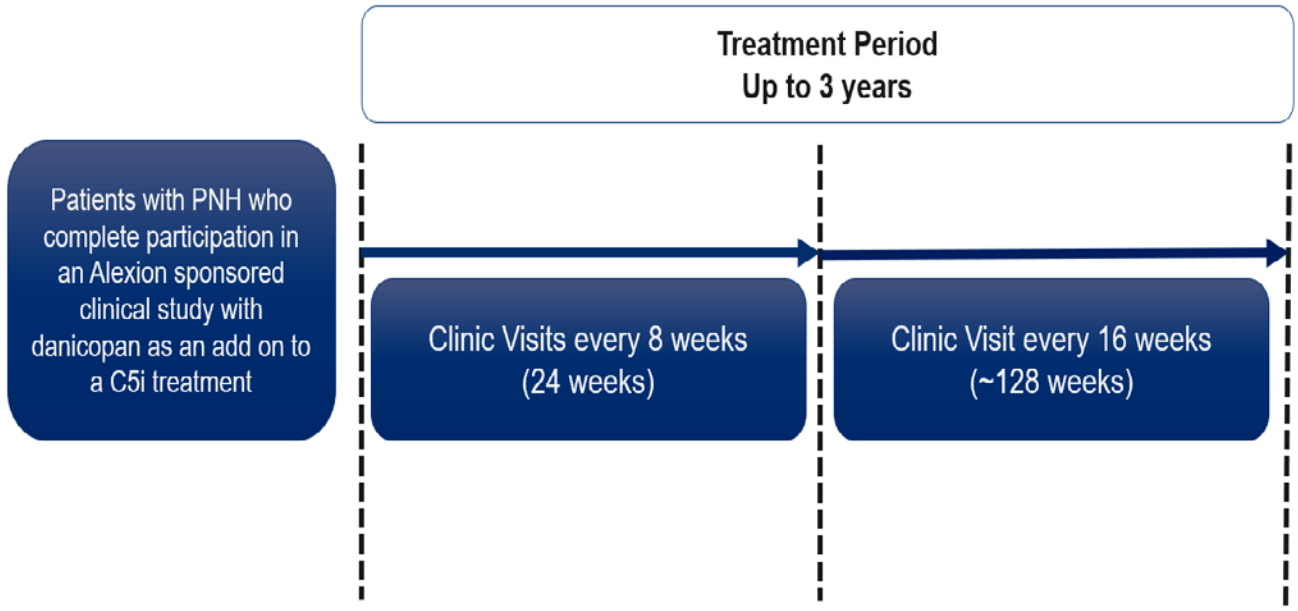
Note: “Enrolled” means a patient’s agreement to participate in a clinical study following completion of the informed consent process and satisfying inclusion/exclusion criteria.

Intervention Groups and Duration: Eligible patients who, in the opinion of the Investigator, are receiving benefit from danicopan will be offered the option to be enrolled directly into this study without treatment interruption from the parent study. The study total duration will be up to 3 years or until: 1) danicopan is commercially available in their country; or 2) the development of danicopan as a potential therapy for PNH is terminated; or 3) the therapy is no longer tolerated or effective; or 4) in the opinion of the Investigator, another treatment option is available; or 5) another appropriate access avenue to danicopan available; or 6) the study is terminated by the Sponsor; whichever is earlier.

Data Monitoring Committee: No

1.2. Schema

Figure 1: Study Design Schematic



Abbreviation: C5i = complement component 5 inhibitor, PNH = paroxysmal nocturnal hemoglobinuria

1.3. Schedule of Assessments

Table 1: Schedule of Assessments

Procedure		**Treatment Period**					**Taper Period**[1]		**Follow-up**[1]
	Day -1[2]	**Day 1**	**Week 8 (± 7 days)**	**Week 16 (± 7 days)**	**Week 24 (± 7 days)**	**Week 40 up to ~Week 152 (Every 16 weeks ± 7 days) and End of Treatment (ET)**[3]	**Day 3**	**Day 6**	**(30 [+7] days After Last Dose of Danicopan)**
Informed consent	X								
Inclusion and exclusion criteria	X								
Demography		X							
Physical examination including height and weight[4]		X	X	X	X	X			X
Recent medical history (new history since consenting to parent protocol)		X							
Pregnancy test (WOCBP only)[5]		X	X	X	X	X			X[6]
Laboratory assessments (hematology, chemistry, and urinalysis)[7]		X	X	X	X	X			X
LDH, D-dimer, coagulation		X	X	X	X	X			X
Vital signs[8]		X	X	X	X	X			X
Danicopan dispensation/ accountability[9]		X	X	X	X	X			X[10]
Safety card review		X	←==========→						X
AE review		X	←==========→						X

Table 1: Schedule of Assessments

Procedure		Treatment Period					Taper Period[1]		Follow-up[1]
	Day -1[2]	Day 1	Week 8 (± 7 days)	Week 16 (± 7 days)	Week 24 (± 7 days)	Week 40 up to ~Week 152 (Every 16 weeks ± 7 days) and End of Treatment (ET)[3]	Day 3	Day 6	(30 [+7] days After Last Dose of Danicopan)
SAE review		X	←==========→						X
Concomitant medication review		X	←==========→						X
Neisseria meningitidis revaccination[11]		X	←==========→						
PROs/QoLs (FACIT-Fatigue/ EORTC-QLQ-C30)		X[12]			X	X[13]			X
RBC transfusion review		X	X	X	X	X	X	X	X
PK[14]			←==========→						
PD/Biomarker[13]			←==========→						

[1] Taper Visits and the Follow-up Visit (30 [± 7] days) are only required for patients that discontinue danicopan treatment. Patients that continue onto commercially available danicopan must complete ET Assessments but will not require have the Taper or Follow-up Visits

[2] Day -1 is the day the patient took the last dose of danicopan in the parent study. There is no formal Screening or Eligibility Visit. For each patient, the Investigator should make the decision whether participation in this extension study would be appropriate, approximately 1 month prior to the ET Visit on the parent protocol and communicate this decision to the Medical Monitor. The last study day for the parent protocol will be Day -1 of this study. Data collected as part of the final visit on the parent protocol may be entered as the Day 1 data for this study as appropriate. Patients may be consented prior Day -1 while participating on the parent protocol or on Day 1. All required assessments from the parent protocol at ET must be completed.

[3] Refer to Section 4.4 for definition of EOS and Section 6.7 for intervention after the EOS

[4] A full physical examination should be done on Day 1 and EOS and ET. An abbreviated physical examination should be done at all other clinic visits.

[5] Urine pregnancy test at Day 1 and for the duration of the study must be done for WOCBP. Day 1 urine pregnancy test must be done predose and must be negative to continue. Any positive urine pregnancy test will be confirmed by a follow-up serum pregnancy test and result in discontinuation of study treatment. Serum follicle stimulating hormone, as needed, in women of nonchildbearing potential only. Serum pregnancy test should be conducted at the Follow-up Visit.

[6] Please refer to Section 10.2 for the list of hematology, chemistry, and urinalysis assessments required or reference the study Laboratory Manual.

[7] Vital signs include systolic/diastolic blood pressure (seated/lying down), heart rate, and temperature.

[8] Eculizumab/ravulizumab dose should follow the patients prescribed dose and schedule, as appropriate. Danicopan drug accountability must be documented within IRT and EDC.

[9] For danicopan accountability only. Danicopan bottle return and accountability may be completed at any visit. All danicopan bottles and remaining drug must be returned at or prior to the Follow-up Visit 30 days post last dose of danicopan.
[10] Please see Section 6.5.2.
[11] PROs/QoL scales will be administered to patients before danicopan administration.
[12] Starting Week 40, PROs/QoLs will be collected at every other clinic visit.
[13] PK, PD, and biomarker samples may be collected anytime during the study if deemed clinically necessary in response to a drug-related safety event or clinical deterioration as determined by the Investigator, and in discussion with the Medical Monitor. Actual sampling time and the most recent dose time prior to sample collection should be recorded, if feasible.

Abbreviations: AE = adverse event; EDC = electronic data capture; EORTC-QLQ-30 = European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 Scale; EOS = end of study; ET = end of treatment; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; IRT = Interactive Response Technology; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcome; QoL = quality-of-life; RBC = red blood cell; SAE = serious adverse event; WOCBP = women of childbearing potential

2. INTRODUCTION

Danicopan (ALXN2040), a small molecule, orally administered, factor D (FD) inhibitor, is being developed for the treatment of complement-mediated diseases, such as PNH. Factor D is a serine protease that catalyzes the cleavage of factor B (FB) into Ba and Bb, a rate-limiting step in the alternative pathway (AP) of complement, which allows the formation of the complement component 3 (C3) convertase (C3bBb). The cleavage of C3 and further amplification via the tick over mechanism, in the context of blockade of the complement cascade at complement component 5 (C5) by eculizumab, allows C3 fragment accumulation on PNH-red blood cells (RBCs) that have survived membrane attack complex (MAC)-mediated intravascular hemolysis (IVH), marking (opsonizing) these PNH-RBCs for extravascular hemolysis (EVH). Although danicopan does not inhibit components specific to classical (CP) or lectin (LP) pathways, nor does it inhibit components of the terminal complement pathway, it will inhibit the AP-mediated amplification of complement activity initiated via the CP and LP (Harboe, 2004).

Treatment with danicopan is expected to address the unmet medical need in patients with PNH who are treated with anti-C5 monoclonal antibodies (mAbs) but continue to experience clinically evident EVH and is expected to offer a significant clinical improvement in these circumstances.

A detailed description of the chemistry, pharmacology, efficacy, and safety of danicopan is provided in the Investigator's Brochure (IB).

2.1. Study Rationale

This LTE study is designed to continue to characterize the safety and efficacy of danicopan as an add-on therapy to a C5i in patients with PNH and who have completed participation in a prior Alexion study of danicopan as an add-on therapy to a C5i.

2.2. Background

2.2.1. Disease Background

PNH is an ultra-rare and life-threatening acquired hemolytic disorder caused by uncontrolled activation of the terminal complement pathway (Brodsky, 2014; Brodsky, 2015). Estimates suggest that there is a worldwide prevalence of 1.59 per 100000 people, with approximately 1.3 new cases per million people per year (Hill, 2007).

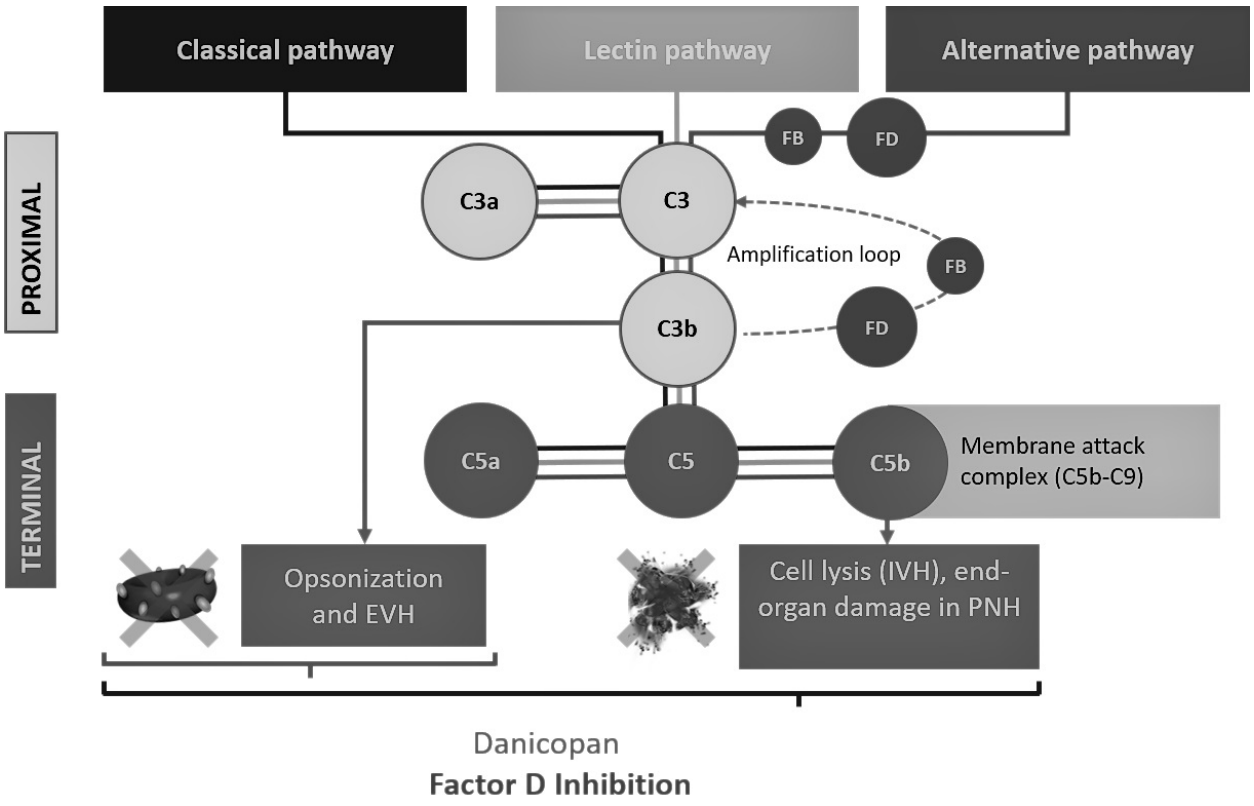
PNH is characterized by destruction of RBCs (hemolytic anemia), blood clots (thrombosis), impaired bone marrow function, and a risk of developing leukemia. The disease evolves from the clonal expansion of hematopoietic stem cells that have a somatic mutation in the phosphatidylinositol N-acetylglucosaminyltransferase subunit A (*PIGA*) gene, resulting in the clonal loss of glycosylphosphatidylinositol anchored proteins, including the complement regulatory proteins CD55 and CD59, from the surface of mutant RBCs. This leaves the RBCs susceptible to complement-mediated IVH – the typical clinical hallmark of PNH (Schubert, 2015). In addition to anemia requiring frequent transfusion, this condition has other serious sequelae related to the liberation of intracellular hemoglobin (Hgb) and its consequent derangement of nitric oxide levels in the vasculature. These effects include an increased risk of thrombotic events as well as painful vascular crises.

2.2.2. Treatments and Unmet Medical Need

The only curative treatment for PNH is hematopoietic stem cell transplantation using allogeneic donors. Currently approved treatments for PNH are the humanized mAbs C5i eculizumab (SOLIRIS®), ravulizumab (ULTOMIRIS®), and recently, in some countries, pegcetacoplan (Empaveli™), a C3 inhibitor. The two C5 inhibitors, eculizumab and ravulizumab, inhibit C5 in the terminal complement pathway and prevent formation of MAC and are effective in controlling IVH (Konar, 2017).

A subset of patients with PNH treated with C5i continue to be anemic and further experience EVH (Hill, 2010; McKinley, 2017; Notaro, 2018; Risitano, 2019). It has been proposed that the blockade of the complement cascade at C5 allows C3 fragment accumulation on PNH-RBCs that have survived MAC-mediated IVH, marking (opsonizing) these PNH-RBCs for EVH (Brodsky, 2017).

Figure 2: Complement Pathways in PNH (EVH and IVH)



Abbreviations: C3 = complement component 3; C5 = complement component 5; C9 = complement component 9; EVH = extravascular hemolysis; FB = factor B; FD = factor D; IVH = intravascular hemolysis; PNH = paroxysmal nocturnal hemoglobinuria
Source: Yuan, 2017; Lee, 2020; Data on File, Alexion Pharmaceuticals Inc., 2020.

Recently pegcetacoplan, a new agent for the treatment of patients with PNH has been approved in the US and in the EU. Pegcetacoplan is a pegylated pentadecapeptide that targets C3 and it is administered subcutaneously twice weekly. A 16-week Phase 3 study of pegcetacoplan showed an adjusted mean increase of 3.84 g/dL with pegcetacoplan compared to eculizumab (95% CI, 2.33-5.34), however there was no statistically significant difference in change in baseline lactate

dehydrogenase (LDH) level compared to eculizumab at Week 16. About 10% of these patients developed breakthrough hemolysis with an elevated LDH to more than 3 times the upper limit of normal (ULN) range. This resulted in these patients switching back to eculizumab. There were also injection site reactions (37%), infections (29%), and diarrhea (22%) as the most common adverse events (AEs). This study showed that despite the inhibition of C3 in the upstream portion of the complement pathway, pegcetacoplan achieved suboptimal control of IVH in these patients as evidenced by the occurrence of breakthrough hemolysis (Hillmen, 2021).

An unmet medical need remains for a therapy that may adequately control EVH while maintaining adequate IVH control. This unmet need can potentially be addressed by adding a compound able to block the AP pathway of the complement cascade in combination with a C5i (ie, inhibiting FD).

2.2.3. Danicopan (ALXN2040)

Danicopan is a small molecule, oral FD inhibitor being developed for the treatment of complement-mediated diseases such as PNH. By inhibiting FD, danicopan targets the control point for the amplification loop of the complement cascade, blocking C3 convertase formation and therefore, significantly reducing the production of C3 cleavage fragments and downstream MAC formation.

2.3. Benefit/Risk Assessment

2.3.1. Benefit Assessment

Treatment with danicopan is expected to address the unmet medical need in patients with PNH who are treated with anti-C5 mAb but continue to experience clinically evident EVH (defined as: presence of anemia with Hgb $\leq$ 9.5 g/dL with absolute reticulocyte count $\geq 120 \times 10^9$/L) and is expected to offer a clinically significant improvement in these circumstances without losing the IVH control offered by anti-C5 mAb. This has been demonstrated in the ongoing Phase 2 Study ACH471-101 by a near elimination of transfusion dependence and a sustained improvement of > 2 g/dL in Hgb values, as well as clinically meaningful improvements in reticulocytes, PNH-RBC clone size, LDH, bilirubin, and patient self-reported outcome scores, in patients with PNH receiving eculizumab (Kulasekararaj, 2021). Study ACH471-103 is an ongoing Phase 2 study to evaluate the safety and efficacy of long-term therapy with danicopan monotherapy in patients with PNH. A registrational, Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of danicopan as add-on therapy to an anti-C5 mAb (eculizumab or ravulizumab) in patients with PNH who have clinically evident EVH is also ongoing (Study ALXN2040-PNH-301).

2.3.2. Risk Assessment

There are 2 potential risks closely monitored in this clinical trial: *Neisseria meningitidis* (*N meningitidis*) infection and liver enzyme elevation.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Danicopan		
Meningococcal infections	Patients receiving complement inhibitor therapy in general may have increased risk of infections, particularly *N meningitidis*.	Patients must be revaccinated against meningococcal infections as described in this protocol. Patients should be monitored for early signs of meningococcal infection and treated with appropriate antibiotics, if necessary. Patients must carry the Patient Safety Card at all times for quick disclosure of any potential signs or symptoms of infection. See Section 6.5.2 for more information on vaccinations and revaccinations.
Liver enzyme elevation	Hepatobiliary cholestasis was seen in dog toxicology studies and was characterized by icterus, elevated AST, ALT, ALP, GGT and TBIL (primarily direct bilirubin), with histological findings. Dose limiting toxicity of transient and self-limiting liver enzyme elevation was observed in healthy volunteer study at doses of 500 mg bid and 800 mg bid	Routine laboratory monitoring and strict stopping criteria are included ensuring prompt discontinuation of any patient with evidence of liver injury. See Section 7.1.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase, bid = twice daily; GGT = gamma glutamyltransferase; TBIL = total bilirubin

2.3.2.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This risk assessment for COVID-19 and COVID-19 vaccinations are described in Section 10.7 and Section 10.8, respectively.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to patients in this study, the potential risks identified in association with danicopan are justified by the anticipated benefits that may be afforded to patients with PNH.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of danicopan may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

Objective	Endpoints
Primary	
To characterize the long-term safety of treatment with danicopan as an add-on therapy to a complement component 5 inhibitor (C5i)	• Incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs
Secondary	
To characterize the long-term efficacy of danicopan as an add-on therapy to a C5i	• Change in hemoglobin (Hgb) values over time • Proportion of patients with Hgb increase of ≥ 2g/dL in the absence of transfusion over time • Change in absolute reticulocyte count over time • Change in lactate dehydrogenase (LDH) over time • Proportion of patients with LDH ≤ 1.5 × upper limit of normal (ULN) over time • Proportion of patients with transfusion avoidance (TA), defined as patients who remain transfusion-free and do not require transfusion as per protocol-specified guidelines
To characterize the long-term effect of treatment with danicopan as an add-on therapy to a C5i on Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores and on European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 Scale (EORTC-QLQ-C30) scores	• Change in FACIT-Fatigue scores over time • Change in EORTC-QLQ-C30 scores over time
To further characterize the safety of danicopan as an add-on therapy to a C5i	• Change in safety laboratory parameters over time • TEAEs leading to discontinuation

4. STUDY DESIGN

4.1. Overall Design

This is a single arm LTE study that will enroll patients with PNH who have completed participation in Alexion-sponsored clinical studies with danicopan as an add-on therapy to a C5i. Eligible patients must complete all study assessments on the parent protocol before starting this study. All patients entering this study will receive danicopan as an add-on to a background C5i therapy. The only allowed C5i therapies are eculizumab and ravulizumab.

The total duration of the study will be up to 3 years. Patients who, in the opinion of the Investigator, are receiving benefit from danicopan will be offered the option to be enrolled directly into this study from the parent study, without dose tapering or treatment interruption. Patients will receive their last dose of danicopan from the parent study the night prior to Day 1 of this LTE study and will continue daily treatment with danicopan together with their background C5i therapy. There is no formal Screening or Eligibility Visit. For each patient, the Investigator should make the decision whether participation in this extension study would be appropriate, approximately 1 month prior to the End of Treatment Visit in the parent protocol and communicate this decision to the Medical Monitor. The End of Treatment Visit on the parent protocol will be Day 1 (Week 1) of this study. Data collected as part of the final visit for the parent protocol may be entered as the Day 1 data for this study as appropriate. Safety and efficacy monitoring will be conducted for this study.

During the first 24 weeks in this LTE study, patients will be followed up every 8 weeks. For the remainder of the study, patients will be followed up every 16 weeks. Following the last dose of danicopan in this study, all patients will complete the ET visits assessments. Patients that discontinue danicopan and do not transition onto commercially available danicopan will have a 6-day Taper Period and a Follow-up Visit 30 (+ 7) days after the last danicopan dose. Patients that transition to commercially available danicopan will not be required to complete the dosing Taper Period Visits or the Follow-up Visit.

A patient is considered to have completed the study if he or she has completed all study visits per the SoA (Section 1.3). Patients can withdraw from the study at any time. In this case, the patients are required to complete the assessments of the ET Visit, complete the 6-day danicopan Taper Period, and complete a Follow-up Visit approximately 30 (+ 7) days after receiving the last dose of danicopan. The EOS is defined as the date the last patient completes the last visit as shown in the SoA (Section 1.3). Patients who terminate the study to receive commercial danicopan, will be considered to have completed the study.

It is expected that patients who enter this study will continue therapy until: 1) danicopan is commercially available in their country; or 2) the development of danicopan as a potential therapy for PNH is terminated; or 3) the therapy is no longer tolerated or effective; or 4) in the opinion of the Investigator, another treatment option is available; or 5) another appropriate access avenue to danicopan available; or 6) the study is terminated by the Sponsor; whichever is earlier.

4.2. Scientific Rationale for Study Design

The primary purpose of this study is to characterize the long-term safety and efficacy of danicopan administration as an add-on to a C5i in patients with PNH who were previously treated with danicopan in an Alexion-sponsored clinical study. Patients enrolling into this study from a parent Alexion study, have been on danicopan treatment and have completed the Extension Period from the parent study. These patients will continue to receive danicopan treatment in this study until therapy is readily available to them or danicopan development is discontinued.

4.3. Justification for Dose

Details regarding healthy volunteer dose-ranging studies can be found in the IB. To date, in PNH patients, doses up to 200 mg 3 times per day (tid) have been studied in danicopan monotherapy Phase 2 Study ACH471-100 in addition to the ongoing danicopan Phase 2 Study ACH471-101, which continues to assess danicopan as an add-on to C5i treatment at doses ranging from 100 mg to 200 mg tid. These studies have demonstrated that doses up to 200 mg tid have been generally well tolerated with clinically significant improvements in Hgb, LDH levels, and patient-reported well-being. For the ongoing Phase 3 Study ALXN2040-PNH-301, doses of 150 mg tid to 200 mg tid are being used.

Patients will continue to receive danicopan at the dose level that they were receiving at the end of the parent study, either 150 mg tid or 200 mg tid. The maximum danicopan dose on this study will be 200 mg tid. Patients will continue to receive treatment with C5i according to their usual dose and schedule.

4.4. End of Study Definition

A patient is considered to have completed the study if:

- The patient has completed all periods of the study including the last scheduled procedure shown in the SoA (Section 1.3), or
- In the event the study is stopped early, the patient has completed all applicable periods of the study, including the ET Visit, or
- The patient initiates commercial danicopan because danicopan is registered or approved (in accordance with country-specific regulations).

The EOS is defined as the date the last patient completes the last visit as shown in the SoA (Section 1.3).

A patient is considered to have terminated early from the study if the patient discontinues danicopan treatment and does not transition to commercially available danicopan (See Section 7).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

1. All patients who completed their participation in an Alexion-sponsored clinical study with danicopan as an add-on to a C5i treatment.
2. Documentation of vaccination for *N meningitidis*: All patients must be revaccinated as per national vaccination guidelines or local practice for vaccination use with complement inhibitors.
3. Female patients of childbearing potential and male patients must follow protocol-specified contraception guidance as described in Section 10.4.
4. Patient is capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.

5.2. Exclusion Criteria

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

1. Patient has been permanently discontinued from danicopan in the parent study for any reason other than enrollment into this LTE study.
2. Any medical condition (eg, cardiac, pulmonary, renal, oncologic, or psychiatric) that, in the opinion of the Investigator, might interfere with participation in the study, pose any added risk to the patient, or confound the assessment of the patient.
3. Female patients who have a positive pregnancy test on Day 1.
4. Female patients who are pregnant, breastfeeding, or intending to conceive during the course of the study.

5.3. Lifestyle Considerations

This study has no lifestyle restrictions.

Clinic staff will instruct the patient how to take their medication at home and record the time they took each dose and whether or not the dose was taken with food. It is recommended that the first dose of the day be taken at the same time each morning; all doses should be taken approximately 15 to 30 minutes after completion of a meal or snack (see Section 6.4). Patients will be instructed to store danicopan at room temperature.

Patients will continue to receive C5i therapy at their usual location according to their usual dose and schedule for the entirety of the study.

5.4. Screen Failures

Not applicable.

6. STUDY INTERVENTION

"Study Intervention" in this protocol refers to danicopan.

6.1. Study Intervention Administered

For this study, the study intervention is danicopan and details are shown in Table 3.

Table 3: Danicopan

Intervention Name	Danicopan
Type	Small molecule, factor D inhibitor
Dose Formulation	Tablet
Unit Dose Strength(s)	50 mg or 100 mg
Dosage Level(s)	150 mg and 200 mg[1]
Route of Administration	Oral, Nasogastric (NG) tube
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided by Sponsor
Packaging and Labeling	Tablets are provided in bottles
Other Names and Aliases	ALXN2040, ACH-0144471

[1] Patients will continue dosing at the dose level that they were receiving at the end of the parent study.
Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product

Danicopan may be administered via nasogastric tube to patients who are unable to swallow the study drug. Further details will be provided in the Pharmacy Manual.

6.1.1. Danicopan Packaging and Labeling

At a minimum, danicopan will be labeled with:

1. The protocol number
2. Lot number/expiry date
3. Alexion name and address
4. Instructions for use and storage

Danicopan will be labeled according to the country's regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

At the pharmacy, danicopan must be stored as provided at controlled room temperature (20°C to 25°C). Patients should be instructed to keep their danicopan in the original container at room temperature.

1. When the medication is stored at the investigational site, the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit (a

temperature monitor will accompany each shipment) for all danicopan received and that any discrepancies are reported and resolved before use of danicopan.

2. Only patients enrolled in the study may receive danicopan and only authorized site staff may supply or administer danicopan. When the medication is stored at the investigational site, all danicopan must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for danicopan accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any temperature excursions and product complaints to AlexionIMPTE@alexion.com and productcomplaints@alexion.com within 1 business day of awareness. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
4. Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused danicopan is provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an LTE study in patients with PNH who roll-over from other Alexion-sponsored clinical studies evaluating danicopan as an add-on therapy to a C5i. There is no randomization in this study and all patients will continue to receive danicopan at the dose level they were receiving at the end of the parent study. If Study ALXN2040-PNH-301 has not reached study database lock and unblinding at the time of a patient rolling over to the current Study ALXN2040-PNH-303, the patient's dose level will remain blinded until database lock and unblinding has occurred in Study ALXN2040-PNH-301.

6.4. Danicopan Compliance

Patients will self-administer danicopan at home, unless instructed otherwise. Compliance with danicopan will be assessed by direct questioning and counting returned tablets during the site visits and recorded in the source documents. Deviation(s) from the prescribed dosage regimen which includes missed dose(s) should be recorded in the electronic case report form (eCRF).

A record of the quantity of the number of tablets dispensed to and taken by each patient must be maintained and reconciled with the number of tablets and compliance records. Treatment start and stop dates, including dates for planned and unplanned dose delays and/or dose reductions will also be recorded in the eCRF.

Patients should be advised on the importance of taking danicopan according to the protocol. Patients who do not adhere to protocol-specified visit schedules and procedures, and who do not

adhere to danicopan administration (eg, generally considered as having < 80% treatment compliance during the identified Treatment Period) may be regarded as non-compliant to the protocol. If poor compliance with the study protocol continues, discontinuation should be considered.

6.5. Concomitant Therapy

Potential drug-drug interactions (DDI) between danicopan and commonly used drugs have been evaluated. Results of the DDI studies showed that danicopan may increase exposure to tacrolimus (a substrate of CYP3A4 and P-gp, and potential P-gp inhibitor), which can be addressed by monitoring of drug levels. No other clinically meaningful drug interactions were observed. Please refer to the IB for additional details regarding the DDI evaluation of danicopan.

Details of all concomitant medication use, including all medications administered for the treatment of AEs and nonprescription drugs (including vitamins and dietary or herbal supplements), must be recorded in the patient's eCRF. The following are some general guidelines for concomitant medication use based on currently available data:

- Oral, injectable, implantable, transdermal, or intravaginal hormonal therapies are allowed for either contraception or hormonal replacement therapy.
- Prophylactic antibiotics may be administered if deemed appropriate by local clinical practice and/or guidelines for treatment with a complement inhibitor. Because commercially available products will be used, information about any specific antibiotics administered can be found on the package inserts/product labels for those products.

The use of concomitant medications during the study will be assessed at the time points indicated in the SoA (Section 1.3).

6.5.1. Background C5 Inhibitor Therapy

All patients entering this study will receive danicopan as an add-on to a background C5i therapy. The only allowed C5i therapies are eculizumab and ravulizumab.

Data regarding C5i infusion, including but not limited to, dose, frequency, and infusion date, will be collected throughout the study.

During the study, the only authorized switch in C5i therapy is from eculizumab to ravulizumab in countries where ravulizumab is commercially available.

C5i therapy will be provided according to local regulations and approvals.

6.5.2. Vaccines

To reduce the risk of meningococcal infection, all patients were required to be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating danicopan within their parent protocols. Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes.

Patients must be revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors. Vaccination may not be sufficient to

prevent meningococcal infection. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

Vaccinations and/or boosters may be administered during study treatment according to national or local guidelines and will be recorded within the patient source documents and eCRF.

For any vaccines or boosters given as part of this study, full identifying information, including brand, should be recorded in the patient's eCRF.

6.5.3. Transfusion Guidelines During the Study

It is recommended to administer packed RBC (pRBC) transfusion when a patient has a:

1. Hemoglobin value of less than 7 g/dL regardless of presence of clinical signs or symptoms, or
2. Hemoglobin value of less than 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion.

In the event of life-threatening anemia, transfusion of ABO- and RhD-matched blood is appropriate. If further matching for Kell and JK antigens can be conducted without delaying making the blood available for emergent transfusion, this additional testing is recommended. The reason for transfusion as well as signs or symptoms associated with the patient's need for transfusion, will be documented on the eCRF for each individual patient. Typical anemia-related symptoms warranting transfusions include angina, change in mental status, syncope, light headedness, confusion, shortness of breath, and fatigue.

The Investigator will determine the appropriate number of units of pRBCs to be transfused. In the event that a transfusion is required, a blood sample for central laboratory is to be collected as an assessment prior to transfusion. Administration of transfusion including the reason for transfusion (Hgb result, signs, and symptoms) and the number of units transfused, will be documented in the eCRF.

6.6. Dose Modification & Interruption

Patients who enter the LTE study on Day 1 will receive the same dose of danicopan and following the same and dosing interval as that from the parent study. Patients who begin the study at the 150 mg tid dose, will be allowed to escalate to 200 mg tid based on their clinical response, Investigator assessment of potential benefit, and previous discussion with the Alexion Medical Monitor. If during the study, danicopan as an add-on to C5i therapy is approved for commercialization, all patients will be given the option to transition to the commercial approved dose(s). Patients that transition to commercially available danicopan will not be required to complete the dosing Taper Period Visits or the Follow-up Visit. Patients that discontinue danicopan and do not transition onto commercially available danicopan will have a 6-day Taper Period and a Follow-up Visit 30 (+ 7) days after the last danicopan dose.

In the event that the patient's safety or tolerability warrants dose reduction to a lower dose, this may occur in consultation with the Alexion Medical Monitor. This dose reduction will only occur, if both Investigator and the Alexion Medical Monitor agree that the patient will benefit from the lower dose.

6.6.1. Missed Doses

Danicopan should be taken as described in the protocol and without interruption during the course of the study, whenever possible. Information on missed doses should be recorded in the eCRF. Doses should be taken at approximately the same time each day and as close as possible to 8 hours apart. If a dose is missed, it should be taken within 4 hours of the originally scheduled time. After 4 hours, the missed dose should be skipped. In either case, the next dose should be taken according to the original dosing schedule.

6.6.2. Dose Interruptions

If danicopan dose is interrupted for any reason, an assessment should be made if the stop is temporary or the patient is to be withdrawn based on the criteria described in Section 7. Discussion about the reasons for interruption and plans for potential re-initiation should occur between the Investigator and the Alexion Medical Monitor. Re-initiation of treatment with danicopan should be done under careful clinical monitoring, including laboratory monitoring and after consultation with the Alexion Medical Monitor. If upon resumption of treatment, the patient has a recurrence of the event, permanent discontinuation should be considered as described in Section 7.1.

Any temporary preplanned treatment interruption should be discussed between the Investigator and the Alexion Medical Monitor and tapering should be considered (refer to Section 7.2).

The patient should continue participation until the end of the study unless the prespecified events for treatment discontinuation have been met. Any interruption of study drug and the reason for the interruption should be fully documented in the source documents and eCRF.

6.6.3. Permanent Dose Discontinuation

If danicopan is permanently discontinued for any reason (see Section 7), the dose of danicopan will be tapered over a 6-day period as described in Section 7.2.

A patient who permanently discontinues danicopan is also permanently discontinued from the study.

6.7. Intervention After the End of the Study

If danicopan is permanently discontinued for any reason, the dose will be tapered over a 6-day period as described in Section 7.2. Danicopan will not be provided to the patients after the last taper dose. After the ET Visit, all patients that discontinue danicopan will have a Safety Follow-up Visit 30 (+ 7) days after the last dose of danicopan. Patients will continue to receive their approved C5i at the same dose and interval during the Taper and Follow-up Period that they were receiving during the Treatment Period.

If a patient is transitioned to commercially available danicopan, the patient will complete the ET Visit and return all study medication at the ET Visit. Patients will continue to receive their approved C5i at the same dose and interval and will transition to commercially available danicopan during this visit.

7. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Danicopan

In rare instances, it may be necessary for a patient to permanently discontinue danicopan. If danicopan is permanently discontinued, the patient will taper the dose as described in Section 7.2, and will remain in the study for 56 days after the last dose of danicopan to be evaluated for safety.

A patient is free to withdraw from the study at any time without jeopardizing future medical care. In addition, the Principal Investigator (or designee) may decide, for reasons of medical prudence or patient noncompliance, to discontinue dosing of danicopan for an individual patient. The Principal Investigator will discontinue dosing danicopan in any patient who meets any of the reasons listed below, and should notify Alexion Medical Monitor immediately, and if possible, before dosing is terminated. Patients will continue to receive C5i therapy, as per the Principal Investigator's judgment but danicopan will be permanently discontinued.

Reasons for patient withdrawal may include:

- Intercurrent illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree
- Development of any of the following liver function test abnormalities in the absence of hemolysis:
  - Alanine aminotransferase (ALT) > 8 × ULN
  - ALT > 5 × ULN for more than 2 weeks
  - ALT > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5, in the absence of warfarin anticoagulation
  - Increase of ALT > 3 × ULN and >3 × from baseline and total bilirubin > 2 × ULN or INR > 1.5, in the absence of warfarin anticoagulation
  - Increase of ALT > 3 × ULN and > 3 × from baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Patient withdrawal from their background C5i. Investigators should follow the instructions on discontinuation and monitoring of the patient as outlined in the approved corresponding Summary of Product Characteristics (SmPC)/Local Product Information for eculizumab or ravulizumab
- Pregnancy or planned pregnancy in female patients and partners of male patients
- Patient noncompliance with the protocol. In case of significant deviations from the protocol for any reason (eg, oversight, accident, inadvertent error, etc.), the Investigator (or designee) and Alexion Medical Monitor will discuss and reach a joint decision about patient discontinuation from the study. This joint decision will be fully documented per study procedures

- Discontinuation of the study at the request of the Sponsor, regulatory agency, or Ethics Committee or Institutional Review Board (IRB)
- Any other condition or circumstance that would jeopardize the welfare of the patient if she or he were to continue in the study

Data collected at the time of danicopan discontinuation and follow-up and for any further evaluations that need to be completed is provided in the SoA (Section 1.3).

The reason for any patient's discontinuation and the date of withdrawal will be recorded in the patient's eCRF. The patient's eCRF, which will be completed up to the point of withdrawal, will be retained for Alexion. If a patient discontinues from the study for any reason, all protocol procedures as defined in the SoA (Section 1.3) should be performed as an ET Visit.

Upon first observation of ALT > 3 × baseline, a repeat test must be performed within 48 to 72 hours. The site should contact the patient and inquire about the presence of any symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash).

If necessary, for safety reasons, local laboratories are permitted to identify patients that may need to be discontinued from the study and results need to be discussed with the Alexion Medical Monitor, however the final discontinuation from the study requires central laboratory determinations and discussion with the Medical Monitor.

7.2. Dose Taper

If danicopan is discontinued or the dose is interrupted (Section 6.6.2) for any reason, the dose of danicopan will be tapered over a 6-day period. The dosing taper regimen is described in Table 4. In addition, the taper schedule may be adjusted to allow for slower taper in a patient who is not tolerating discontinuation of drug.

If the patient withdraws from the study at any time, the patient will complete the ET Visit as soon as possible prior to tapering. Patients should take danicopan per protocol until the Taper Period begins.

Table 4: Danicopan Taper Schedule

Danicopan Dose at Discontinuation	Taper Period 1 (T1) (Taper Days 1 – 3)	Taper Period 2 (T2) (Taper Days 4 – 6)
150 mg tid	100 mg tid	50 mg tid
200 mg tid	100 mg tid	50 mg tid

Note: T1 and T2 visits may be done by phone call on Day 3 and Day 6, respectively.
Patients will be given instructions on how and when to start to taper their danicopan dose at the ET Visit.
T1 should assess safety and give instructions to taper dosing for Taper Period 2. T2 should give instructions to terminate dosing.
Abbreviations: T = taper; tid = three times per day

Patients will continue to receive their approved C5i at the same dose and interval during the Taper and Follow-up Period that they were receiving during the Treatment Period, if applicable.

7.2.1. Follow-up Period

After completion of the Taper Period, patients will enter the Follow-up Period. Patients will be evaluated at the clinical site 30 (+ 7) days after the last dose of danicopan. During the Follow-up Period, assessments will be performed as specified in the SoA (Section 1.3).

7.3. Patient Discontinuation/Withdrawal from the Study

All efforts should be made to ensure patients are willing to comply with study participation prior to conducting the Day 1 procedures.

The reason for patient discontinuation must be recorded in the source documents and eCRF.

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This activity is expected to be uncommon.

At the time of discontinuing from the study, if possible, an ET Visit should be conducted if possible, as shown in the SoA (Section 1.3). Refer to the SoA for data to be collected at the time of danicopan taper, discontinuation, and follow-up, and for any further evaluations that need to be completed.

The patient will be permanently discontinued both from danicopan and the study after the Taper Period and the 30 (+ 7) days Follow-up Visit is completed.

If the patient withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Patients that transition to commercially available danicopan will complete the assessments at ET Visit, as shown in the SoA (Section 1.3) and will not be required to complete the dosing Taper Period Visits or Follow-up Visit.

7.4. Lost to Follow-up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient to reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the patient should continue or discontinue danicopan.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All Day -1 and Day 1 evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- See Section 10.2 for the list of clinical laboratory tests.

8.1. Efficacy Assessments

8.1.1. Disease-Related Laboratory Parameters

Blood will be collected according to the SoA (Section 1.3) to assess the efficacy endpoints of change in Hgb values, change in absolute reticulocyte count, change in LDH values, and proportion of patients with LDH $\leq 1.5 \times$ ULN.

8.1.2. Transfusion Avoidance

TA is defined as patients who remain transfusion free and do not require transfusion as per protocol-specified guidelines throughout the study duration. Transfusion data which the is number of RBC transfusions administered, the associated pre-Hgb value (with reticulocyte count, if available), symptoms that triggered the transfusion, and the number of units transfused, will be followed and documented in the eCRF to assess the proportion of patients with TA.

8.1.3. Patient-Reported Outcome Measures

Two validated quality of life (QoL) scales will be administered to patients before danicopan administration at the time points specified in the SoA (Section 1.3).

- The Functional Assessment of Chronic Illness Therapy (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: 0 (Not at all) to 4 (Very much). Total scores range from 0 to 52, with higher score indicating better QoL.

- The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 Scale (EORTC QLQ-C30), Version 3.0, is a questionnaire developed to assess the QoL of cancer patients. 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 (1 = not at all to 4 = very much) 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%, with a high score representing a higher response level. Thus, a high score for a functional scale represents a high level of functioning but a high score for a symptom scale represents a high level of symptomatology/problem.

The FACIT-Fatigue and EORTC-QLQ-C30 scales are provided in Section 10.6.1 and Section 10.6.2, respectively.

8.2. Safety Assessments

The primary endpoint for this study is the incidence of treatment-emergent adverse events TEAEs and serious TEAEs. Secondary safety endpoints include change in safety laboratory parameters over time and TEAEs leading to danicopan discontinuation. Safety will be evaluated by monitoring and assessment of AEs, clinical laboratory tests, physical examination findings, vital signs measurements, and review of patient safety cards. Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination should be done on Day 1 and will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- An abbreviated physical examination should be done at all other clinic visits and will include a body-system relevant examination based on Investigator judgment and patient symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Body temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (mmHg) will be assessed.
- Blood pressure and pulse measurements will be assessed in a seated and supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each patient should be used for measurements.
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

8.2.3. Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for efficacy and safety as listed in Section 10.2 at the times indicated in Section 1.3.

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the final dose of danicopan should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments samples, as defined in Section 10.2, must be collected in accordance with the Laboratory Manual and the SoA (Section 1.3).
  - Laboratory assessments performed at the institution's local laboratory that require a change in patient management or are considered clinically significant by the Investigator must be recorded in the AE or serious adverse event (SAE) eCRF. When possible, parameter value outside of the reference range should be entered in a free-text field.

8.2.4. Pregnancy

- Pregnancy data from female patients and female partners of male patients will be collected from the first dose of danicopan and at the time points specified in the SoA (Section 1.3). Any female patient who becomes pregnant during the study should be considered for discontinuation from danicopan and withdrawn from the study. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.4.3.
- Urine pregnancy test should be performed on Day 1 and for the duration of the study including follow-up for women of childbearing potential (WOCBP). Day 1 urine

pregnancy test must be done predose and must be negative to continue. Any positive urine pregnancy test will be confirmed by a follow-up serum pregnancy test and result in discontinuation of study treatment.

8.2.5. Patient Safety Card

Before the first dose of danicopan in this LTE study, a Patient Safety Card will be provided to patients to carry with them at all times until 3 months after last dose of eculizumab and 8 months after last dose of ravulizumab. The card is provided to increase patient awareness of the risk of meningococcal infections and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced during the course of the study and to inform patients on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit throughout the study, the study staff will ensure that the patient has the Patient Safety Card.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

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

The Investigator or qualified designee is responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to danicopan or study procedures, or that caused the patient to discontinue danicopan (see Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

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

All AEs and SAEs will be collected from the signing of the ICF until the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to Alexion immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of the date the investigational site became aware of the event.

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, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to danicopan or study participation, the Investigator must promptly notify Alexion.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each patient at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities toward the safety of patients and the safety of danicopan under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of danicopan under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/Independent Ethics Committees (IECs), and Investigators.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.3.2) in the format of MedWatch 3500 or Council for International Organizations of Medical Sciences (CIOMS) I Form to health authorities and Investigators as required. Forms submitted to Investigators will be blinded to treatment assignment. In limited circumstances, the blind may be broken in the case of urgent safety issues that could compromise patient safety.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4. Treatment of Overdose

For this study, any dose of danicopan greater than that specified in the protocol will be considered an overdose.

Alexion does not recommend specific treatment for an overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose, the Investigator should:

1. Contact the Alexion Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE.

3. Obtain a plasma sample for pharmacokinetic (PK) analysis if requested by the Alexion Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Alexion Medical Monitor based on the clinical evaluation of the patient.

8.5. Pharmacokinetics

PK samples may be collected anytime during the study if deemed clinically necessary in response to a drug-related safety event or clinical deterioration as determined by the Investigator, and in discussion with the Medical Monitor. Actual sampling time and the most recent dose time prior to sample collection should be recorded, if feasible.

8.6. Pharmacodynamics

Pharmacodynamic (PD) samples may be collected anytime during the study if deemed clinically necessary in response to a drug-related safety event or clinical deterioration as determined by the Investigator, and in discussion with the Medical Monitor. Actual sampling time and the most recent dose time prior to sample collection should be recorded, if feasible. PD will be evaluated using serum (for AP activity) and plasma (for Bb fragment of complement factor B [Bb]) from whole blood, as needed.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarker samples may be collected at any time during the study, if deemed clinically necessary, in response to a drug-related safety event or clinical deterioration as determined by the Investigator, and in discussion with the Medical Monitor. Actual sampling time and the most recent dose time prior to sample collection should be recorded, if feasible. Biomarkers will be evaluated using serum (for C3, CP activity, and free C5) and plasma (for FD) from whole blood, as needed. In addition, PNH clone size and C3 fragment deposition on PNH-RBCs will be evaluated using whole blood.

8.9. Immunogenicity Assessments

Immunogenicity is not applicable in this study.

8.10. Health Economics Data and/or Medical Resource Utilization

Health economics data and/or medical resource utilization parameters are not evaluated in this study.

8.11. Other Assessments and Procedures

Not applicable.

8.12. Remote Visit Options in Times of Emergency

To ensure patient safety and treatment continuity in times of emergency (eg, COVID-19 pandemic), the following will apply where patients are not able to reach the study sites, and until patients are able to resume study visits at the site.

Remote visit options may be at the Investigator's discretion and oversight, in accordance with local regulations. Remote visit options may include visits conducted at the patient's home (eg, lab collection by home health care services), an alternative qualified healthcare facility, or virtually through phone or video conference. All assessments for the study visit day should be conducted according to the SoA (Section 1.3), whenever possible. Information about AEs, concomitant medications, and disease-related signs or symptomatology must be sent to the Investigator for evaluation on the day of the remote visit. In case of any signs or symptoms indicating an SAE, the patient will need to be evaluated at the study site

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary objective of the study is to characterize the long-term safety of treatment with danicopan as an add-on therapy to a C5i. There will be no formal statistical hypothesis testing conducted for primary endpoint analysis.

9.2. Sample Size Determination

This is a study in patients with PNH who rollover from other Alexion-sponsored clinical studies evaluating danicopan as an add-on therapy to a C5i. Approximately 100 patients will be enrolled in this study.

9.3. Populations for Analyses

The population sets used for analysis are defined in the following:

Analysis Set	Description
Full Analysis Set	All patients who receive at least 1 dose of danicopan during the LTE study
Safety Set	All patients who receive at least 1 dose of danicopan during the LTE study

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP). Summary statistics will be computed and displayed by patient group and by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of patients, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate.

Analyses will be performed using the SAS® software Version 9.4 or higher.

9.4.1. Primary Analysis

The number and percentage of patients with TEAEs and SAEs will be summarized.

9.4.2. Secondary Analyses

The proportion of patients with Hgb increase of ≥ 2g/dL in the absence of transfusion over time, with TA, and with LDH ≤ 1.5 × ULN will be summarized. Change in Hgb, absolute reticulocyte count, LDH, FACIT-Fatigue score, EORTC-QLQ-C30 scores, safety laboratory parameters, and TEAEs leading to discontinuation of danicopan will be summarized over time.

9.4.3. Pharmacokinetic/Pharmacodynamic/Biomarker Analysis

PK, PD, and biomarker samples may be collected anytime during the study, if clinically necessary, in response to a drug-related safety event or clinical deterioration as determined by the Investigator in discussion with the Medical Monitor. PK samples will be evaluated for

danicopan concentrations in plasma. PD will be evaluated using serum (for AP activity) and plasma (for Bb fragment of complement factor B [Bb]) from whole blood, as needed. Biomarkers will be evaluated using serum (for C3, CP activity, and free C5) and plasma (for FD) from whole blood, as needed. In addition, PNH clone size and C3 fragment deposition on PNH-RBCs will be evaluated using whole blood. Actual sampling time and the most recent dose time prior to sample collection should be recorded, if feasible.

9.4.4. Efficacy Analyses

Please refer to Section 9.4.2.

9.4.5. Safety Analyses

All safety analyses will be conducted on the Safety Set.

Descriptive statistics using summary statistics will be calculated for quantitative safety data as well as for the difference to baseline by visit. Frequency tables will be provided for categorical variables. No inferential statistical analysis of safety data is planned.

Adverse events will be coded using latest version of the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs (ie, those AE that newly occur or worsen in severity after the first dose of danicopan) will be summarized by System Organ Class and Preferred Term. Tabulated listings of patients with SAEs and those who discontinue from the study due to an AE will be provided.

Incidence of clinical laboratory abnormalities Grade 3 and above (based on Version 5.0 or higher of the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]) will be summarized. For laboratory tests with NCI CTCAE toxicity grades available, laboratory abnormalities will be summarized by worst treatment-emergent grade. Any laboratory AE will also be classified by the site based on clinical AE severity in addition to CTCAE and will be reported with the clinical AE.

Shift tables will be provided for liver function test results and other selected laboratory test results based on CTCAE grades. In addition, shift tables based on multiples of ULN will also be produced for liver function test measurements.

Data on vital signs will be examined through patient listings and by summary statistics of selected parameters.

9.5. Interim Analyses

Interim analyses may be performed as needed in response to regulatory requests or to support submissions and/or publications. Details of interim analysis will be described in the SAP.

9.6. Data Monitoring Committee

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, substantial protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion, and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC and regulatory/health authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- For studies to be approved by the Medicines and Healthcare products Regulatory Agency: The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by UK legislation as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Directive 2001/20/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible

for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent from all study patients, or the patient's legally authorized representative, prior to performing any study-related procedures.
- The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the patient's rights and responsibilities) to the patient or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent or a certified translation, if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The patient's medical record must include a statement that signed (written or electronic) informed consent was obtained before any study-specific procedures were performed with a patient, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Patients must be reconsented to the most current version of the ICF(s) during their participation in the study, as applicable.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of patient information sheets and fully executed signature pages) must be provided to the patient or the patient's legally authorized representative, as applicable. This document may require translation into the local language. Original signed (written or electronic) consent forms must remain in each patient's study file and must be available for verification at any time.

10.1.4. Data Protection

- Patients will be assigned a unique identifier by Alexion. Any patient records or datasets that are transferred to Alexion will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- Patients must be informed that their personal study-related data will be used in accordance with applicable data protection law, and patients must also be informed of any individuals rights they may have with regard to their personal data. Patients will be informed about how their personal study-related data will be disclosed and will be required to agree to the information contained in the informed consent and provide consent to the processing of their personal data, if required by applicable data protection law.

- Patients must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and inspectors from regulatory authorities.
- Alexion as a data controller has implemented privacy and security controls designed to help protect patient personal data; including information security controls, firewalls, incident detection, and secure transfer measures.
- In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented procedures and measures to promptly address and mitigate any risk to the data patient. In the event of a breach, the controller will notify the appropriate regulatory authorities and/or the data patient in accordance with applicable data protection law.

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.6. Data Quality Assurance

- All patient data relating to the study will be recorded on the eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator after study completion per local regulations

or institutional policies. No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, electrocardiograms [ECGs], AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. eCRFs must be completed by the Investigator or designee as indicated in the site delegation log. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available to Alexion, Alexion delegates, and health authorities, as requested. Source documents are filed at the investigational site.

Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the first patient is consented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all patients have completed the EOS or ET Visit, all data have been collected and entered into the electronic data capture (EDC) system, all required documents and study supplies have been collected and reconciled, and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion’s procedures, or ICH GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further danicopan development

Alexion or health authority may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk of danicopan to patients enrolled or continuing in the study

- Alexion decision to suspend or discontinue testing, evaluation, or development of danicopan

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, IRBs/IECs, regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.9. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or EOS, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors and per the Alexion Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

- Alexion will publish Patient Lay Summaries and include patients and/or caregivers as reviewers for readability and understanding of lay person language.

10.1.10. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 R2, EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of Alexion and/or the company organizing/managing the research on behalf of Alexion to inspect study data, patients' medical records, and eCRFs in accordance with current GCP and respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

Alexion ensures that local regulatory authority requirements are met before the start of the study. Alexion (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of danicopan for shipment to the site.

10.2. Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the central laboratory as indicated.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either danicopan administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a danicopan decision or response evaluation, the results must be available in the patient's source documents.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: WOCBP should only be enrolled after a negative urine pregnancy test result on Day 1. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the SoA (Section 1.3).

Table 5: Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Red blood cell (RBC) count Free hemoglobin (Hgb) Hgb Hematocrit Erythrocytes Complete blood count, including: RBC count Red cell distribution width (RDW)	RBCs indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Absolute and % Reticulocytes Mean Corpuscular hemoglobin content (MCHC)	White blood cell count with differential (absolute and %): Neutrophils, segmented Lymphocytes Monocytes Eosinophils Basophils Platelet count Mean platelet volume (MPV)
Clinical chemistry	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bicarbonate (HCO3) Bilirubin (fractionated) Blood urea nitrogen (BUN) Calcium Calculated estimate glomerular filtration rate (eGFR) Chloride	Creatine kinase Creatinine Gamma-glutamyl transferase (GGT) Glucose Lactate dehydrogenase (LDH)	Potassium Sodium Total protein Uric acid

Table 5: Laboratory Assessments

Laboratory Assessments	Parameters
Other assessments	• D-dimer • PNH clone size and C3 fragment deposition on PNH-RBCs • Haptoglobin (optional) • Prothrombin time (PT)/ partial thromboplastin time (PTT)/ international normalized ratio (INR) • Urine pregnancy test (as needed for women of childbearing potential) • Serum human chorionic gonadotropin pregnancy test • Serum follicle stimulating hormone (as needed in women of non-childbearing potential only)
Routine urinalysis (by dipstick)	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, erythrocytes, calcium, calcium/creatinine, leukocytes • Microscopic examination (if any leucocytes, trace protein, nitrites, and blood [if not menstruating] are abnormal)

Investigators must document their review of each laboratory safety report within the patient source documents.

10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). • **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 danicopan, whether or not considered related to danicopan.

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 (ie, not related to progression of underlying disease).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 danicopan 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 danicopan 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 sequelae.

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 danicopan 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 patient'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 patient's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or

Events Not Meeting the AE Definition
clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.2. 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 patient 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 patient 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 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 patient 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.

A suspected unexpected serious adverse reaction (SUSAR) is defined as:

An event that is assessed as serious by the Investigator and/or Alexion that is not listed in the appropriate Reference Safety Information (IB) and has been assessed that there is at least a reasonable possibility that the event is related to the investigational medicinal product by the Investigator and/or Alexion.
Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.

Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

10.3.3. 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.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion in lieu of completion of the Alexion AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Alexion.
- 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 one of the following categories from NCI 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

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.

Assessment of Causality

- The Investigator is obligated to assess the relationship between danicopan, background C5i, 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 and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility danicopan caused the AE.
    a. 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.
    b. The event does not follow a reasonable temporal relationship to administration of danicopan.
  - Related: There is a reasonable possibility danicopan caused the AE.
    a. The AE has a temporal relationship to the administration of danicopan.
    b. The event does not have a likely alternative etiology.
    c. The event corresponds with the known pharmaceutical profile of danicopan.
    d. 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 danicopan administration will be considered and investigated.
- The Investigator will also consult the 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.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. 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 Alexion.
- 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.

Assessment of Causality
• 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 Alexion 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. • If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool
• All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness. • The primary mechanism for reporting an SAE to Alexion will be the EDC system. • If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE Reporting via facsimile or email. Facsimile transmission or email may also be used in the event of electronic submission failure. – Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347 • The site will enter the SAE data into the EDC system as soon as it becomes available. • When further information becomes available, the EDC should be updated immediately with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS) within 24 hours of Investigator/site awareness. • After the patient has completed the study, no new data or changes to existing data are expected to be entered in the EDC system. o If a site receives a report of a new SAE from a study patient which the Investigator considers to be related to danicopan, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email.

10.4. Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of danicopan, additional evaluation should be considered.

Women in the Following Categories Are Not Considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral tubal ligation or bilateral salpingectomy
    - Documented bilateral oophorectomy

- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
- **Note**: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause prior to the Day 1 Visit.
        – A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required. In the absence of 12 months of amenorrhea the reason for not obtaining FSH levels should be documented by the Investigator on Day 1.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective or acceptable contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
4. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

10.4.2. Contraception Guidance

Contraceptive use by male or female patients should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If

teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male patient, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.4.3.1). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female patient who becomes pregnant during the study.

10.4.2.1. Guidance for Female Patients

Female patients of childbearing potential must have a negative pregnancy test (urine or serum) as required by local regulations before the first dose of danicopan on Day 1 of this study. Additional requirements for pregnancy testing during and after dosing with danicopan are indicated in the SoA (Section 1.3).

The Investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

The Investigator should evaluate the potential for contraceptive method in relationship to the first dose of danicopan in this study.

Female patients of childbearing potential must use a highly effective or acceptable method of contraception, including at least 1 of the following until at least 30 days after the final dose of danicopan.

Highly effective methods of contraception include:

1. Intrauterine device in place for at least 6 weeks prior to first dose of danicopan in this study.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of danicopan in this study.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of danicopan in this study.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of danicopan in this study.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of danicopan in this study.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of danicopan in this study). Male partner is still required to use condom during sexual intercourse.
7. Sexual abstinence for female patients:
    a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent female patients must refrain from heterosexual intercourse for at least 30 days after the final dose of danicopan in this study.

Acceptable contraceptive methods include:

- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

Female patients must not donate ova from the Day 1 Visit at least until 30 days after their final dose of danicopan.

The following methods of contraception are considered unacceptable in this study:

- Periodic abstinence (calendar, symptothermal or post ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Female condom and male condom should not be used together

10.4.2.2. Guidance for Male Patients

All non-sterile male patients must use highly effective or acceptable methods of contraception with their partner(s) of childbearing potential from the first day of dosing (Day 1) through 90 days (a spermatogenesis cycle) after their last dose of study drug.

Sterile is defined as having bilateral orchiectomy.

Highly effective contraception for males is defined as any of the following:

- Vasectomy with confirmed medical assessment of surgical success
- Condom plus use of one of the following by partner(s) of child-bearing potential:
  - Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
  - Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion

Acceptable contraceptive methods include:

- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

10.4.2.2.1. Sexual Abstinence for Male Patients

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent male patients who become heterosexually active must use a condom and spermicide during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post ovulation methods for a female partner) is not considered a highly effective method of contraception for male patients.

Male patients must not donate sperm from the Day 1 Visit until 90 days after their final dose of danicopan.

10.4.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female patients and female spouses/partners of male patients from the first dose of danicopan until 30 days after the last dose of danicopan. Any female patient who becomes pregnant during the study should be considered for discontinuation from danicopan and withdrawn from the study. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of danicopan via semen following paternal exposure. If a female patient or a male patient's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to danicopan during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion GDS via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the danicopan may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

10.4.3.1. Male Patients with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome Form" and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.3.2. Female Patients Who Become Pregnant

The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The information will be recorded on the "Pregnancy/Breastfeeding Reporting and Outcome Form" and submitted to Alexion within 24 hours of learning of a patient's pregnancy.

For all Alexion products, both in development or post approval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie,

spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the patient discontinues danicopan or withdraws from the study. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to danicopan use by the Investigator will be reported to Alexion. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue danicopan and be withdrawn from the study.

10.5. Biomarkers

- Biomarker samples may be collected at any time during the study, if deemed clinically necessary, in response to a drug-related safety event or clinical deterioration as determined by the Investigator, and in discussion with the Medical Monitor.
- Blood samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to danicopan or PNH and related diseases. The samples may also be used to develop tests/assays including diagnostic tests related to danicopan and PNH.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to danicopan to understand study disease or related conditions.
- The results of biomarker analyses may be reported in the clinical study report or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on danicopan continues but no longer than 5 years after the study ends or other period/time point per local requirements.

10.6. Patient-Reported Outcome Instruments

10.6.1. FACIT-Fatigue Subscale Version 4

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

16 November 2007
Page 1 of 1

10.6.2. EORTC Quality-of-Life Questionnaire (EORTC-QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your first initial: |____|
Your birth date (Day, Month, Year): |__|__||__|__||__|__|__|__|
Today's date (Day, Month, Year): |__|__||__|__||__|__|__|__|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you:

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

10.7. COVID-19 Risk Assessment

PNH can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a patient may receive from joining an investigational study with a therapeutic treatment is potentially significant. In this particular case, the fact that every patient is treated with danicopan also contributes to the potential benefit a patient may derive from partaking in the study. Given that treatment for PNH does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in patients not receiving immunosuppressants. However, there is no specific data to further inform this risk. The site Investigator will therefore balance the risk/benefit considerations in the study patient taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 6.

Table 6: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new patients at sites unless the sites have the resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules, and increase missed visits and/or patient study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Day 1. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason

Table 6: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		the data is missing (eg, missed study visits or patient study discontinuations due to COVID-19).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form.

10.8. COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant danicopan administration, based on the mechanism of action of danicopan. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in patients treated with danicopan. Same precautions should be taken as described in Section 6.5.2 for vaccines.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Because vaccines may activate complement, if possible, consider vaccination when the underlying complement-mediated disease is clinically controlled and when systemic C5 inhibitor concentration (and subsequent complement blockade) is relatively high, shortly after administration.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination

The potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 7.

Table 7: Potential Risks and Mitigation Measures due to COVID-19 Vaccine

Risks Category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules, and increase missed visits and/or patient study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	Capture specific information in the eCRF that explains the reason for missing data (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form.

10.9. Abbreviations

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

Table 8: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
AE	adverse event
ALT	alanine aminotransferase
AP	alternative pathway
AST	amino transferase
Bb	b fragment of factor B
C3	complement component 3
C5	complement component 5
C5i	complement component 5 inhibitor
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CP	classical pathway
DDI	drug-drug interaction(s)
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 Scale
EOS	end of study
ET	end of treatment
EVH	extravascular hemolysis
FB	factor B
FD	factor D
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committees
IMP	investigational medicinal products
IRB	Institutional Review Board
IV	intravenous
IVH	intravascular hemolysis
INR	international normalized ratio
LDH	lactate dehydrogenase
LP	lectin pathway
LTE	long-term extension
mAbs	monoclonal antibodies
MAC	membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities

Table 8: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
pRBC	packed red blood cells
QoL	quality-of-life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of assessments
SUSAR	suspected unexpected serious adverse reaction
TA	transfusion avoidance
TEAE	treatment-emergent adverse events
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.10. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY	
Document/Type of Amendment (Global or Country-specific)/Date	**Summary of Key Changes in the Amendment**
Protocol Amendment 0.1 (Local Multiple Countries)/02 Jun 2022	The primary purpose of the amendment was to create a local version of the original protocol for countries where background C5 inhibitors are being supplied as study drug. Also added a new secondary endpoint of proportion of patients with Hgb increase of ≥ 2g/dL in the absence of transfusion over time. Removed "at least 1 packed RBC or whole blood transfusion within 6 months prior to the start of the study" from the definition of clinically evident EVH. Updated procedures for dose interruptions. Added the term "acceptable" to highly effective contraception methods. Also added acceptable contraceptive methods for both male and female participants.
Original protocol/13 Sep 2021	Not applicable

11. REFERENCES

Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804-2711.

Brodsky RA. Complement in hemolytic anemia. Blood. 2015;126:2459-2465.

Brodsky RA. Eculizumab: another breakthrough. Blood. 2017;129(8):922-923.

Harboe M, Ulvund G, Vien L, Fung M, Mollnes TE. The quantitative role of alternative pathway amplification in classical pathway induced terminal complement activation. Clin Exp Immunol. 2004;138(3):439-446.

Hill A, Platts PJ, Smith A, et al. The incidence and prevalence of paroxysmal nocturnal haemoglobinuria (PNH) and survival of patients in Yorkshire. Br J Haematol. 2007;137:31.

Hill A, Rother RP, Arnold L, et al. Eculizumab prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and unmasks low-level extravascular hemolysis occurring through C3 opsonization. Haematologica. 2010;95(4):567-573.

Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021;384:1028-1037.

Konar M, Granoff DM. Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. Blood. 2017;130(7):891-899.

Kulasekararaj A, Risitano AM, Maciejewski JP, et al. Phase 2 study of danicopan in paroxysmal nocturnal hemoglobinuria patients with an inadequate response to eculizumab. Blood. 2021. Online ahead of print.

Lee JW, Kulasekararaj A. Ravulizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Exp Opin Biol Ther. 2020;20(3):227-237.

McKinley CE, Richards SJ, Munir T, et al. Extravascular hemolysis due to C3-loading in patients with PNH treated with eculizumab: Defining the clinical syndrome. Blood. 2017;130(Suppl 1):3471.

Notaro R, Sica M. C3-mediated extravascular hemolysis in PNH on eculizumab: Mechanism and clinical implications. Semin Hematol. 2018;55(3):130-135.

Risitano AM, Marotta S, Ricci P, et al. Anti-complement treatment for paroxysmal nocturnal hemoglobinuria: time for proximal complement inhibition? A position paper from the SAAWP of the EBMT. Front Immunol. 2019;10:1157.

Schubert J, Röth A. Update on paroxysmal nocturnal haemoglobinuria: on the long way to understand the principles of the disease. Eur J Haematol. 2015;94(6):464-473.

Yuan X, Gavriilaki E, Thanassi JA, et al. Small-molecule factor D inhibitors selectively block the alternative pathway of complement in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Haematologica. 2017;102(3):466-475.

EMENDAMENTO N.1 AL CONTRATTO PER LA CONDUZIONE DELLA SPERIMENTAZIONE CLINICA SU MEDICINALI

Il presente Emendamento n. 1 al Contratto di sperimentazione clinica ("Emendamento") è stipulato tra **IQVIA RDS Italy srl**, con sede legale in via Fabio Filzi 29, 20124 Milano ("IQVIA"), per incarico dello sponsor della sperimentazione, Alexion Pharmaceuticals, con sede legale in 121 Seaport Boulevard, Boston MA 02210, Stati Uniti ("Promotore")

E

L'Azienda 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

Premesse

PREMESSO CHE, IQVIA e l'Azienda ULSS 7 Pedemontana sono Parti di un Contratto intitolato *"Studio di estensione a lungo termine (LTE) per caratterizzare la sicurezza e l'efficacia di danicopan come terapia aggiuntiva a un inibitore del componente 5 del complemento (C5i) in pazienti affetti da emoglobinuria parossistica notturna (EPN) precedentemente trattati con danicopan in uno studio clinico sponsorizzato da Alexion"* con numero di protocollo ALXN2040-PNH-303 ("Sperimentazione"); in vigore a partire dal [*inserire la data del CTA*]

PREMESSO CHE, a seguito all'Emendamento 1 al Protocollo, approvato dal Comitato Etico nella seduta del 14marzo2023, che oltre al protocollo v1.0 datato 26 giugno 2022, introduce le modifiche relative alla fornitura centralizzata di Ravulizumab e Eculizumab e alla documentazione correlata al paziente (versione aggiornata dei consensi e materiale pazienti), è necessario rivedere il budget dello studio; e

PREMESSO CHE, il Promotore si impegna a fornire all'Azienda a livello centralizzato i farmaci C5i previsti dal protocollo,

PREMESSO CHE, le Parti desiderano emendare tale Contratto tenendo conto degli accordi e impegni reciproci ivi esposti e a fronte di una controprestazione adeguata, della cui avvenuta ricezione e adeguatezza si prende qui atto, le Parti acconsentono a emendare il Contratto come segue:

1. **Allegato A, Budget e programma dei pagamenti**

1.1 A partire dalla data di decorrenza, La tabella relativa alle procedure condizionali della Parte 2, Allegato A, Budget e programma dei pagamenti, dovrà essere aggiornata per includere le seguenti procedure relative al rimborso C5i:

Procedura	**Importo della procedura (euro + iva)**
Somministrazione di anticorpo monoclonale, per via endovenosa (EV); tecnica di infusione, fino a un'ora; sostanza/farmaco singolo o iniziale (ravulizumab) per somministrazione endovenosa di ravulizumab	**90,00**
Somministrazione di anticorpo monoclonale, per via endovenosa (EV); tecnica di infusione, ogni ora aggiuntiva (ravulizumab) per somministrazione endovenosa di ravulizumab della durata superiore a 1 ora	**37,00**
Farmacia, complesso (ravulizumab) - Per preparazione; dispensazione del farmaco per somministrazione endovenosa di ravulizumab	**50,00**
Tariffa giornaliera della struttura - Al giorno, per somministrazione endovenosa di ravulizumab	**59,00**
Medico - All'ora, per somministrazione endovenosa di ravulizumab	**95,00**
Coordinatore dello studio - All'ora, per somministrazione endovenosa di ravulizumab	**37,00**
Somministrazione di anticorpo monoclonale, per via endovenosa (EV); tecnica di infusione, fino a un'ora; sostanza/farmaco singola/o o iniziale (eculizumab) per somministrazione endovenosa di eculizumab	**90,00**
Somministrazione di anticorpo monoclonale, per via endovenosa (EV); tecnica di infusione, ogni ora aggiuntiva (eculizumab) per somministrazione endovenosa di eculizumab della durata superiore a 1 ora	**37,00**

Farmacia, complesso (eculizumab) - Per preparazione; dispensazione del farmaco per somministrazione endovenosa di eculizumab	**50,00**
Tariffa giornaliera della struttura - Al giorno, per somministrazione endovenosa di eculizumab	**59,00**
Medico - All'ora per somministrazione endovenosa di eculizumab	**95,00**
Coordinatore dello studio - All'ora, per somministrazione endovenosa di eculizumab	**37,00**

2. Il presente Emendamento, una volta completamente perfezionato, costituisce parte ed è incorporato nel Contratto. Tutti i termini e le condizioni del Contratto non espressamente modificati dal presente Emendamento rimarranno in piena validità ed efficacia.

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 sono a carico del Promotore. Il presente emendamento è efficace a partire dalla data della sua sottoscrizione.

A TESTIMONIANZA DI CIÒ, le Parti succitate hanno accettato e sottoscritto il presente Emendamento tramite i propri funzionari debitamente autorizzati nella/e data/e riportata/e di seguito.

IQVIA RDS Italy Srl

Firma:_____

Nome e cognome: Dr. Fabrizio Forini

Titolo: Il Procuratore

Data:_____

Per l'Azienda ULSS 7 Pedemontana

Firma:_____

Nome e cognome: Dott. Carlo Bramezza

Titolo: Il Direttore Generale

Data:_____